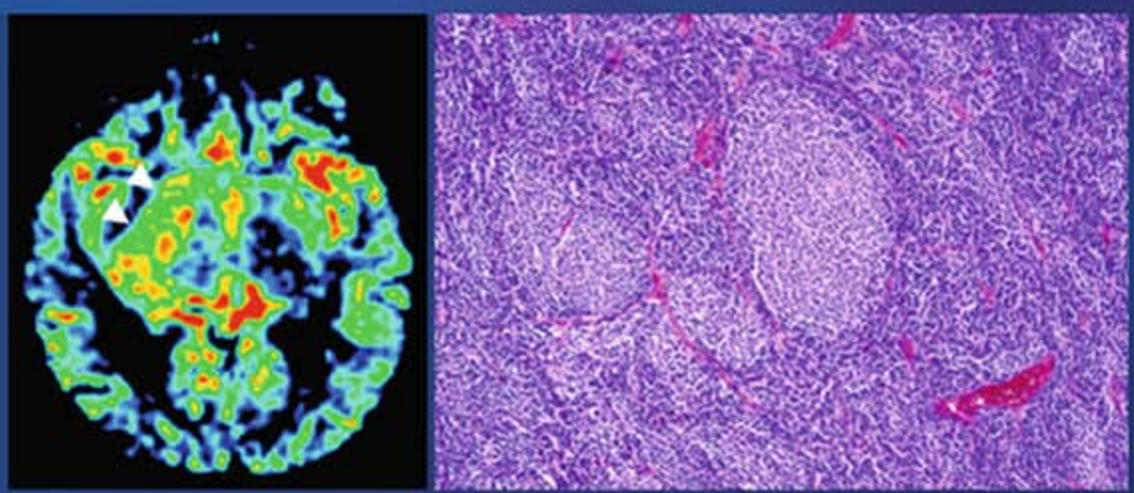
NALIN GUPTA
ANURADHA BANERJEE
DAPHNE HAAS-KOGAN
Editors

PEDIATRIC ONCOLOGY

Pediatric CNS Tumors



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Nalin Gupta
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Dedication

We dedicate this book to our children:
Naya, Kavi
Shabnam, Hrittik
Yonatan, Shira, and Maetal.

Preface

Pediatric brain tumors are a tremendous challenge for the treating physician. Their diverse biological behaviors, in the unique context of the developing nervous system, require flexible and tailored treatment plans. In the last 20 years, there has been an exponential increase in our understanding of the molecular and genetic basis of human malignancy. We are just now seeing the promise of this knowledge translate into biologically-directed therapies being routinely tested in collaborative research networks. The effectiveness of these new agents, however, remain undefined.

The goal of this textbook is to provide a current, biologically-based perspective of the management of central nervous system tumors in children. Rather than present every tumor type in an encyclopedic manner, the common tumor types encountered in clinical practice are presented in the initial chapters. The epidemiology, pathological features, clinical presentation, diagnosis, and treatment are discussed for each tumor type. We have separated high- and low-grade glial tumors into separate chapters, mainly because the management and outcome for these two classes of tumors are very different. In the final chapters, many of the diagnostic and treatment modalities common to all tumors are discussed with an emphasis on emerging and experimental techniques. For the second edition, new chapters have been added: Rare Tumors (Chap. 11) and Late Effects and Palliative Care (Chap. 17). A valuable resource is the WHO classification of tumors of the central nervous system; the fourth edition of which was published in 2007 (Louis et al. 2007).

It is recognized that a variety of treatment strategies are utilized by many different practitioners and institutions. For the most part, the general management principles used at the University of California, San Francisco, are presented, usually in the context of standard therapy. Although this approach may underemphasize other equally valid approaches, we believe that the reader will benefit from a coherent approach to the management of childhood tumors.

The editors acknowledge the contribution of the authors, our colleagues at the University of California, San Francisco, the editorial staff at Springer, and our many mentors in preparation and assembly of this book. We are indebted to Judi Chesler, who provided ongoing administrative assistance, and Ilona Garner, who carefully edited the manuscript.

California, USA

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1.1 Introduction

Astrocytomas are the most common subgroup of central nervous system (CNS) tumors in children. The most frequent histological types are pilocytic and fibrillary astrocytomas, which are considered low-grade astrocytomas. A variety of other, less-common glial tumors are also seen in children, including pleomorphic xanthoastrocytoma (PXA), subependymal giant cell astrocytoma, high-grade gliomas, gangliglioma and desmoplastic infantile ganglioglioma, astroblastoma, ependymoma, and oligodendroglioma. This chapter focuses on low-grade astrocytomas with an emphasis on infiltrating astrocytoma, cerebellar astrocytoma, optic pathway glioma, and oligodendroglioma.

1.2 Astrocytomas

1.2.1 Epidemiology

Supratentorial tumors account for approximately 40–60% of all pediatric brain tumors, and are almost twice as common in infants as in older children (Farwell et al. 1977; Dohrmann et al. 1985; Dropcho et al. 1987). The majority of supratentorial tumors are gliomas (astrocytoma, oligodendroglioma, and ependymoma) with the most common subtype, low-grade glioma, accounting for half of these. In contrast to the distribution of gliomas in adults, malignant gliomas account for only 20% of all childhood supratentorial gliomas.

The incidence of pediatric brain tumors was, until recently, believed to be rising, based on studies from the United States and Europe (Gurney et al. 1996; Gjerris et al. 1998). This trend has been refuted and is now attributed to increased surveillance and reporting (detection bias) during the preceding two decades, and in the initial recruitment phase of large population-based studies (Smith et al. 1998; Rickert and Paulus 2001). For the majority of gliomas, the etiology remains unknown. Children with familial cancer predisposition syndromes have an increased risk of developing both low- and high-grade gliomas. Environmental factors, such as parental smoking and residential proximity to electromagnetic field sources, have not been linked to pediatric brain tumors, although parental occupation in the chemical/electrical industry might be associated with an increased risk of astroglial tumors in the offspring (Gold et al. 1993; Rickert 1998). Conversely, prenatal vitamin supplementation in mothers may confer a slight protective effect (Preston-Martin et al. 1998). To date, the only environmental agent clearly implicated in developing glioma is exposure to ionizing radiation, which results in a 2.6-fold increased risk of developing this cancer (Ron et al. 1988). For example, development of malignant cerebellar astrocytomas is associated with prior cranial radiation therapy and is observed in children as they enter the later decades of life (Steinbok and Mutat 1999). Recent case reports have implied that radiation-induced mutagen sensitivity of lymphocytes may be associated with an increased risk for glioma (Bondy et al. 2001).

1.2.1.1 Neurofibromatosis Type I

Neurofibromatosis type 1 (NF1) is associated with an increased risk of intracranial tumors, and approximately 15–20% of patients with NF1 present with low-grade intracranial tumors. Pilocytic astrocytomas arise in a variety of locations in NF1 patients, but are most commonly located in the optic nerve, optic chiasm, hypothalamus, and/or brainstem. They may also occur within the cerebral hemisphere and cerebellum (Listernick et al. 1999). The growth of intracranial tumors is the main cause of death among NF1 patients.

The *NF1* gene is located on chromosome 17q and encodes a GTPase activating protein (GAP), termed neurofibromin, involved in regulating the ras-p21 signaling pathway. Mutations in the *NF1* gene lead to manifestations of the disease. How loss of neurofibromin expression or expression of defective neurofibromin leads to formation of astrocytomas is under investigation. Neurofibromatosis may arise from sporadic mutations in the *NF1* gene or through germline transmission of an established mutation (Gutmann et al. 2000). Proteomic analysis of *NF1*-deficient human and mouse brain tumors

has revealed elevated levels of mammalian target of rapamycin (mTOR) activity (discussed in Sect. 1.2.5.4) and its downstream targets associated with protein translation and growth (Dasgupta et al. 2005). Neurofibromin is a GTPase that negatively regulates the G-coupled protein, Ras, whose downstream targets include Akt and mTOR (Dasgupta et al. 2005; Sabatini 2006). Therefore, mTOR may be an attractive molecular target worth further examination. However, NF1-associated CNS tumors such as pilocytic astrocytomas, rarely demonstrate alterations in other known oncogenic genes such as *p53*, *EGFR*, *PDGFR*, and *p21* and these tumors are considered to be benign (Gutmann et al. 2000; Vinchon et al. 2000).

1.2.1.2 World Health Organization Grading

The recent World Health Organization (WHO) classification of CNS tumors organizes astrocytomas into four grades. WHO grade I corresponds to the noninfiltrating pilocytic astrocytoma, while diffuse astrocytomas are considered WHO grade II. Grade III and IV correspond to anaplastic astrocytoma and glioblastoma multiforme, respectively. Cerebellar astrocytomas, grade I and II, comprise approximately 70–80% and 15% of childhood cases, respectively (Steinbok and Mutat 1999). Experimental evidence suggests that grade I and II cerebellar astrocytomas develop from different precursor cells (Li et al. 2001). PEN5, a recently identified oligodendroglial antibody epitope, is present in grade I tumors, but not in grade II tumors. Also, NF1-related cerebellar astrocytomas demonstrate PEN5 immunoreactivity, indicating that both spontaneous grade I and NF1-related grade I cerebellar astrocytomas arise from the same precursor cells.

1.2.2 Pathology

1.2.2.1 Grade I and II Astrocytoma

Because pilocytic astrocytomas are most common in the first two decades of life, they are often termed juvenile pilocytic astrocytomas (JPA). JPAs can be found throughout the neuraxis (optic pathway, hypothalamus, cerebral hemisphere, brainstem, and spinal cord), although 80% are found in the cerebellum (Dirven et al. 1997). In general, these tumors tend to be well-circumscribed and do not infiltrate into the surrounding brain. One exception is optic pathway glioma, a subtype of JPA that arises within the visual pathways and typically presents with vision loss. These gliomas can infiltrate widely, even extending into the posterior visual cortex. This subtype is discussed in greater detail in Sect. 1.4.

JPAs exhibit a biphasic pattern of compact, bipolar, highly fibrillated astrocytes, accompanied by Rosenthal fibers alternating with loose-textured microcystic regions of eosinophilic granular astrocytes (Fig. 1.1). Unlike malignant astrocytomas, pleomorphism, mitotic figures, hypercellularity, endothelial proliferation, and necrosis may be present, but this does not indicate malignancy or poor prognosis (Steinbok and Mutat 1999). Local leptomeningeal invasion is apparent in half of all cases and has no prognostic significance (Burger et al. 2000).

Grade II astrocytomas are distinct from pilocytic tumors because of their location, degree of infiltration, and presence of genetic aberrations (Kleihues et al. 1993; Louis et al. 2007). Grossly, grade II astrocytomas are ill-defined lesions that tend to enlarge and distort involved structures. Destruction of brain tissue, however, is more characteristic of higher-grade tumors. Microscopic examination of resected grade II tumor specimens invariably shows diffuse infiltration of the surrounding gray and white matter. Low-power microscopy may show a subtle increase in overall cellularity and disruption of the orderly pattern of glial cells along myelinated fibers. Higher-power examination reveals neoplastic astrocytes with indistinct cytoplasmic features. The diagnosis is often based on the appearance of the nuclei, which are characteristically elongated. Nuclear atypia is minimal in low-grade astrocytomas and mitotic activity is infrequent.

1.2.2.2 Other Low-Grade Subtypes

Low-grade astrocytomas can be further subdivided on the basis of their microscopic appearance. The prognostic value of these subgroups is not entirely

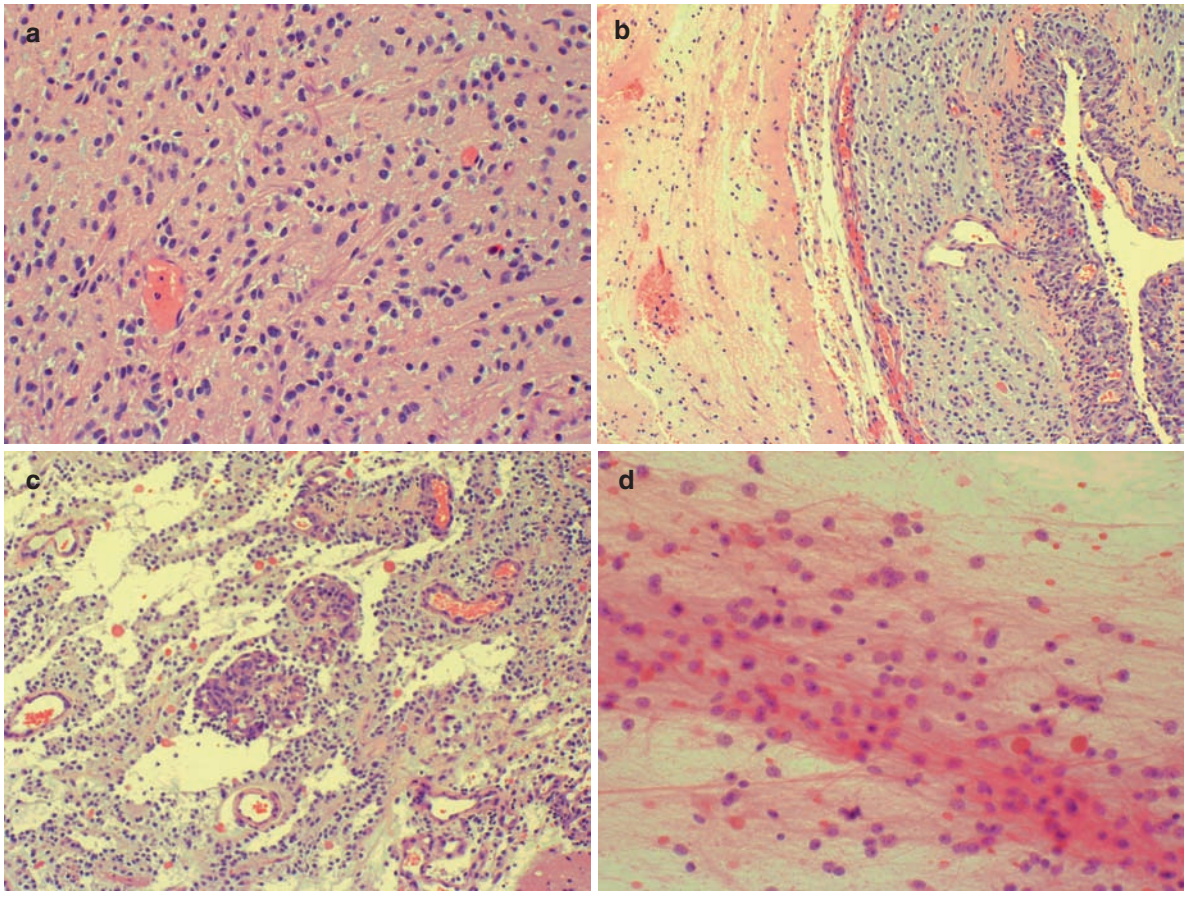

Figure 1.1

Histopathological features of pilocytic astrocytoma. (**a**) Field of tumor cells demonstrating increased cellularity, mild nuclear atypia, and lack of mitoses. (**b**) Tumor edge with gliotic border (*left* of image) and neovascularization. (**c**) Biphasic pattern of compact, fibrillated astrocytes and loosely textured microcysts with a focus of endothelial proliferation. (**d**) Squash preparations demonstrating thin glial processes ("pili") extending from bipolar tumor cells

clear. Fibrillary astrocytoma is the most common grade II astrocytoma subtype and demonstrates a uniform, compact arrangement of fibrillary astrocytes with varying degrees of cellular atypia on a background of loosely structured tumor matrix (Steinbok and Mutat 1999). Gemistocytic astrocytomas are composed of neoplastic astrocytes with abundant eosinophilic, glial fibrillary acidic protein (GFAP)-positive cytoplasm with nuclei displaced to the periphery (Kaye and Walker 2000). The WHO classification identifies the gemistocytic subtype as low-grade astrocytoma, as long as cellularity and nuclear atypia remain mild (Louis et al. 2007). The PXA, a recently described subtype, is a rare, GFAP-positive, astrocytic tumor typically occurring in the cerebral hemispheres of children and young adults (Kepes et al. 1973).

Histologically, PXA is characterized by large, neoplastic astrocytes with substantial nuclear pleomorphism and very atypical nuclei. The borders

are often infiltrative, and tumor cells may display clustering in an epitheliod fashion (Lindboe et al. 1992; Powell et al. 1996). Desmoplastic infantile astrocytoma (DIA) is a rare tumor occurring in infants 18 months or younger. These tumors are usually large, cystic, supratentorial in location, and have a dural attachment. Histologically, they are loose to dense collagenous stroma with wavy fascicles of spindle cells (Taratuto et al. 1984). The rarest subtype is the protoplasmic astrocytoma, which has prominent microcysts, mucoid degeneration, and a paucity of GFAP positivity (Kaye and Walker 2000). Some consider this a histological pattern of fibrillary astrocytoma, rather than a true variant. Diffuse cerebellar astrocytomas resemble low-grade astrocytomas of the cerebral hemispheres with poorly circumscribed borders and invasion of the surrounding parenchyma. These tumors generally occur in older children, and young adults can undergo malignant transformation (Burger et al. 2000). Regardless of subtype, all low-grade astrocytomas have low cellularity, limited nuclear atypia, and rare mitotic activity. Low-grade astrocytomas with single mitotic figures have prognoses similar to other low-grade tumors (Giannini et al. 1999). A single mitotic figure suggests that the presence of isolated mitoses may not be sufficient to transform an otherwise low-grade astrocytoma to a higher-grade lesion.

1.2.2.3 Genetics

Cytogenetic abnormalities occur less frequently and with different patterns in children than in adults (Cheng et al. 1999). In adult low-grade astrocytomas, mutations in the *p53* tumor suppressor gene are common, and may herald an early event in malignant progression (Watanabe et al. 1998; Kosel et al. 2001). In contrast, *p53* mutations are not frequently found in the pediatric population (Litofsky et al. 1994; Felix et al. 1995; Ishii et al. 1998). The majority of pediatric pilocytic astrocytomas demonstrate normal cytogenetic findings (Griffin et al. 1988; Karnes et al. 1992; Bigner et al. 1997). In a recent study of 58 pediatric patients, 70% of grade I astrocytomas had a normal cytogenetic profile (Roberts et al. 2001). In another study of 109 pediatric brain tumors, which included 33 low-grade astrocytomas, low-grade astrocytomas mostly showed changes in chromosome copy number (Neumann et al. 1993). Reported cytogenetic abnormalities include gains on chromosomes 1, 7, and 8 and losses of 17p and 17q (White et al. 1995; Wernicke et al. 1997; Zattara-Cannoni et al. 1998).

High-density single-nucleotide polymorphism-based genotyping and comparative genome hybridization (CGH), have revealed duplication or gain in chromosomes 5 and 7, with particular amplification of 7q34 in JPA (Pfister et al. 2008; Sievert et al. 2008). Two genes of potential interest identified from 7q34 were *HIPK2*, a gene for a homeobox-interacting protein kinase, and *BRAF*, a protooncogene. In 26 of 61 JPAs, *HIPK2* was shown to be amplified using CGH and confirmed by quantitative PCR (Deshmukh et al. 2008). Using CGH, *BRAF* was duplicated in 28 of 53 JPAs. In vitro inhibition of BRAF signaling, directly by lentivirus-mediated transduction of BRAF-specific shRNAs or indirectly by pharmacological inhibition of MEK1/2, the immediate downstream target of BRAF, caused G_2/M cell-cycle arrest in astrocytic cell lines (Pfister et al. 2008). Thus, aberrant activation of the mitogen-activated protein kinase (MAPK) pathway, due to gene duplication or activating mutation of BRAF, is a common event in the tumorgenesis of pediatric low-grade astrocytomas.

Another abnormal chromosomal marker of JPA is the unique allelic imbalance of chromosome arm 22q13. Medulloblastoma and high-grade glioma also have unique allelic imbalances (Entz-Werle 2008). Other aberrations include allelic losses on chromosomes 10p, 19, and 22q (Bello et al. 1994; von Deimling et al. 1994). However, larger patient populations in future studies are needed in order to validate these findings. Patients who lack NF1 and develop JPAs often possess distinct genetic profiles. However, constitutive activation of the mTOR pathway appears to be consistent, through different mechanisms, in patients who develop either spontaneous or NF1-deficient JPA (Dasgupta et al. 2005; Sharma et al. 2005). In JPA and diffuse astrocytoma, genes associated with proliferation, migration, invasion, and angiogenesis, including TIMP1, TIMP2, and YKL-40, have been found to be activated (Huang

et al. 2000; Colin et al. 2006; Zhang et al. 2008). Further experimental studies demonstrate that grade II tumors have higher mitotic indices, higher percentages of cells in S phase, and more vascular endothelial growth factor (VEGF) expression than grade I tumors (Reddy and Timothy, 2000). To date, no molecular prognostic criteria exist to predict malignant tumor progression. However, the identification of these markers may not only direct us to novel molecular targets for drug therapy, but may also allow rapid pathologic characterization and classification of these tumor types.

1.2.3 Clinical Features

Symptoms and signs caused by low-grade gliomas depend on the anatomic location, biological aggressiveness of the tumor, and age of the patient. These signs and symptoms may be nonspecific, such as those associated with increased intracranial pressure (ICP), or focal, related to tumor location. Nonspecific symptoms include headache, nausea, and vomiting, subtle developmental delay, and behavioral changes. Some of the behavioral changes associated with slow-growing tumors in children include alterations in personality, irritability, altered psychomotor function, apathy, and declining school performance. It is not uncommon for symptoms to have been present for months or years prior to diagnosis. In infants with open cranial sutures, a tumor may reach a massive size with a gradual increase in head circumference without signs of increased ICP or any other symptoms. Focal symptoms depend upon the location of the tumor, and may include hemiparesis, monoparesis, hemisensory loss, dysphasia, aphasia, and impairment of recent memory. Tumors involving the optic pathways can present with quadrantanopsia, homonymous hemianopsia, or in cases with bilateral occipital lobe involvement, cortical blindness. Hemorrhage occurs rarely in low-grade tumors, although one report noted the presence of hemorrhage in 8% of patients with pilocytic astrocytoma (White et al. 2008).

Epilepsy is the major presenting feature of pediatric patients with brain tumors, and seizures occur in more than 50% of children with hemispheric tumors (Keles and Berger 2000). The majority of patients with tumor-associated epilepsy harbor slow-growing, indolent neoplasms such as low-grade gliomas. Other relatively slow-growing tumors, for example, astrocytomas, gangliogliomas, and oligodendrogliomas, may also present with a history of generalized seizures. Rapidly growing lesions are more likely to produce complex partial motor or sensory seizures, although generalized tonic clonic seizures are also common. Malignant gliomas are less-frequently associated with seizures and are more likely to cause focal neurologic deficits; mainly due to infiltration of normal tissue, or by local mass effect.

1.2.4 Diagnostic Imaging

Magnetic resonance imaging (MRI) and computed tomography (CT) are essential tools in the diagnosis and treatment of brain tumors. Although CT is more commonly available, MRI provides higher sensitivity in differentiating tumor tissue from normal brain, allowing more detailed anatomic characterization of the lesion, and should be obtained in all children with a diagnosis of a brain tumor. A complete series should include the following sequences: T1-weighted axial and coronal (both before and after gadolinium), T2-weighted axial and coronal, and fluid attenuated inversion recovery (FLAIR). In addition, sagittal plane sequences are helpful in defining anatomy of suprasellar and midline tumors. Other sequences such as fat suppression and MR angiography may also be required in specific situations. Newer techniques, such as magnetic resonance spectroscopy (MRS), functional MRI, and perfusion measurements offer the potential of obtaining biochemical and functional information noninvasively (see Chap. 13). It is possible that in the future a pathologic diagnosis may be reached with substantial confidence without the need for open biopsy.

Although low-grade gliomas may produce considerable mass effect upon surrounding structures, neurologic deficits may be minimal due to the slow growth of these tumors and the absence of tissue destruction. Low-grade astrocytomas are usually nonenhancing, iso- or hypodense masses on CT scan. Calcification may be detected in 15–20% of cases, and mild to moderate inhomogeneous contrast enhancement can be seen in

up to 40% of all cases (Lote et al. 1998; Bauman et al. 1999; Roberts et al. 2000; Scott et al. 2002). Some tumors, characteristically JPAs, may have cystic changes. On MRI, T1-weighted images show an iso- to hypointense nonenhancing mass that is hyperintense on T2-weighted images. Low-grade astrocytomas have minimal to no contrast enhancement following gadolinium administration (Fig. 1.2b, d). For this reason, the tumor boundary is difficult to determine with any T1-weighted sequence. Fortunately, the FLAIR sequence is very sensitive for defining the extent of tumor infiltration (Fig. 1.2a, c).

Recurrence is an unavoidable feature of most glial neoplasms, and serial imaging over time is often the only method of determining whether tumor progression has occurred. For low-grade astrocytomas, high-quality MRI scans should be obtained every 6 months. If there is concern that any changes have occurred, the interval should be decreased to 3 months. In general, for grade II astrocytoma, the two most important features are an increase in the volume of T2-weighted abnormality, and/or new enhancement on post-gadolinium T1-weighted images. These features are also observed in patients who have received radiation treatment, and differentiating tumor recurrence from radiation necrosis continues to present a challenge. Additional information may be obtained from MR spectroscopy and positron emission tomography (PET) scans, but at times, the only method is to obtain a surgical biopsy.

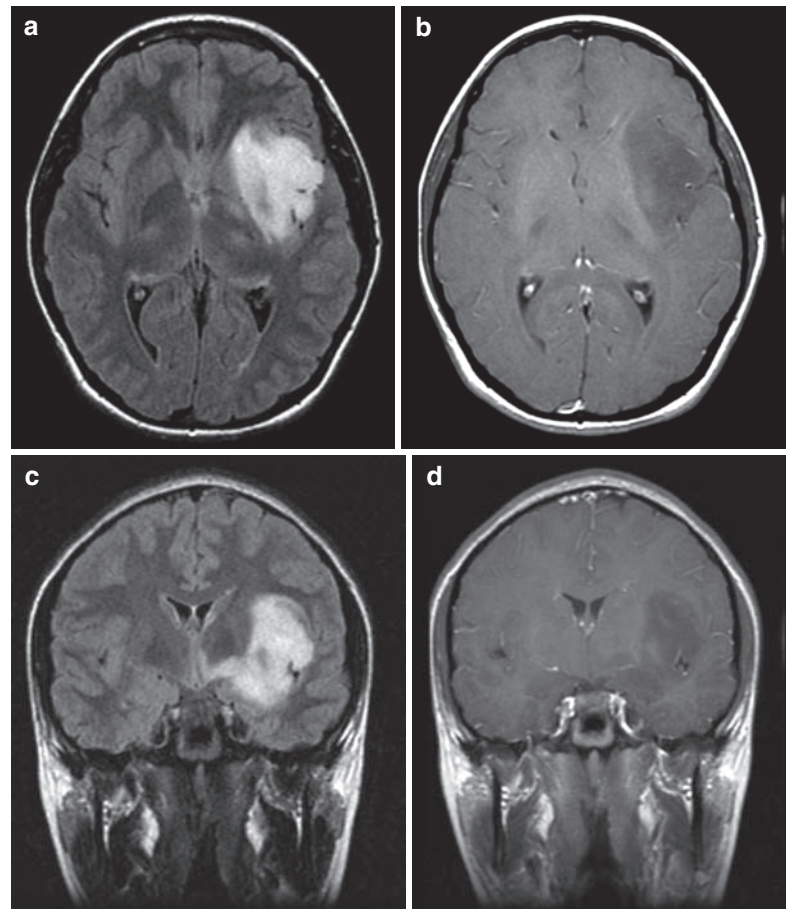

Figure 1.2

MR images from a teenage girl with a low-grade astrocytoma of the insula who presented with a single seizure. Her neurologic exam was normal. (**a**, **c**) Axial and coronal FLAIR images showing the extent of involvement. Note the tumor infiltration medially under the lentiform nucleus towards the hypothalamus. (**b**, **d**) Corresponding T1-weighted post-gadolinium images showing no appreciable enhancement

1.2.5 Treatment

1.2.5.1 Surgical Indications

A surgical procedure is usually the initial step in the management of low-grade gliomas. The primary objective is to obtain tissue for pathologic diagnosis. A relative exception would be for tumors in locations not amenable to surgery, such as optic pathway/chiasmatic gliomas, although a stereotactic biopsy can safely obtain tissue for pathologic confirmation. The secondary objective is to perform as extensive a resection as possible with acceptable neurologic outcome for the patient. The two variables that must be considered are the extent and timing of resection. Extent of resection is the most important prognostic factor for 5-year overall and progression-free survival (PFS). Patients who have partial resections or residual disease often recur or experience tumor progression (Shaw and Wisoff 2003). The feasibility of an open-surgical approach depends upon several factors. The most important is the exact location of the tumor. Deep lesions within the basal ganglia, thalamus, motor cortex, or brainstem are usually not amenable to open surgical resection, while tumors in other locations can be accessed through various standard approaches. Other factors that modify the decision to attempt surgical resection are the patient's clinical condition, age, associated hydrocephalus, and the surgeon's assessment of risk of neurologic sequelae.

Timing of resection is a controversial topic, and few conclusive studies have been published to date. There are reports questioning the value of immediate treatment when an imaging study suggests a low-grade glioma, as no definitive evidence exists which demonstrates improvement in long-term survival following early intervention (Cairncross and Laperriere 1989; Recht et al. 1992).

In addition to reducing tumor burden and providing tissue diagnosis, resection permits management of increased ICP, prevention of irreversible neurologic deficits, decompression of adjacent brain structures, and control of seizures (Berger et al. 1991, 1993; Haglund et al. 1992; Keles and Berger 2000). For patients with discrete JPAs (WHO grade I), gross total resection (GTR), when possible, is curative. Contemporary neurosurgical methods, including ultrasonography, functional mapping, frameless navigational resection devices, and intraoperative imaging techniques enable more extensive resections with less morbidity (see Chap. 14 for more details).

1.2.5.2 Chemotherapy

Although indolent and slow growing, overall 5-year survival rates for patients with diencephalic and hemispheric tumors who have received radiation therapy vary, ranging from 40 to 70%. Additionally, the morbidity associated with radiation treatment can be substantial, prompting numerous investigators to explore chemotherapy as an alternative adjuvant treatment to control tumor progression. Chemotherapy effectively provides disease control in many optic pathway tumors (see below), and may improve prognosis for vision maintenance. Studies of early combination chemotherapy regimens with vincristine and actinomycin D, used in children less than 6 years of age, reported 62% PFS without further therapy; those who did progress did so at a median of 3 years from the start of therapy. The median IQ in this group was 103 (Packer et al. 1988). It is important to recognize that prolonged periods of stable tumor size are considered a treatment "response" by many investigators. Alternative combination chemotherapy regimens have also resulted in tumor response in pilot studies. Other drug combinations that have been reported include lomustine and vincristine; 6-thioguanine, procarbazine, lomustine, and vincristine (TPCV); and combinations using cisplatin (Edwards et al. 1980; Gajjar et al. 1993). The combination regimen of carboplatin and vincristine (CV) has been associated with objective response rates (stable disease as well as tumor shrinkage) in the range of 60–70% (Packer et al. 1997). The combination of TPCV has also been associated with a substantial response rate in a small cohort of patients (Prados et al. 1997).

A large-scale, randomized, Phase III, multiinstitutional clinical trial conducted by the Children's Oncology Group (COG) examined the relative effectiveness of CV versus TPCV. Four hundred and

one children less than 10 years old were enrolled in COG A9952. Of these 401 eligible children, 137 were randomized to receive CV, 137 were randomized to receive TPCV, and 127 patients with NF1 and radiographically verified progressive optic pathway glioma were nonrandomly assigned to the CV arm because of the heightened leukemogenic potential of TPCV in this patient population. Tumor response rates, defined as a decrease in both enhancement and T2 signal on MRI at the end of protocol therapy, were 57% for CV, non-NF1; 61% for CV, NF1; and 58% for TPCV. The 5-year overall survival rates in CV-treated, non-NF1 versus NF1 patients were 86 and 98%, respectively. Similarly, 5-year event-free survival (EFS) was improved in NF1 versus non-NF1 patients (69 vs. 42%, respectively) and no difference in EFS was found when comparing CV versus TPCV. The median time to progression for CV versus TPCV was 3.2 versus 4.9 years (Ater et al. 2008). These findings demonstrate that both therapies can be used successfully to treat low-grade glioma with good overall EFS, thus allowing a delay in radiotherapy.

Although primary therapy is now more regimented in pediatric patients with low-grade gliomas, effective therapy for recurrent low-grade glioma remains largely nonstandardized. Investigators are exploring the role of mono- and combinatorial therapy to extend treatment response. A Phase II study examining the role of weekly vinblastine in pediatric patients with recurrent low-grade glioma demonstrated that patients who had previously failed single or multiple rounds of chemotherapy and/or radiotherapy were well controlled on vinblastine therapy. Of the 51 patients initially treated, 29 completed 52 weeks of therapy, while the rest either progressed, or had adverse reactions to therapy. With a median follow-up of 31 months, 19 of the 29 patients who had completed therapy remained progression-free (Bouffet et al. 2008).

The HIT-LGG 96 study examined the role of second-line chemotherapy in patients who had disease progression in the chemotherapy arm (94 patients). Of those 94 patients, 27 went on to receive a second round of chemotherapy consisting of vincristine/carboplatin and/or cyclophosphamide regimen, vinblastine alone, temozolomide alone, or other regimen. The median age in this group was 11.8 months. Best achievable response was tumor reduction in 8 patients and stable disease in 13 patients. Thirteen patients recurred 15.7 months after starting second-line chemotherapy. The overall 3-year PFS in the second chemotherapy group was 34% (Kordes et al. 2008).

A Phase II study assessed the efficacy of temozolomide in children with progressive optic pathway glioma and pilocytic astrocytoma. Thirty patients were treated with oral temozolomide for 5 days every 4 weeks. The 2-year PFS and overall survival rates were 49 and 96%, respectively, with manageable toxicity (Gururangan et al. 2007). These findings illustrate the potential to further delay radiotherapy in this pediatric population by using chemotherapy.

1.2.5.3 Radiation Therapy

As discussed above, low-grade astrocytoma may be curable with GTR. For those patients with unresectable or incompletely resected disease, the use of radiation therapy is controversial. There is some evidence to suggest that while radiation therapy may prolong PFS, it has little impact on overall survival (Pollack et al. 1995). Its use is largely limited to patients with progressive or recurrent disease, or in the setting of a highly symptomatic patient who requires tumor stabilization to avert the progression of symptoms. As of January 2008, 1121 patients are under evaluation in a large-scale multiinstitutional trial, SIOP-LGG 2004, to address the role of adjuvant chemotherapy and radiotherapy in order to assess their optimal therapeutic effect and toxicity on pediatric low-grade glioma after total or subtotal surgical resection (Gnekow et al. 2008).

Because of neurocognitive toxicity associated with radiotherapy, minimizing the dose and radiation fields using stereotactic radiosurgery or proton therapy may provide an effective alternative to standard conformal radiotherapy (Hadjipanayis et al. 2003; Marcus et al. 2005). One prospective trial using stereotactic radiosurgery demonstrated effective control of small, pediatric LGGs that had progressed either after surgery or chemotherapy. The 8-year PFS and overall survival rates using stereotactic radiosurgery in these patients were 65 and 82%,

respectively (Marcus et al. 2005). Clinical outcomes using proton therapy in 30 pediatric patients treated for primary low-grade gliomas were comparable to standard radiotherapy. Neurocognitive and psychiatric exams two years posttreatment appeared stable, with minimal negative changes in working memory and processing speed (Yock et al. 2008). While proton therapy appears to be safe and provide good short-term outcomes, long-term neuropsychiatric results are required.

Alternatively, the use of microsurgery combined with interstitial radiosurgical I-125 seed implantation (IRS) has demonstrated promising results. Nineteen children with low-grade glioma received IRS and/or microsurgery to the tumor site. With a median follow-up of 26 months, 5 tumors had a complete response, 11 tumors had reduction in size, 2 children developed radionecrosis requiring resection, and 1 child had progression and died (Peraud et al. 2008). While this therapy appears feasible, long-term neurocognitive toxicity needs to be assessed.

1.2.5.4 Targeted Molecular Therapy

Overall prognosis and clinical outcome for patients with glioma are associated with tumor grade. Genes associated with glial cell grade and tumorigenesis continue to be identified. Understanding the pattern of genes activated in glioma will likely provide insight into the natural history and potential clinical course of these tumors, and whether they will respond to standard chemotherapeutic regimens or novel molecular targeted therapies. For this reason, the PI3K/Akt/mTOR pathway has been studied in great detail as it plays a large role in the tumorigenesis of many cancers including glial tumors (Sabatini 2006; Guertin and Sabatini 2007).

Two complexes of mTOR exist: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). The tumor suppressor genes TSC1/hamartin and TSC2/tuberin are important for regulation of mTOR activity. Germline mutations of TSC lead to tuberous sclerosis and predisposition to a variety of benign tumors including hamartomas and lymphangioleiomyomas. Many upstream growth factor receptors and PI3K signal through the downstream mediator, mTOR. Since there are no known somatic mutations which constituitively activate mTOR making mTOR an attractive target for therapeutic intervention (Houghton and Huang 2004).

Further characterization of mTOR's signaling pathway may lead to better application of mTOR inhibitor therapy. Franz et al. used rapamycin, an mTOR inhibitor, to treat 5 TSC patients who had either subependymal giant cell astrocytoma ($n=4$) or pilocytic astrocytoma ($n=1$). In all five cases, tumor regression was observed, and in one case tumor necrosis occurred, (Franz et al. 2006). Inhibition of mTOR signaling is emerging as a provocative target for treatment of LGGs.

Further exploration of gene expression profiles of grade I and II gliomas have already led to the introduction of novel therapies for pediatric low-grade gliomas. Recent reports strongly implicate BRAF in the molecular pathogenesis of pediatric low-grade astrocytoma, and open a new avenue for molecularly targeted agents. In these studies, aberrant MAPK signaling could be inhibited in low-grade astrocytoma cell lines when treated with an inhibitor of the MAPK signaling component MEK. Therefore, a potent and selective inhibitor of MEK, AZD 6244, will soon enter clinical trials for the treatment of pediatric low-grade gliomas. AZD 6244 can reduce levels of phosphorylated extracellular signal-regulated kinase (ERK) 1/2 in cells with high basal ERK 1/2 phosphorylation, as well as in cells with growth factor-induced (EGFR overexpressing) ERK 1/2 phosphorylation. Inhibition of MEK 1/2 with AZD 6244 resulted in arrest of cell growth in several cancer cell lines including colon cancer, melanoma, pancreatic cancer, and breast cancer (Yeh et al. 2007). Expression of growth, stromal, or neovascular factors by low-grade gliomas, such as platelet-derived growth factor receptor, matrix metalloproteinases, and VEGF, similarly warrants further examination. Novel agents are currently being examined in higher-grade gliomas either alone or in combination with chemoradiotherapy. As our understanding of low-grade gliomagenesis and gene expression improves, selective use of these targeted molecular therapies can offer great promise for disease control or cure when combined with standard surgery, chemotherapy, and radiation.

1.2.6 Outcome

Age and histological type are significant prognostic predictors. Although patients appear to benefit from more extensive resections, this issue remains controversial. In a majority of patients with tumor-associated epilepsy, including those patients with malignant astrocytomas, the seizures are infrequent and easily controlled with a single antiepileptic drug. In this setting, removal of the tumor alone usually controls seizure activity without the need for additional anticonvulsants. Children with indolent tumors, however, may have seizure activity that is refractory to medical therapy. Optimal seizure control without postoperative anticonvulsants in this situation is achieved when perioperative electrocorticographic mapping of separate seizure foci accompanies tumor resection. When mapping is not utilized, and a radical tumor resection includes adjacent brain, the occurrence of seizures will be lessened, but most patients will have to remain on antiepileptic drugs (Berger et al. 1991).

Dedifferentiation or malignant transformation is a well-described phenomenon in low-grade gliomas (Fig. 1.3). The incidence of recurrence as a higher histologic grade ranges from 13 to 86% of tumors initially diagnosed as low-grade (Keles et al. 2001). Similar to its broad range of incidence, the time to malignant differentiation is also variable, ranging from 28 to 60 months. However, factors resulting in change to a malignant phenotype remain unclear. In

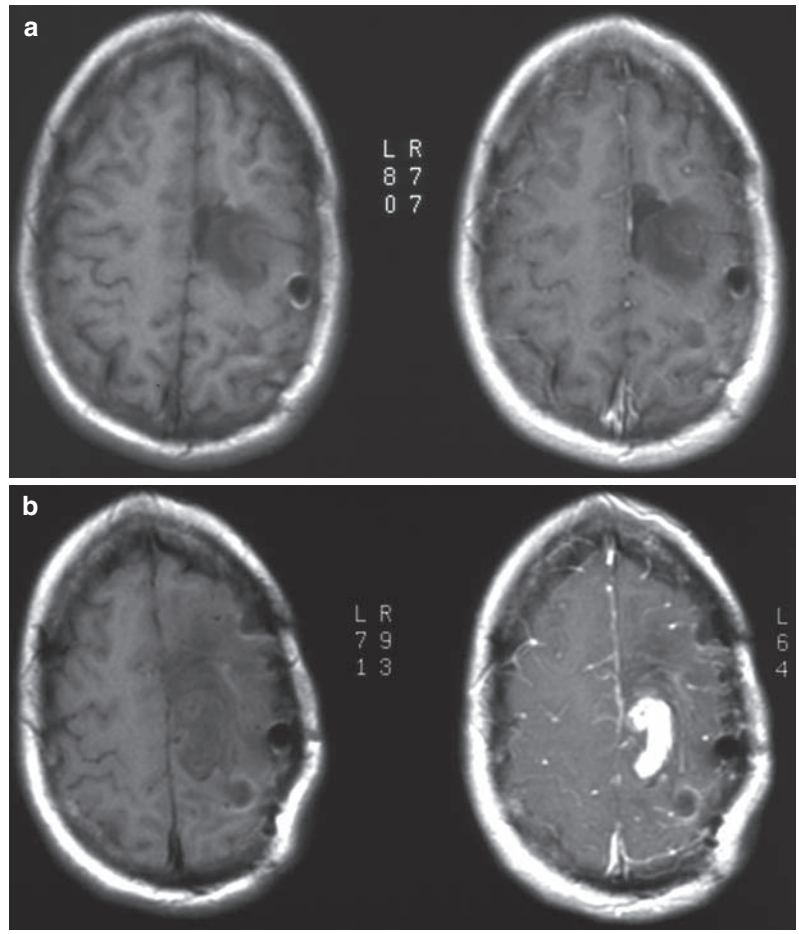

Figure 1.3

Low-grade astrocytoma can recur higher grade. (**a**) Initial MRI demonstrates a nonenhancing mass in the left parietal lobe. Pathology was consistent with grade II astrocytoma. (**b**) Five years later, follow-up imaging demonstrates a new area of enhancement posterior to the original tumor. Pathology of the enhancing component was consistent with glioblastoma multiforme

a recent study investigating the relationship between anaplastic transformation and patient's age, a strong inverse relationship was found between age at initial diagnosis and time to progression to a higher-grade glioma (Shafqat et al. 1999).

In both low- and high-grade astrocytomas, the extent of surgical resection appears to correlate with outcome and quality of life (Pollack et al. 1995; Campbell and Pollack 1996; Keles et al. 2001; Wolff et al. 2002). Patients with GTRs live longer than those with partial resections, who in turn live longer than those who have biopsies only. A further consideration is that partial resection is often accompanied by significant postoperative edema surrounding residual tumor tissue, along with increased neurologic morbidity. However, the literature regarding the prognostic impact of surgery is controversial due to a lack of randomized studies addressing the issue. An additional complicating factor is the inconsistent and less-subjective methodology used in determining extent of resection. Overall, PFS at 3 years ranges from 61 to 75% for patients with low-grade gliomas (Packer et al. 1997; Gururangan et al. 2002). These patients have a 10-year survival rate of 70–90%.

1.3 Cerebellar Astrocytoma

Although astrocytomas as a group represent the most common tumor of the CNS in childhood, cerebellar astrocytomas comprise only 10–20% of all pediatric brain tumors (Lapras et al. 1986; Rutka et al. 1996; Smoots et al. 1998; Reddy and Timothy, 2000) and 20–40% of all posterior fossa tumors in children (Lapras et al. 1986; Rutka et al. 1996; Morreale et al. 1997; Steinbok and Mutat 1999; Reddy and Timothy, 2000; Viano et al. 2001). Infratentorial tumors comprise approximately 50% of all intracranial tumors in childhood and include medulloblastoma/PNET (20% of the total), cerebellar astrocytomas (15%), ependymoma (5%), brainstem glioma (3%), and other miscellaneous types (5%) (Pollack 1999). Significant long-term survival after surgical resection is common and is dependent on histological type, extent of invasion, and completeness of tumor removal.

Recent laboratory investigations are attempting to define the molecular features of different grades of cerebellar astrocytomas. Clinical studies have focused on approaches to the treatment of residual/recurrent tumor, the role of adjuvant therapy, functional outcomes after treatment, and the management of complications, such as pseudomeningocele, cerebrospinal fluid (CSF) shunting, and cerebellar mutism.

1.3.1 Epidemiology

The incidence of cerebellar astrocytoma is difficult to determine accurately, but is estimated to be 0.2–0.33 cases per 100,000 children per year (Berger 1996; Gjerris et al. 1998; Rosenfeld 2000). The incidence peaks between ages 4 and 10 years, with a median age at diagnosis of 6 years (Steinbok and Mutat 1999). Twenty percent of these tumors occur in children less than 3 years of age (Rickert 1998). Gender does not play a role in disease predominance, prognosis, or survival (Rickert and Paulus 2001; Viano et al. 2001). International studies do not demonstrate a geographic or ethnic propensity for the occurrence of cerebellar astrocytomas, unlike craniopharyngiomas and germ-cell tumors (Gjerris et al. 1998; Rickert 1998; Rickert and Paulus 2001).

The term "cerebellar astrocytoma" has become synonymous with a benign tumor, although this is not always accurate because a variety of histological grades are encountered. The majority (80%) of cerebellar astrocytomas in children are JPAs (WHO grade I and demonstrate a benign histology (Morreale et al. 1997). Fibrillary astrocytomas (WHO grade II) comprise 15% of the total, while anaplastic astrocytomas (WHO grade III) and glioblastoma (GBM, WHO grade IV) each represent less than 5% of the total (Steinbok and Mutat 1999). In patients who present with NF1, about 5% will develop cerebellar JPAs (Li et al. 2001).

1.3.2 Pathology

1.3.2.1 Gross Appearance

Grossly, cerebellar astrocytomas can be cystic, solid, or have mixed features. JPAs (WHO grade I) are typically cystic tumors containing yellow–brown fluid and neoplastic mural nodules. The cyst wall may

contain either neoplastic cells or a pseudocapsule of glial tissue (Steinbok and Mutat 1999). This classic appearance occurs in less than 50% of cases. Diffuse subtypes are almost always solid tumors composed of circumscribed neoplastic cells without evidence of cysts. Very commonly, however, cerebellar astrocytomas demonstrate mixed appearance and consist of both cystic and solid portions of tumor. Cystic lesions tend to occur in the cerebellar hemispheres, while solid tumors often arise in the midline near the vermis and potentially extend to the brainstem (Abdollahzadeh et al. 1994).

1.3.2.2 Miscellaneous Grading Scales

Several other histopathologic classifications for cerebellar astrocytomas have been published. Winston and Gilles identified three clusters of histological features that correlated with prognosis (Conway et al. 1991; Steinbok and Mutat 1999). "Glioma A" tumors have microcysts, leptomeningeal deposits, Rosenthal fibers, or foci of oligodendroglioma. "Glioma B" tumors have a combination of perivascular pseudorosettes, hypercellularity, mitosis, necrosis, and/or calcification in the absence of any glioma A features. "Glioma C" tumors are the remaining tumors that do not match with either of these categories. Five-year survival for groups A and B were 100 and 41%, respectively, while 10-year survival was 94% for glioma A, 29% for glioma B, and 69% for glioma C (Campbell and Pollack 1996). However, this schema has been criticized for including a heterogeneous group of tumors encompassing features such as mitosis/necrosis and pseudorosettes that indicate higher grade glioma and ependymoma, respectively, in the "glioma B" group, which may contribute to its association with a poorer prognosis (Campbell and Pollack 1996). The Kernohan and St. Anne-Mayo grades, which are used to describe astrocytomas in any location, are rarely used to describe pediatric cerebellar astrocytomas.

1.3.3 Clinical Features

The mean age at diagnosis for cerebellar astrocytomas in children is 6.8 years and the average duration of symptoms is 3–5 months (Steinbok and Mutat 1999; Reddy and Timothy, 2000). The slow-growing, indolent characteristics of these tumors allow functional compensation of adjacent brain tissue, and most cerebellar astrocytomas tend to be large at time of diagnosis. With greater availability of high-resolution neuroimaging, detection of these lesions is occurring earlier than in the past. Attempts to correlate age at diagnosis and prognosis have been inconclusive, and though patients diagnosed at younger ages tend to have better outcomes, more of these tumors tend to have a benign pathology (Morreale et al. 1997).

Initial signs and symptoms are usually mild and nonspecific and are caused by ICP. Headache is the most common presenting complaint (75–97%) (Abdollahzadeh et al. 1994; Berger 1996; Steinbok and Mutat 1999; Viano et al. 2001) and frequently occurs with recumbency. Decreased venous return and hypoventilation during sleep and recumbency exacerbate raised ICP (Steinbok and Mutat 1999). Headaches begin frontally and may migrate to the occiput. Constant occipital headache and neck pain with hyperextension are ominous signs of tonsillar herniation into the foramen magnum. Respiratory depression, preceded by cluster or ataxic breathing, may follow shortly (Rosenfeld 2000). Vomiting, found in 64–84% of patients, is the second most frequent presenting symptom and is also caused by hydrocephalus and raised ICP (Steinbok and Mutat 1999; Viano et al. 2001). Papilledema occurs in 40–80% of patients along with cerebellar dysfunction (Rashidi et al. 2003). In the absence of tumor infiltration of the area postrema, vomiting is usually not accompanied by nausea, unlike ependymomas and other lesions arising from the fourth ventricle itself.

Signs of cerebellar dysfunction include ataxia (88%), gait disturbance (56%), appendicular dysmetria (59%), and wide-based gait (27%) (Abdollahzadeh et al. 1994; Pencalet et al. 1999; Steinbok and Mutat 1999; Viano et al. 2001). Lesions of the cerebellar hemisphere produce ataxia and dysmetria in the ipsilateral limbs, while midline lesions produce truncal and gait ataxia (Berger 1996). Other clinical features include behavioral changes (32%), neck pain (20%), and papilledema (55–75%) (Abdollahzadeh et al. 1994; Steinbok and Mutat 1999). Some degree of hydrocephalus occurs in 92% of cases, while seizures are extremely rare (2–5%) (Abdollahzadeh et al. 1994). Cranial

nerves and descending motor tracts are usually not affected, unless there is significant tumor extension, and involvement indicates probable brainstem infiltration. The only clinical feature related to poor prognosis is the presence of brainstem dysfunction (level of consciousness, motor-tract signs) regardless of histology (Sgouros et al. 1995).

1.3.4 Natural History

Cerebellar astrocytomas were once considered congenital posterior fossa brain tumors, requiring treatment only when symptomatic. Patients would typically report longstanding headaches and emesis, with occasional periods of relief. Patients with cerebellar symptoms often developed symptoms of syringomyelia, indicating unrelieved hydrocephalus. It was commonly believed that the cyst wall and cyst fluid were the cause of the patients' symptoms. Thus, early treatment consisted of cyst-fluid decompression and cyst-wall removal. Symptoms were relieved temporarily, but patients often returned within months to years with cyst recurrence and sometimes tumors with malignant progression. Not until Cushing reported his surgical experience with 76 cerebellar astrocytomas in 1931 did it become clear that the true pathology lay in the mural nodule. If left untreated, patients would experience increasing bouts of cerebellar fits, become blind, and ultimately succumb to coma and death.

1.3.5 Diagnosis and Neuroimaging

1.3.5.1 Computed Tomography and Magnetic Resonance Imaging

The classic radiological appearance of a JPA, observed in 30–60% of cases, is a large cyst with a solid mural nodule (Fig. 1.4) localized to one of the cerebellar hemispheres (Steinbok et al. 1996; Reddy and Timothy, 2000). On CT, the cyst is hypodense to brain and hyperdense to CSF due to its high protein content, while on MRI, the cyst appears hypointense to brain on T1-weighted images and hyperintense on T2-weighted images. The mural nodule is hypo- to isodense to brain on CT and hyperintense to brain on T1-weighted images. The mural nodule enhances uniformly following contrast administration on both CT and MRI, while the cyst is not affected by contrast. The cyst wall, however, may demonstrate contrast enhancement if neoplastic cells are present (Fig. 1.4). In certain cases, the compressed glial reactive tissue surrounding a cyst may also show limited enhancement (Fig. 1.5). Other variations include multiple

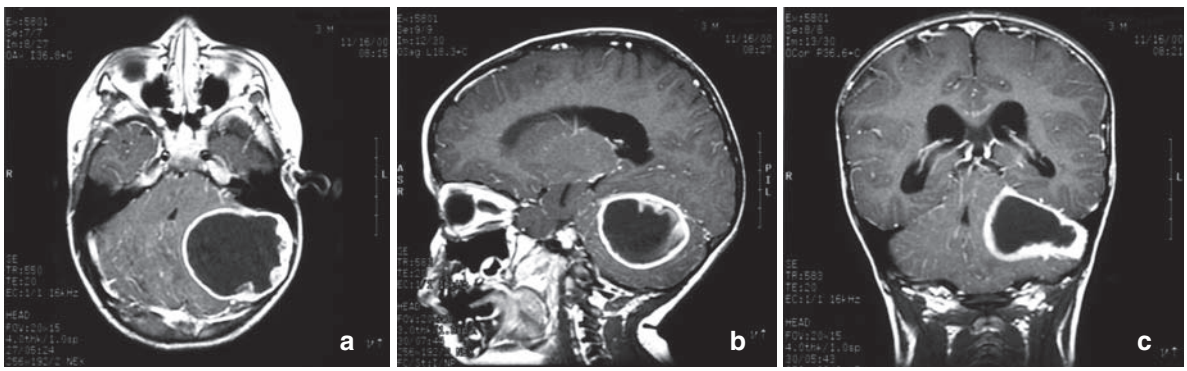

Figure 1.4

Magnetic resonance (MR) images of a typical pilocytic cerebellar astrocytoma. (**a**) Axial, (**b**) sagittal, and (**c**) coronal T1-weighted MR images with gadolinium contrast demonstrating a cystic hemispheric lesion with mural nodule. In this case the cyst wall enhances brightly following gadolinium and does represent tumor

mural nodules; a single, large nodule filling in a portion of the cyst; and/or an irregular cyst contour.

Cerebellar astrocytomas can also appear as solid lesions in 17–56% of cases, with 90% arising from or involving the vermis (Pencalet et al. 1999; Reddy and Timothy, 2000). The CT shows a lesion hypo- to isodense to brain, and MRI demonstrates a solid mass hyperintense to brain. The solid tumor enhances uniformly following contrast administration in the majority of cases, but variations include regions of nonenhancement and small intratumoral cysts in up to 30% of solid tumors (Campbell and Pollack 1996). Quite often, cerebellar astrocytomas will appear with both cystic and solid features and may have a rind-like enhancement pattern with varying degrees of cyst formation. Brainstem involvement is seen in 8–30% (Steinbok and Mutat 1999; Reddy and Timothy, 2000; Viano et al. 2001) of cases, while the cerebellar peduncles are affected in 34% (Hayostek et al. 1993; Pencalet et al. 1999). Calcifications are present in 10–17% of tumors and hemorrhage in only 4.5% (Berger 1996). Edema may be evident in some cases, but does not indicate malignancy or poor prognosis.

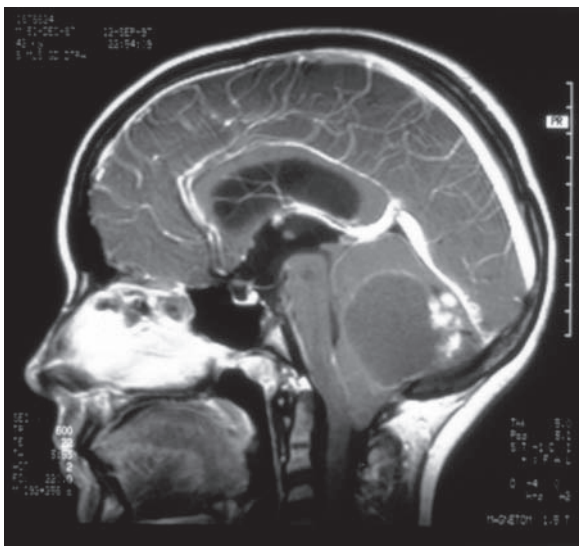

Figure 1.5
Sagittal magnetic resonance image of a cerebellar astrocytoma showing an irregular enhancing nodule located posterior to a large cyst. The cyst wall appears to enhance slightly but this represents gliotic brain tissue

1.3.5.2 Magnetic Resonance Spectroscopy

Unfortunately, neither classic tumor appearance nor location on neuroimaging can confidently distinguish cerebellar astrocytoma from PNET or ependymoma. Biopsy with histological examination is necessary to establish a definitive diagnosis. Recently, MRS has been used to distinguish various pediatric cerebellar tumors based on differential levels of tumor metabolites and macromolecules. Pilocytic astrocytomas demonstrate increased choline:*N*-acetyl-aspartate (CHO:NAA) ratios and elevated lactate levels when compared to normal brain, similar to many other tumor types (Wang et al. 1995; Hwang et al. 1998; Warren et al. 2000). In one study, low-grade astrocytomas had higher NAA:CHO ratios than PNETs, but lower ratios than ependymomas, while creatine:CHO ratios were highest for ependymoma and lowest for PNET (Wang et al. 1995; Hwang et al. 1998). MRS may be useful to identify posterior fossa tumors in children after initial CT or MRI scanning. Other metabolites differentially detected in PNET and astrocytoma *in vitro* include glutamate, glycine, taurine, and myo-inositol. One study examined subtotally resected low-grade astrocytomas and reported that higher normalized CHO levels significantly related to tumor progression 2 years following resection (Lazareff et al. 1998). Alternatively, high levels of lactate in pilocytic astrocytoma carry no indication of malignancy and may reflect aberrant glucose utilization in these tumors (Wang et al. 1995).

1.3.6 Treatment

1.3.6.1 Preoperative Management

Preoperative management depends on the clinical presentation of the patient. An asymptomatic, incidentally discovered lesion can be treated with an elective surgical intervention. More commonly, patients present with signs of increased ICP and cerebellar dysfunction and warrant urgent intervention.

High-dose dexamethasone can relieve headache, nausea, and vomiting within 12–24 h and allow for several days of relief prior to a surgical procedure. An initial loading dose of 0.5–1.0 mg/kg given intravenously followed by a dose of 0.25–0.5 mg/kg/day divided every 6 h is the typical regimen (Rosenfeld 2000). In a patient who is stuporous and lethargic, with cardiorespiratory instability, relief of elevated ICP is of utmost importance and should be performed immediately. This is done by placing an external ventricular drain. In less urgent situations, an endoscopic third ventriculocisternostomy (ETV) can also be considered (Sainte-Rose et al. 2001). This procedure consists of placing a fenestration in the floor of the third ventricle to allow CSF to bypass an obstructive lesion in the posterior fossa. The ETV, although not always successful, can avoid permanent shunt placement. Currently, most surgeons will promptly proceed with tumor resection in the hope that relief of the obstructing mass will also treat associated hydrocephalus.

Ventriculoperitoneal (VP) shunting has been shown to improve survival after surgical resection of posterior fossa tumors. This procedure carries the risk of upward herniation and subdural hematoma from overshunting, while also rendering the patient shunt-dependent for life with all of its associated complications. The risk of upward herniation is estimated at 3% and presents with lethargy and obtundation around 12–24 h after shunt placement, with the potential for compression of the PCA at the tentorial hiatus, causing occipital lobe ischemia (Steinbok and Mutat 1999). Postoperative CSF diversion (with VP shunting) following complete tumor removal and unblockage of the aqueduct and fourth ventricle are required in 10–40% of cases (Imielinski et al. 1998).

1.3.6.2 Surgical Treatment

GTR is the treatment goal and is achieved in 60–80% of operative cases (Campbell and Pollack 1996; Gajjar et al. 1997). GTR is defined as the removal of all identifiable tumor tissue during surgery, and is accomplished only when both the surgeon's report and postoperative neuroimaging are concordant. An MRI with gadolinium enhancement is recommended within 24–48 h after resection. Postoperative changes, including swelling, edema, and gliosis appear by 3–5 days following surgery and may interfere with identification of residual tumor (Berger 1996). Residual tumor after GTR as noted by imaging is detected in 15% of cases, while postoperative imaging fails to demonstrate known residual tumor as reported by the surgeon in 10% of cases (Dirven et al. 1997). The clear presence of residual tumor is managed by reoperation to achieve complete resection.

Cystic tumors with a mural nodule may only require removal of the nodule to achieve complete resection, but removal of the cyst wall is dependent upon whether tumor is present. In some cases, contrast enhancement of the cyst wall on postcontrast MRI scans is clearly visualized (Fig. 1.4) and complete removal of all enhancing portions is considered essential to prevent recurrence. Nonenhancing areas do not require resection, and recent studies have shown that enhancement of the cyst wall does not always indicate tumor and may only represent vascularized reactive gliosis (Fig. 1.5) (Steinbok and Mutat 1999; Burger et al., 2000). There is also some evidence to suggest that patients who undergo complete cyst wall removal may have a poorer prognosis at 5 years than those with cyst walls left intact (Sgouros et al. 1995). Some support biopsy of the cyst wall during resection for frozen section; however, pathologic assessment is usually indeterminate and the sampling error is high, making biopsy of little value. Surgeons may choose conservative management of an enhancing cyst wall, especially if wall enhancement is thin (suggesting gliosis rather than tumor), biopsy samples do not demonstrate clear pathology, and gross appearance is benign (Steinbok and Mutat 1999).

Subtotal resection (STR) is recommended when GTR would result in unacceptable morbidity and neurologic dysfunction, usually in the setting of brainstem invasion, involvement of the floor of the fourth ventricle, leptomeningeal spread, or metastasis. Involvement of the cerebellar peduncles was once thought to preclude GTR, but several authorities contend that GTR can be achieved in this circumstance (Berger 1996; Steinbok and Mutat 1999), as postoperative deficits from resection involving the cerebellar peduncles tend to be transient. Management of

incompletely resected tumors remains controversial, and depends upon clinical circumstances.

1.3.6.3 Follow-Up Neuroimaging

Postoperative surveillance imaging in children with benign cerebellar astrocytomas depends on the extent of initial resection and the histology of tumor. While no standard schedule for surveillance imaging exists, large centers tend to obtain MRI scans at 3 and 6 months, then annually for 3–4 years. Routine imaging after confirmed GTR for a typical JPA can be stopped 3–5 years following resection if there is no evidence of recurrence. However, due to the well-documented late recurrence behavior of a small percentage of benign cerebellar astrocytomas, sometimes decades after GTR, clinical changes should warrant reimaging. STR requires closer serial neuroimaging due to higher rates of tumor recurrence. Diffuse/fibrillary histology (grade II) is associated with STRs, however, GTRs of this histological subtype seem to demonstrate prognosis and recurrence rates rivaling those of juvenile pilocytic cerebellar tumors (grade I). Regardless of the extent of resection, most practitioners tend to follow grade II lesions more closely with serial exams and neuroimaging.

1.3.6.4 Management of Recurrence

Recurrence following GTR is rare and can occur after several years to decades from the initial operation. Reoperation with the goal of GTR is the recommended treatment for recurrence following STR, although this is usually not possible because the primary reason for incomplete resection is usually due to involvement of vital structures such as the brainstem (Akyol et al. 1992). At reoperation, only 30% of recurrences result in GTR, while 70% continue to have residual tumor (Dirven et al. 1997). An interesting biologic feature of low-grade astrocytomas is spontaneous regression or involution of residual tumors. For this reason, many authors advocate a period of observation for residual disease prior to reoperation. This approach is favored at our institution, particularly because a second procedure is associated with increased morbidity (Dirven et al. 1997).

Following STR, 30–40% of patients have recurrence within 3 years (mean 54 months), while >60% have recurrence by 5–6 years (Schneider et al. 1992). Tumors with diffuse/fibrillary histology are more prone to recurrence, but this association is not reported consistently in all series. Of all recurrent tumors, 65% are pilocytic, 31% are diffuse/fibrillary; 48% are cystic; and 52% are solid (Sgouros et al. 1995; Gjerris et al. 1998). Recurrences are found more often in the midline or vermis. Smoots et al., using multivariate analysis, noted that the only factor that predicted disease progression was volume of residual disease (Smoots et al. 1998). This study also showed that only fibrillary histology, and not brainstem invasion or postoperative radiation therapy, significantly affects postoperative tumor volume. Unfortunately, the relationship between STR, brainstem invasion, residual tumor volume, and histology confound each other in almost all other series.

1.3.6.5 Adjuvant Therapy for Recurrence

Radiation therapy after resection plays an important role in the control of PNET and ependymoma, but its utility in cerebellar astrocytoma is incompletely understood. Postoperative irradiation in subtotally resected tumors of any grade improves local control and recurrence rates, but survival rates seem to be unaffected (Garcia et al. 1990; Herfarth et al. 2001). One retrospective, nonrandomized study comparing patients with recurrence of grade I and II cerebellar astrocytoma found no significant difference in survival at both 5 and 9 years follow-up (Akyol et al. 1992). Radiation doses range from 30 to 54 Gy over 3–6 weeks and some evidence suggests that doses greater than 53 Gy are necessary to see beneficial effects (Tamura et al. 1998; Herfarth et al. 2001). However, detrimental effects on the developing nervous system preclude its use in patients less than 3 years of age and current trends favor delaying radiation therapy as long as possible to allow for maximal cognitive development prior to radiation therapy. The risks of radiation therapy include decreased cognitive function (Chadderton et al. 1995) and an increased risk of malignant transformation (Herfarth et al. 2001).

Currently, there is no consensus for the use of radiation therapy for the treatment of benign recurrent cerebellar astrocytoma, though some authors suggest its use if the recurrent tumor displays more aggressive growth features (Garcia et al. 1990; Akyol et al. 1992). Experience with Gamma Knife radiosurgery for the treatment of small-volume residual or recurrent tumors is still too limited at this time, although it may have a role for the treatment of very limited disease (Campbell and Pollack 1996; Somaza et al. 1996).

Chemotherapy has a limited role in the treatment of benign cerebellar astrocytoma, but has only been used in rare instances of multifocal disease, leptomeningeal spread, and malignant transformation (Castello et al. 1998; Tamura et al. 1998). Combination chemotherapy has been used in adjuvant management of inoperable low-grade astrocytomas. The most widely used regimens are CV (Packer et al. 1993) and TPCV (Prados et al. 1997). Both regimens have been associated with complete and partial responses in a subgroup of tumors. Chronic etoposide treatment showed stable tumor lesions at 7 months in patients with recurrent, nonresectable cerebellar astrocytomas in one study (Chamberlain 1997). Cyclophosphamide has been applied in the treatment of cerebellar astrocytoma with leptomeningeal spread (McCowage et al. 1996). To date, no study has yet shown a clear benefit in recurrence or survival with chemotherapy for residual or recurrent cerebellar astrocytomas.

1.3.7 Outcome

1.3.7.1 Prognostic Factors

Few clinical characteristics at time of presentation contribute to overall outcome. Gender and age at diagnosis do not correlate with survival (Gilles et al. 1995; Campbell and Pollack 1996; Smoots et al. 1998), though younger age at presentation might indicate earlier progression of disease in those with recurrences (Gajjar et al. 1997). A short duration of symptoms at time of presentation is generally associated with a more rapidly growing tumor, and therefore more likely to be a higher grade. Longer preoperative symptomatology may indicate progressed disease and larger tumor volume (Pencalet et al. 1999). Patients with NF sometimes present with malignant histology; the majority of cerebellar astrocytomas in NF patients appear to have a quiescent course (Freeman et al. 1998; Smoots et al. 1998), though absolute numbers are small.

The only clinical feature related to poor prognosis and survival is evidence of brainstem dysfunction. Long-tract signs, nystagmus, apnea, and decreased consciousness indicate brainstem invasion by tumor, but also can result from raised ICP and mass effect. Brainstem invasion carries a poor prognosis with only 40% of patients alive at 5 years after diagnosis (Sgouros et al. 1995). Conversely, 84% of patients with no evidence of brainstem involvement are alive at 5 years (Sgouros et al. 1995). Brainstem invasion significantly impacts survival regardless of histology, as noted in several large series (Campbell and Pollack 1996). However, after multivariate analysis, Smoots et al. contend that residual tumor volume within the brainstem is the only prognostic factor for disease progression (Smoots et al. 1998).

The impact of histology on outcome and PFS has been controversial (Pencalet et al. 1999). Hayostek et al. showed that pilocytic cerebellar astrocytoma has 5-, 10-, and 20-year survival rates of 85, 81, and 79%, respectively, while diffuse subtypes have a dramatically reduced survival rate of 7% at 5, 10, and 20 years each (Hayostek et al. 1993). Unfortunately, the mean age of patients in both groups differed greatly (14 years for pilocytic, 51 years for diffuse), making any meaningful comparison difficult. Also, diffuse tumors in this study had more malignant histology (mitosis, necrosis, etc.), which suggests that higher-grade lesions might have been included inappropriately. More recent series have reported 78% overall survival and 89% PFS for pilocytic histology and 44% overall survival and 52% PFS for diffuse subtypes at 5 years (Sgouros et al. 1995). Diffuse/fibrillary histology is reported as the single most important determinant for residual tumor volume, which in turn is the only predictor of tumor recurrence at any site after multivariate analysis in one study (Smoots et al. 1998). Comparing GTR and STR between grade I and grade II tumors has been difficult because grade II tumors are more likely to be

subtotally resected due to tumor location and invasion. Two authors, after multivariate analyses, suggest that only extent of resection contributes to outcome in children with grade I and II cerebellar astrocytoma (Sgouros et al. 1995; Smoots et al. 1998).

Older reports state that patients with cystic tumors have longer 5-year PFS than those with solid tumors. More recent studies have now shown that cystic tumors are more often completely resectable, in contrast to solid tumors that often invade surrounding parenchyma, making their complete removal difficult. After controlling for the extent of tumor removal, most series do not demonstrate a survival advantage based on tumor morphology (Sgouros et al. 1995; Smoots et al. 1998). Also, tumor location (hemispheric vs. vermian/midline) does not appear to affect prognosis (Smoots et al. 1998). Complete resection is more often achieved with a hemispheric location than in the midline, probably due to the ability to perform a more aggressive resection.

1.3.7.2 Gross Total and Subtotal Resection

The prognosis for patients with grade I tumors and GTR is excellent with 5- and 10-year PFS of 80–100% in nearly all studies. Thirty-year PFS is not uncommon with long-term follow up in these patients. Patients with grade II tumors after total resection have 5-year survival rates of 50–80% (Morreale et al. 1997). As expected, grade III and IV lesions continue to have poor survival despite GTR. In one study, a small group of EGFR negative cerebellar GBMs demonstrated improved overall survival compared to supratentorial GBMs. Saito, et al hypothesized that the lack of EGFR was the reason for increased chemoradiosensitivity and the resultant improved overall survival (Saito et al. 2006). GTR is more commonly reported in tumors of pilocytic histology with cystic morphology and peripheral/hemispheric location. Recurrence after confirmed GTR is rare and occurs in less than 5% of grade I cases, though recurrences have been reported as far as 45 years after initial resection (Boch et al. 2000). GTR is reported in 53% of patients operated on with pilocytic cerebellar astrocytomas, but only in 19% of those with nonpilocytic cerebellar tumors (Campbell and Pollack 1996).

In general, STR is associated with future tumor recurrence and poorer outcome (Pencalet et al. 1999). Approximately 75% of patients will have recurrence during follow-up. The 5-year survival rate varies from 29 to 80%, and 10-year survival ranges from 0 to 70% (Sgouros et al. 1995; Campbell and Pollack 1996). These variations in survival are explained by inconsistent study designs. STR is more commonly reported with solid, midline tumors that are usually grade II or higher. A number of reports demonstrate that patients with STRs remain stable, both clinically and on serial imaging, without any evidence of progression for several years (Krieger et al. 1997). In one prospective study, only 50% of patients with STRs and no brainstem involvement demonstrated progression of disease at 8-years follow-up (Sutton et al. 1996).

An interesting biologic feature of low-grade astrocytomas is spontaneous regression or involution of residual tumors (Steinbok et al. 2006). In one study of cerebellar pilocytic astrocytomas, nearly 50% of patients with STRs were noted to have spontaneous regression (Gunny et al. 2005). Specific factors that would predict regression or stability are not known (Palma et al. 2004). JPAs of the optic pathway or hypothalamic region are also known to resolve without any treatment (Berger 1996; Freeman et al. 1998). The biologic reasons behind tumor quiescence or regression are unknown. For this reason, many authors advocate a period of observation for residual disease prior to reoperation (Benesch et al. 2006). This approach is favored at our institution, particularly because a second procedure is associated with increased morbidity (Dirven et al. 1997).

1.3.7.3 Malignant Transformation

Malignant transformation of pilocytic astrocytomas is an exceedingly rare event (Mamelak et al. 1994; Berger 1996). Several case reports describe malignant degeneration of pilocytic cerebellar astrocytomas at recurrence several years from initial resection. Standard indices of aggressive histology, such as necrosis, vascular proliferation, and mitoses, do not indicate malignancy in pilocytic astrocytomas, though increased perivascular cellularity

may serve as a marker of future anaplastic change (Krieger et al. 1997).

1.3.7.4 Metastasis

Leptomeningeal dissemination (LMD) of low-grade astrocytomas occurs rarely and is associated mainly with hypothalamic tumor location (Pollack et al. 1994; Morikawa et al. 1997; Tamura et al. 1998). Spinal metastases are the most common and were found in 3 of 72 patients in one series (Pollack et al. 1994) and in 7% of diffuse cerebellar astrocytoma patients at the time of diagnosis in a second study (Hayostek et al. 1993). Long-term outcome is not known, but there is anecdotal evidence that LMD indicates impending malignant degeneration (Krieger et al. 1997). Aggressive resection of isolated metastasis, combined with aggressive chemotherapy and additional radiation therapy may control progression (Pollack et al. 1994; Berger 1996; Tamura et al. 1998). CSF sampling offers no aid in detecting early LMD (Pollack et al. 1994).

1.3.7.5 Survival

PFS and overall outcome depend on several factors including extent of resection, brainstem involvement, and histological subtype. Patients with complete tumor removal enjoy 10-year PFS in greater than 90% of cases (Gajjar et al. 1997; Steinbok and Mutat 1999). Incomplete tumor resection results in only about 50% 5-year survival in most series, but with reoperation to remove residual tumor, outcome may improve to 80% PFS at 5 years, 74% at 10 years, and 40% at 20 years (Gajjar et al. 1997). Twenty-five percent of patients with subtotally resected tumors are progression-free at 5 years from the time of recurrence and reoperation tends to lower subsequent recurrence rates, but does not affect overall survival (Sgouros et al. 1995). Radiation therapy in the setting of STR or recurrence has not been shown to confer any benefit on overall survival in nearly all studies, but some do report lower rates of local progression following radiation.

Although the functional outcome for most children is considered to be good, some data suggest that permanent deficits can occur in language function, visual–spatial ability, and behavior in up to 25% of patients (Aarsen et al. 2004; Zuzak et al. 2008). In another large group of children ($n = 103$) with cerebellar tumors removed surgically, but not treated with radiation, there was an elevated risk of decline in ognitive and adaptive function (Beebe et al. 2005).

1.3.8 Conclusion

Among pediatric brain tumors, cerebellar astrocytomas have the most favorable prognosis. The great majority of cerebellar astrocytomas are low-grade neoplasms (juvenile pilocytic/grade I tumors) with excellent cure rates and long-term survival following surgery. Only a small minority have dismal outcomes (grade III and IV tumors). Tumor recurrence, when it does occur, is a challenging management problem, and most often seen with grade II tumors, STR, and brainstem invasion. There is no consensus among authorities regarding the optimal method in treating recurrence, though many advocate reoperation for first recurrence, followed by radiation therapy for subsequent recurrence. Chemotherapy is reserved for rare cases of leptomeningeal spread and those tumors that do not respond to radiation; although its use may be considered in young children with inoperable tumors prior to radiation as well. Other management considerations encountered with cerebellar astrocytomas include pre- or postoperative CSF diversion to control hydrocephalus and perioperative steroid administration. Surgical removal of cerebellar astrocytomas may be complicated by cerebellar dysfunction, cranial nerve palsies, and mutism. These risks need to be discussed preoperatively with the patient and parents. Fortunately, the majority of adverse events resolve completely.

1.4 Optic Pathway Gliomas

Optic pathway gliomas, a fascinating subset of low-grade gliomas, occur in some or all anatomical compartments of the optic pathway (optic nerve, chiasm, tract, or radiations). They grow as infiltrative lesions, although large expansile masses are also seen. Their

borders are often poorly defined radiologically and a surgical plane is rarely observed. Because of their infiltrative nature, these tumors are often not confined to a single anatomic area and can extend into adjacent structures, most commonly into the hypothalamus. For this reason, naming these lesions according to their exact anatomical location may be misleading especially for tumors with radiologically ill-defined borders. As only 10% of optic nerve gliomas are confined to one optic nerve, and approximately 30% are bilateral, the majority of optic nerve gliomas involve the chiasm or the hypothalamus (Hoffman and Rutka 1999). Optic chiasmatic and hypothalamic gliomas are often considered as a single entity because of their potential to infiltrate both anatomical sites regardless of the original location of the tumor.

1.4.1 Epidemiology

Optic pathway gliomas account for 4–6% of all CNS tumors in the pediatric age group, 2% in adults, and 20–30% of all pediatric gliomas (Farwell et al. 1977; Borit and Richardson 1982; Alvord and Lofton 1988; Packer et al. 1999). The peak incidence is during the first decade of life with no sex predilection. Overall, NF1 is present in 25–60% of patients with optic pathway tumors (Lewis et al. 1984; Riccardi 1992). Fifteen to twenty percent of patients with NF1 will have an optic glioma on MR scan, but only 1–5% become symptomatic (Ruggieri 1999). There is a higher likelihood of NF1 in patients who have multicentric optic gliomas, and a relatively lower incidence of NF1 in patients with chiasmatic tumors (Housepian 1977). The natural history of optic pathway gliomas is related to the presence of neurofibromatosis and to the location of the tumor. Patients with optic pathway gliomas who have NF1 have a better overall prognosis than those without NF1 (Rush et al. 1982). However, this view is opposed by other studies showing that patients with neurofibromatosis had a similar prognosis as patients without neurofibromatosis following irradiation for chiasmatic gliomas (Alvord and Lofton 1988). A more recent study showed a significantly favorable difference in time to tumor progression, that is, time to recurrence of optic glioma, in the presence of neurofibromatosis (Deliganis et al. 1996). Approximately two thirds of optic gliomas associated with NF1 are indolent lesions with minimal progression. Although any location within the optic pathway from the retrobulbar area to the optic radiation may be affected, chiasmatic gliomas tend to have a more aggressive course both by invading the hypothalamus and by occluding the foramen of Munro causing obstructive hydrocephalus. It is also reported that optic and hypothalamic gliomas are more aggressive in children younger than 5 years of age (Oxenhandler and Sayers 1978; Dirks et al. 1994).

1.4.2 Pathology

Most tumors of the diencephalon and the optic pathways are histopathologically low-grade gliomas, typically pilocytic or fibrillary astrocytomas (Daumas-Duport et al. 1988; Ito et al. 1992). Histologically, optic nerve gliomas demonstrate two different patterns of growth. In patients without NF1, progression tends to be confined to the optic nerve without significant involvement of the meninges. In patients with NF1, tumor cells invade the subarachnoid space causing proliferative fibroblastic response and meningothelial hyperplasia (Stern et al. 1980). Locally, hypothalamic and optic gliomas may extend laterally invading the perivascular space along the arteries of the circle of Willis, as well as posterior expansion toward the brainstem with rostral invagination into the third ventricle. Patients with chiasmatic-hypothalamic gliomas have an increased risk for disease dissemination along the neuraxis (Gajjar et al. 1995). It has been reported that the risk of multicentric dissemination is approximately 20-fold higher in this group of patients than in those with low-grade gliomas located elsewhere (Mamelak et al. 1994).

1.4.3 Clinical Features

Most optic pathway gliomas present with visual loss. Identifying the exact type of visual loss may be difficult early in the course of the disease, especially in very young children. The typical deficits are incongruent field deficits, at times restricted to one eye. Optic atrophy is commonly seen with large tumors. Children less than 3 years of age are usually first

brought to medical attention because of strabismus, proptosis, nystagmus, or loss of developmental milestones. Tumors that involve the hypothalamus will often result in endocrine disturbances, including precocious puberty. Hypothalamic tumors may reach a large size before diagnosis, and may result in diencephalic syndrome characterized by failure to thrive despite apparent normal appetite in an otherwise healthy child. Tumors that extend upward into the third ventricle can cause hydrocephalus. Tumors with thalamic involvement may cause unilateral motor deficits on the side contralateral to the lesion.

1.4.4 Diagnostic Imaging

Optic pathway gliomas are usually well-visualized on MRI. In children with NF1, there is often extensive streaking along the optic pathway and/or optic nerve involvement at the time of diagnosis, in addition to nonspecific white matter abnormalities on T2-weighted sequences (Fig. 1.6). The use of diffusion-weighted MRI in NF1 patients may be useful to differentiate between optic gliomas, hamartomas, and myelin vacuolization (Sener 2002). Optic pathway gliomas in children without NF1 tend to be more globular and somewhat more restricted to one anatomic location. The mass itself enhances homogeneously following gadolinium administration, although cysts are frequently seen (Fig. 1.6). On FLAIR sequences, the infiltrative component of the tumor can be seen extending along the optic tracts. Detailed fine cuts through the sella should be obtained. In these sequences, the optic nerve becomes continuous with the mass, a finding that helps to establish the radiologic diagnosis.

1.4.5 Treatment

1.4.5.1 Surgical Indications

Regardless of whether a patient has NF1, biopsy is not needed for an intrinsic chiasmatic/hypothalamic mass if the appearance on MRI is typical, that is, an expanded sella and/or involvement of the chiasm, optic nerve(s), and/or optic tracts. For patients without NF1 who present with an atypical chiasmatic hypothalamic mass, surgical biopsy may be needed to define the pathologic diagnosis. If mass effect is present with neurologic symptoms, debulking of a large tumor may be the initial approach. Some neurosurgeons limit surgical indications to a subset of exophytic or cystic tumors with significant mass effect and hydrocephalus. However, a progressive visual deficit or progression depicted on follow-up MR scans will necessitate intervention if there is an exophytic or cystic component. These exophytic tumors can remain stable for extended periods after resection (Tenny et al. 1982). As 10–20% of children younger than 10 years of age with NF1 may have a low-grade glioma of the optic pathways, biopsy is not considered mandatory for asymptomatic patients with a chiasmatic/hypothalamic tumor (Lewis et al. 1984; Ruggieri 1999). Asymptomatic patients may be followed with serial clinical and visual examinations, and MRI scans; endocrine replacement and CSF shunting should be instituted if necessary.

The only indication for resection of a unilateral optic nerve tumor is when vision is absent or nonfunctional. A relative indication is extreme proptosis with exposure keratitis caused by a large intraorbital optic nerve tumor. In addition, it is generally agreed that the exophytic portion of the lesion should be removed if vision is reasonable, and that nonresectable unilateral optic nerve lesions should be decompressed. Any surgery that may result in permanent neurologic morbidity should be compared with alternative treatment modalities, in terms of potential benefits and risks. For instance, although a limited resection on an optic nerve glioma extending to the optic chiasm may be indicated, a major chiasmatic resection resulting in visual compromise is virtually never indicated.

Although optic and diencephalic gliomas are almost always histologically low-grade (WHO grade I), no study has addressed the issue of extent of resection as it affects tumor progression or overall survival in this patient population. This is in contrast to hemispheric low-grade gliomas for which extensive surgical resections increase time to tumor progression and decrease risk of malignant differentiation (Berger et al. 1994). Therefore, in addition to obtaining histological diagnosis, if there is doubt

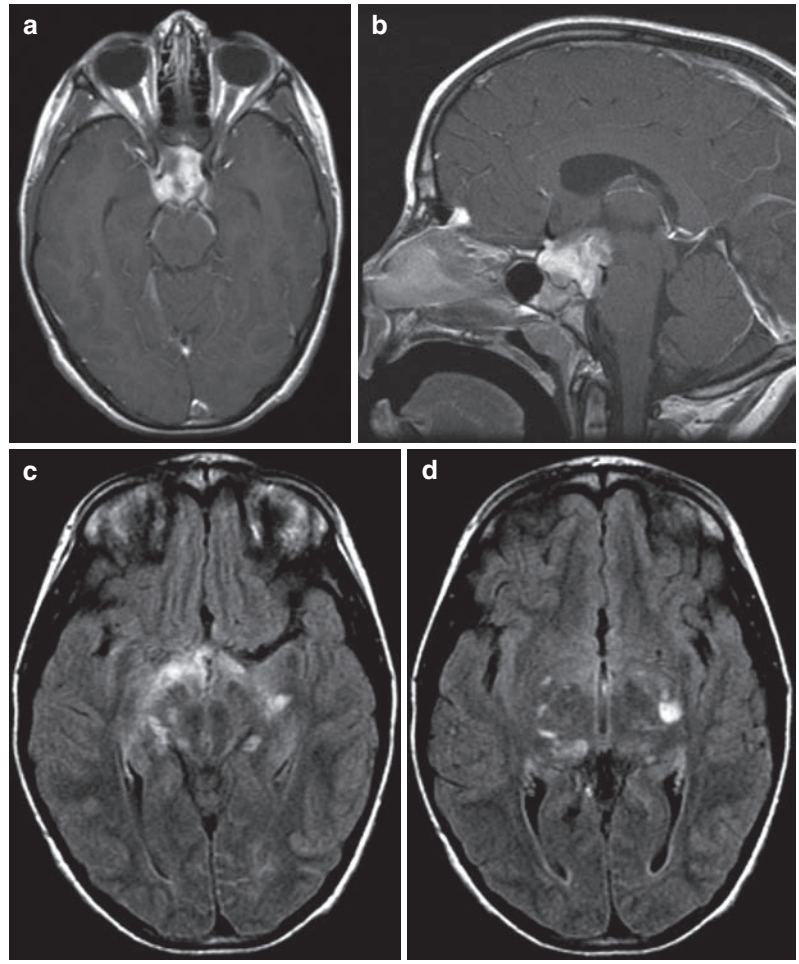

Figure 1.6
A chiasmatic/hypothalamic pilocytic astrocytoma in a 10-year-old girl who presented with headaches. (**a**) The axial T1-weighted image shows the right optic nerve entering the enhancing portion of the tumor. A distinct boundary does not exist between the nerve and tumor. (**b**) The sagittal plane image clearly shows that the enhancing portion of the tumor is continuous with the hypothalamus. (**c**) FLAIR image shows indistinct increased signal intensity along the optic tracts extending posteriorly from the chiasm. (**d**) FLAIR image slightly superior to Fig. 1.6c shows additional abnormalities along the optic tract with a localized area of signal abnormality likely within the lateral geniculate nucleus on the left side

based on MR scans, the goal in surgical resection of optic pathway gliomas is to achieve transient control of the disease and to alleviate symptoms caused by the tumor mass.

1.4.5.2 Surgical Technique

For tumors involving one optic nerve, a frontal or frontotemporal approach may be used. With either technique, intraorbital and intracranial portions of the affected nerve as well as the chiasm are exposed. The optic chiasm and the intracranial portion of the affected optic nerve are inspected to determine a site for division that should be more than 6 mm from the chiasm so as to avoid a contralateral superior temporal field defect. The orbital canal is drilled open allowing decompression of the optic nerve. After closure of the annulus and periorbita, the orbital roof, and supraorbital rim are reconstructed if needed. If the orbital roof is not repaired, one associated complication is pulsatile exophthalmos.

For chiasmatic/hypothalamic tumors, surgical goals should be balanced against risks of increased visual loss and hypothalamic dysfunction. Improved visual and neurologic outcome following surgery has been reported for chiasmatic-hypothalamic gliomas

(Bynke et al. 1977; Baram et al. 1986; Wisoff et al. 1990). Meticulous tumor debulking from the exophytic portion of a chiasmatic tumor may improve vision by relieving external pressure on adjacent optic nerves (Oakes 1990). There are several surgical approaches to the chiasmatic hypothalamic region, each with certain advantages (Apuzzo and Litofsky 1993; Litofsky et al. 1994; Hoffman and Rutka 1999). Regardless of the approach, the aim is tumor debulking without causing additional deficit.

1.4.5.3 Radiation Therapy

The use of radiotherapy for the treatment and control of optic pathway gliomas is beneficial and long lasting (Taveras et al. 1956). However, current practice aims to delay radiotherapy either by implementing watchful waiting, surgery, or chemotherapy, especially in young patients. Alternative treatment options include follow-up without intervention until clinical deterioration, irradiation of all lesions with or without biopsy, biopsy for all lesions followed by radiation only of those located in the hypothalamus or posterior chiasm, and chemotherapy. Each of these options can be considered for certain subgroups of patients. For example, standard initial treatment for patients with chiasmatic gliomas who have progressive visual symptoms is regional radiotherapy. These tumors are typically sensitive to chemotherapy, and this modality is therefore used often in infants and children prior to or instead of radiation therapy. An option for NF1 patients harboring optic pathway gliomas is follow-up with no treatment as long as the tumor remains quiescent on serial imaging studies, and visual function is stable.

If radiation therapy is to be used, the most favorable outcome has been observed with doses of 45–56 Gy (Pierce et al. 1990; Bataini et al. 1991; Tao et al. 1997). Flickenger demonstrated that patients receiving doses >43.2 Gy delivered over 1.8 Gy fractions had statistically superior overall survival and PFS (Flickinger et al. 1988). These findings are corroborated by another study in which doses <40 Gy were associated with poorer PFS (Kovalic et al. 1990). Because of the concern for dose constraint to surrounding normal tissues, radiotherapeutic modalities under investigation include intensity-modulated radiation therapy, Gamma Knife radiosurgery, stereotactic radiosurgery (Combs et al. 2005; Marcus et al. 2005), and proton therapy (Merchant et al. 2008). The current recommended first-line treatment in patients younger than 7 years old is chemotherapy. Patients over 10 years of age are treated with 50–54 Gy in 1.8 Gy daily fractions (Horwich and Bloom 1985; Halperin et al. 1999). The best treatment for patients between the age of 7 and 10 remains controversial.

1.4.5.4 Chemotherapy

As the risk for late sequelae of partial brain radiation is greatest for young children, chemotherapy prior to radiotherapy as a means of delaying the use of radiation in children younger than 5 years of age has been proposed (Griffin et al. 1988). In order to spare young pediatric patients early radiotherapy, alternative chemotherapeutic trials have been explored. One study examined vincristine and carboplatin in 113 children (median age of 3.7 months). Overall response to treatment was observed in 92% of patients and the median time to progression was 22.5 months observed in 42% of patients (Gnekow et al. 2004). Similarly, at the Hospital for Sick Children in Toronto, a retrospective analysis of 26 adolescents diagnosed with optic pathway gliomas and treated with radiotherapy or carboplatin-based chemotherapy as first-line adjuvant therapy demonstrated successful disease control using chemotherapy (Chong et al. 2008). Based on the COG A9952 results described in the previous section, the use of either TPCV or CV provides adequate tumor control that allows delay of radiotherapy.

1.4.5.5 Molecular Targeted Therapies

Recent work by Dasgupta et al. has shown that methionine aminopeptidase-2 (MetAP2) is specifically expressed in the CSF of NF1-associated gliomas in mice and humans. This finding was not observed in sporadic pilocytic or other low-grade gliomas. Subsequent treatment with fumagillin, a MetAP2 inhibitor, reduced NF1-deficient astrocyte proliferation

in vitro (Dasgupta et al. 2005). These findings suggest that fumagillin may be used to selectively treat tumors in NF1 patients. As described earlier in this chapter, mTOR inhibitors have recently entered clinical trials for the treatment of both NF1-associated and spontaneous low-grade gliomas, include optic pathway gliomas. Scientific rationale for the use of mTOR inhibitors is particularly strong, but more definitive clinical promise awaits results of these studies.

1.4.6 Outcome

GTR is often impossible due to the critical location of diencephalic and optic gliomas. Patients with unilateral optic nerve tumors who undergo complete surgical resection have a good postoperative prognosis, with 92% surviving 15 years irrespective of NF status (Jenkin et al. 1993). However, regardless of their histologically benign features, chiasmatic-diencephalic gliomas carry a worse prognosis.

The operative procedures for chiasmatic/hypothalamic gliomas carry significant morbidity. Surgical morbidity may be in the form of immediate endocrinologic or neurologic deficits. Resulting sequelae may include hypothalamic/hypophyseal dysfunction, increased visual impairment, memory loss, altered consciousness, and coma (Wisoff et al. 1990). Following an intraorbital approach, CSF leak may occur if the frontal sinus or any opened ethmoid sinus is not adequately reconstructed. Inadequate reconstruction of the orbital roof may result in pulsatile proptosis. Failure to repair a sectioned levator origin will result in ptosis. Surgical injury to the superior ophthalmic vein and to the nerves supplying the extraocular muscles will result in functional deficits (Housepian 1993). These complications are avoidable with appropriate surgical technique. In a large series of patients treated with intraorbital procedures, no significant CSF leaks, proptosis, infection, or extraocular problems were reported (Maroon and Kennerdel 1976).

Endocrine dysfunction in this patient population may result not only from surgery, but also as a side effect of radiation. The most common manifestations of hypopituitarism following radiotherapy are growth hormone deficiency or growth retardation (Wong et al. 1987; Bataini et al. 1991; Tao et al. 1997). Diabetes insipidus, precocious puberty, and testosterone deficiency are also reported. Furthermore radiotherapy can result in significant cognitive deficits, the severity of which may be proportional to age at diagnosis (Ellenberg et al. 1987).

There are several studies that question whether the presence of NF1 influences prognosis in patients with optic pathway gliomas. Although Rush et al. reported a better outcome for optic glioma patients with NF1, several other studies failed to show a differences in survival (Imes and Hoyt 1986; Alvord and Lofton 1988; Kovalic et al. 1990). In our experience, there was not a significant difference in survival based on the presence or absence of NF1. The 5- and 10-year survival rates for patients with optic gliomas and NF1 were 93 and 81%, respectively, compared with 83 and 76%, respectively, for patients without NF1 (Deliganis et al. 1996). However, a significant difference in time to tumor progression (first relapse) was observed in favor of patients with NF1. In a study including mostly diencephalic low-grade gliomas, Packer et al. did not find any prognostic differences related to the presence of NF1 (Packer et al. 1997)). In this study, the only statistically significant prognostic factor was age and children 5 years old and younger had a 3-year PFS rate of 74% compared with a rate of 39% in older children.

Another study examining clinical characteristics and consequences of treatment of children with hypothalamic/chiasmatic gliomas showed significant tumor progression despite a high survival rate (Janss et al 1995). Although the 5-year survival rate was 93%, more than 80% of the children required surgery, chemotherapy, or radiotherapy within 2 years of diagnosis, and all but 9% eventually required radiation or chemotherapy within a median follow-up period of 6 years. In a recent multivariate analysis of potential prognostic factors in children with optic pathway gliomas, older age, presence of NF1, chemotherapy, and radiotherapy were found to have statistically significant effect on outcome (Chan et al 1998). Overall, 5-year survival for patients with hypothalamic/chiasmatic gliomas is 85% with a continuous decline over subsequent years (Garvey and Packer 1996). Finally, stereotactic radiotherapy should be further examined in prospective studies. Work by Combs

et al., demonstrated in a small number of patients that fractionated stereotactic radiosurgery delivered to a median dose of 52.2 Gy using 1.8 Gy daily fractions provided good tumor control. The 5-year PFS and overall survival rates were 72 and 90%, respectively, without any observed secondary malignancies (Combs et al. 2005).

Results with particularly long follow-up have been recently presented in abstract form and highlight several important themes in treatment of optic pathway gliomas. In this report, 33 children with hypothalamic/chiasmatic low-grade gliomas underwent primary treatment with outpatient TPDCV (6-thioguanine, procarbazine, dibromodulcitol, CCNU, vincristine) chemotherapy on a Phase II prospective trial (UCSF-BTRC protocol 8422). Long-term results were favorable: 5-year overall survival was 90.9% and 15-year overall survival was 71.2%, indicating that salvage therapy consisting of radiation, surgery, and/or chemotherapy is successful in many patients (Fig. 1.7). Five-year PFS was 30.3% and 15-year PFS was 23.4%, with most patients (24 of 25 patients who progressed) experiencing their first progression event within 6 years of diagnosis (Fig. 1.7). Finally younger patients had much poorer prognoses and many could not be successfully treated with salvage therapy. Younger age was significantly associated with poorer overall survival and PFS ($p = 0.037, 0.004$, respectively). Of the 18 children who were 3 years or younger at diagnosis, 17 progressed and of these, 10 died. Comparatively, 15 of the children who were older than 3 years at diagnosis, 8 progressed and none died (Mishra et al. 2007).

1.5 Oligodendroglioma

1.5.1 Epidemiology

Definitive data regarding the incidence of oligodendrogliomas relative to all intracranial gliomas are lacking mainly due to significant differences in diagnostic criteria among neuropathologists. In the general population, the relative incidence of oligodendrogliomas is low (4–7%) in some series (Rubinstein 1972; Mork et al. 1985), but higher (18.8 and 33%) in other series (Zulch 1986; Daumas-Duport et al. 1997). Oligodendrogliomas are rare in children and constitute approximately 1% of pediatric brain tumors (Razack et al. 1998).

Unlike low-grade astrocytomas, *p53* is only rarely mutated in oligodendrogliomas. However, over half

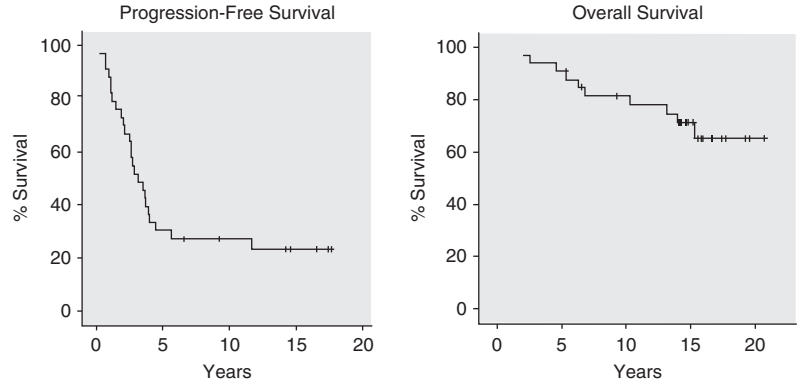

Figure 1.7

Kaplan-Meier plots of progression-free survival and overall survival of a Phase II Protocol evaluating an outpatient TPDCV chemotherapy regimen as primary treatment for pediatric low-grade gliomas. The plots demonstrate favorable long-term survival and highlight the finding that most events occurred in the first 6 years with only one event occurring later than 6 years

of these tumors show a characteristic loss of the long arm of chromosome 1 and the short arm of chromosome 19. As 1p/19q loss is not seen in astrocytic tumors, the combination of *p53* and 1p/19q analysis may serve in the future to distinguish an astrocytic (*p53*-mutant, 1p/19q intact) from an oligodendroglial (*p53*-wild type, 1p/19q deleted) genotype in cases that are difficult to distinguish histologically (Reifenberger et al., 1994).

1.5.2 Pathology

Oligodendrogliomas arise primarily in the white matter, but tend to infiltrate the cerebral cortex more than astrocytomas of similar grade. Oligodendrogliomas tend to form clusters of neoplastic cells in the subpial region, around neurons and blood vessels. Microscopically, classic oligodendrogliomas show uniform cell density at low power. Higher power reveals uniform round nuclei and distinctive perinuclear halos. This histologic appearance has been referred to as "fried eggs." However, frozen sections of oligodendrogliomas fail to show the diagnostically helpful perinuclear halos, nor does it show formalin-fixed material that has been previously frozen. Most oligodendrocytes show positive reactivity for S-100 protein. Low-grade oligodendrogliomas are distinguished from high-grade tumors on the basis of lower cellularity, inconspicuous mitotic activity, minimal nuclear atypia, and absence of endothelial proliferation and necrosis.

1.5.3 Clinical Features

Similar to supratentorial astrocytomas, symptoms and signs of childhood oligodendrogliomas depend on tumor location and patient age. General nonspecific symptoms associated with increased ICP and focal symptoms related to the location of the tumor are outlined earlier in this chapter. Oligodendrogliomas have a slight predilection for the frontal lobes. Grey matter involvement is common, giving them, on average, a more superficial location than astrocytomas.

1.5.4 Diagnostic Imaging

The diagnosis of oligodendroglioma may be suggested on imaging studies by its location and presence of calcifications. Although nonspecific, fronto-temporal location, involvement of the superficial cortex, and intrinsic calcifications are characteristic of oligodendrogliomas. Oligodendroglioma is the most common intracranial tumor to calcify (60–90% of oligodendrogliomas are calcified) and CT has the advantage of better visualizing such calcium deposits. Therefore CT and MRI are complementary methods to characterize the tumor and evaluate its extension. Approximately half of oligodendrogliomas moderately enhance and this enhancement is typically patchy enhancement is typically patchy.

1.5.5 Treatment

As with most gliomas, surgery is usually the initial therapeutic modality in the management of children with supratentorial oligodendroglioma, and may range from a stereotactic biopsy to an extensive resection. The general surgical management principles discussed in reference to low-grade astrocytoma apply to supratentorial oligodendrogliomas. The surgical strategy should favor radical tumor removal when feasible.

The role of postoperative irradiation in the management of patients with oligodendrogliomas is controversial, and conclusions regarding the value of radiotherapy are contradictory. Some authors recommend immediate postoperative irradiation for patients with incompletely resected lesions (Lindegaard et al. 1987), whereas other studies fail to show any survival benefit with this approach (Bullard et al. 1987; Sun et al. 1988). Sufficient data are not available to support the recommendation that all patients with oligodendrogliomas receive radiation therapy. Its efficacy has not been demonstrated, especially in children (Hirsch et al. 1989). Postoperative irradiation may be beneficial for patients with incompletely resected tumors, especially when unfavorable clinical or pathologic characteristics are present. It is reasonable, however, to defer treatment in children until progression.

Aggressive oligodendrogliomas have been shown to respond especially well to chemotherapy with procarbazine, lomustine, and vincristine (PCV) (Cairncross et al. 1992; Glass et al. 1992). It has also been demonstrated that the allelic loss of Chromosomes 1p and 19q predict response to chemotherapy and longer survival in patients with anaplastic oligodendrogliomas (Cairncross et al. 1998), establishing a molecular marker for chemosensitivity in these tumors. Increasingly, neoadjuvant chemotherapy with PCV is being used to treat anaplastic oligodendrogliomas and up to 70% of patients may respond (Paleologos et al. 1999; Streffer et al. 2000). In addition, salvage therapy with PCV may be effective in patients progressing after radiotherapy (Streffer et al. 2000).

1.5.6 Outcome

For oligodendrogliomas, the most promising prognostic marker is combined loss of chromosomes 1p and 19q. The initial finding in anaplastic oligodendrogliomas was recently extended to low-grade tumors, and a similar relationship of 1p/19q loss with improved survival was found (Smith et al. 2000). Furthermore, 1p loss of heterozygosity appears to be a stronger predictor of survival than the well-established prognostic factors of age and performance status (Bauman et al. 2000).

Limited data exist on the predictive role of surgery regarding outcome of patients with oligodendroglioma. Patients with centrally located tumors have significantly poorer outcome compared to those with peripheral tumors. One study demonstrated that even minor excision of cerebral or cerebellar oligodendrogliomas conferred a much better prognosis compared to excision of central masses (Peters et al. 2004). Although most major series with statistical analysis show a favorable outcome associated with more extensive resections, the effect of the extent of resection appears to be less prominent in oligodendrogliomas than in astrocytomas (Keles et al. 2001).

Oligodendrogliomas appear to have a different natural history and a better overall prognosis than astrocytomas. Survival data for oligodendrogliomas depend on the histological criteria used for diagnosis, and show significant variability. Five-year survival rates ranging from 27-85% have been reported. However, case series that include mixed oligodendroglioma and higher-grade tumors complicate the interpretation of overall survival rates.

1.6 Conclusion

In low-grade tumors, GTR is associated with better long-term survival. However, many infiltrative astrocytomas cannot be resected completely. For these tumors, the use of chemotherapy to help control disease as a means to delay radiotherapy is actively being investigated and is the subject of ongoing clinical trials. Newer chemotherapy regimens, the use of stereotactic radiosurgery, and targeted biological agents offer new, promising treatment avenues for glioma therapy.

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High-Grade Gliomas

Sabine Mueller • Daphne Haas-Kogan

Contents

2.1 Introduction

Astrocytomas are the most common childhood tumor of the central nervous system (CNS), representing approximately 40–50% of all pediatric tumors. The World Health Organization (WHO) classifies these tumors into low-grade (WHO grade I and II) and high-grade (WHO grade III and IV) astrocytomas (Kleihues et al. 2002). In contrast to the adult population, high-grade gliomas in children are relatively infrequent and represent less than 20% of cases (Pollack 1994). Although some genetic syndromes are associated with an increased risk of developing CNS tumors, the etiology for most tumors is unknown. Despite advances in treatment for other types of childhood tumors, patients with high-grade gliomas invariably have a poor outcome, and 5-year survival rates are less than 20%.

2.2 Epidemiology

High-grade astrocytomas, which include anaplastic astrocytoma (AA; WHO grade III) and glioblastoma (GBM, WHO grade IV), are less frequent in children than in adults, and account for only 15–20% of all pediatric brain tumors (Pollack 1994; Packer 1999). Anaplastic tumors with an oligodendroglial component are very uncommon in children (Hyder et al. 2007). Overall, malignant gliomas represent 6.5% of all newly diagnosed childhood intracranial neoplasms (Tamber and Rutka 2003). No definite link has been established between any environmental factor and occurrence of high-grade gliomas, except

for prior radiation exposure (Pettorini et al. 2008). There are several genetic syndromes that are associated with high-grade gliomas in children including Neurofibromatosis type 1 (NF1), Turcot syndrome, and Li–Fraumeni syndrome. NF1 is an autosomal dominant disorder that is not only most commonly associated with optic pathway gliomas, but also carries an increased risk for developing high-grade gliomas. Turcot syndrome refers to the combination of colorectal polyposis and primary tumors of the CNS, and mutations are commonly found in the *APC* gene and mismatch repair genes *hMSH2*, *hMLH1,* and *hPMS2* (Turcot et al. 1959; Hamilton et al. 1995). Li–Fraumeni syndrome is a clinically and genetically heterogeneous inherited cancer syndrome associated with a high incidence of childhood brain tumors and mutations in the tumor suppressor gene *p53* (Li et al. 1988; Varley et al. 1997).

2.3 Pathology

2.3.1 Histopathology

The AA and GBM are both diffusely infiltrative, malignant gliomas. In addition to high mitotic activity, the main cellular feature of malignant glial cells is local-tissue invasion that typically occurs along deep white matter tracts, for example, corpus callosum, anterior commissure, fornix, and internal capsule. Gliomatosis cerebri refers to an unusual pattern of growth in which malignant astrocytomas demonstrate diffuse infiltration as a primary feature, often throughout the entire hemisphere.

Compared to grade II astrocytoma, AA exhibits greater cellularity, nuclear atypia, a high degree of cellular pleomorphism, and presence of multiple mitotic figures. The diagnosis of GBM is usually made by the additional presence of necrosis or microvascular proliferation. GBMs are usually circumscribed in appearance, but the borders are poorly defined. As the name implies, the character of the tumor is heterogeneous; firm areas alternate with soft or cystic regions, and mottled areas of hemorrhage and necrosis give the gross specimen an overall moth-eaten appearance. The central area of low attenuation on neuroimaging studies corresponds to confluent areas of tissue necrosis and degeneration. This central region is often surrounded by an irregular zone of denser, and more vascular tissue that corresponds to areas of higher attenuation and contrast enhancement. Finally, there is a peripheral zone of lesser cell density, edema, and microscopic tumor infiltration. This peripheral zone may vary in contour, with finger-like projections extending from the main tumor bulk. Significant variation in cellularity is often seen in different parts of the tumor that can lead to misdiagnosis if the tumor is sampled incompletely.

Other tumor types included in the high-grade glioma category according to the WHO criteria are anaplastic oligodendrogliomas (AO), anaplastic mixed gliomas (AMG) and anaplastic variants of pleomorphic xanthoastrocytoma, ganglioglioma, and pilocytic astrocytoma.

2.3.2 Molecular Biology

Pediatric high-grade gliomas differ in their molecular characteristics from their adult counterparts despite histological similarities. Further, molecular features identify adult primary (de novo) GBMs as distinct from secondary (progressive) GBMs that have developed from lower-grade gliomas. Whereas the former are associated with epidermal growth factor receptor (EGFR) amplification and phosphatase, and tensin homolog (*PTEN*) mutations, the latter occur in younger adults and have *p53* mutations as well as amplification and overexpression of the platelet-derived growth factor receptor-α (PDGFR).

Little is known about the molecular characteristics of pediatric gliomas. Some studies have identified frequent mutations in the tumor-suppressor gene *p53*, which is linked to poor outcome in the pediatric population. This is in contrast to tumors presenting in adulthood. Children with low p53 expression had a 5-year progression-free survival (PFS) rate of 44% compared to 17% in patients with p53 overexpression (Pollack et al. 2001, 2002a). *EGFR* amplification (Bredel et al. 1999) and *PTEN* mutations (Nakamura et al. 2007) are less frequent in children than in adults.

One study analyzed *EGFR* amplification and *PTEN* mutation in samples derived from a multiinstitutional

trial, the Children's Cancer Group (CCG) study 945, the largest pediatric high-grade glioma therapeutic trial published to date (Finlay et al. 1995; Pollack et al. 2006). In this study, only one *PTEN* mutation was detected in 42 centrally reviewed GBM and AA samples. Twenty-four percent of the 42 tumors had *PTEN* deletions, which is significantly less than generally reported for adult gliomas (Liu et al. 1997). Similarly, *EGFR* amplification was a rare event. This study also confirmed the high incidence (40.5%) of *p53* mutations in pediatric high-grade gliomas (Pollack et al. 2006).

Allelic loss of Chromosome 1p and 19q is associated with favorable outcome in adult oligodendrogliomas (Ino et al. 2000). Similar analyses could not duplicate such associations in children with oligodendrogliomas (Raghavan et al. 2003). An analysis of 107 pediatric samples from CCG 945 revealed that 30% of these tumors displayed 1p deletions and 28% had 19q deletions, although neither deletion was associated with age, sex, tumor location, *p53* status, or improved 5-year PFS (Pollack et al. 2003).

Table 2.1 summarizes the percentage of key genetic alterations in pediatric high-grade gliomas. The same tumor samples from the CCG 945 study were also evaluated for MIB-1 labeling as an indicator of cell proliferation. Ninety-eight tumors were analyzed, and a strong association between MIB-1 labeling, histology, and patient outcome was found. Mean labeling indices were 19.4 ± 2.66 for tumors classified as AA versus 32.1 ± 3.08 for those classified as GBM ($p = 0.0024$). Five-year PFS was $33 \pm 7\%$ in 43 patients, whose tumors had MIB-1 indices of less than 18%, $22 \pm 8\%$ in the 27 patients whose tumors had indices between 18 and 36%, and $11 \pm 6\%$ in the 28 patients whose tumors had indices greater than 36% ($p = 0.003$), reflecting a significant inverse correlation between proliferative indices and PFS (Pollack et al. 2002a). Current studies are aiming to further delineate the underlying molecular biology of high-grade gliomas in children. Given the rarity of these tumors, however, significant sample sizes can only be obtained through multiinstitutional studies. The identification of the underlying molecular make up of these tumors remains crucial for the development of targeted therapies that have already begun to affect the treatment of pediatric gliomas.

2.4 Clinical Features

Exact signs and symptoms caused by high-grade supratentorial gliomas depend upon the anatomic location, biologic aggressiveness, and patient age. These signs and symptoms may be nonspecific, such as those resulting from the effects of increased intracranial pressure, or those directly related to the location of the tumor. Nonspecific symptoms include headache, nausea, and vomiting. Worrisome features of headaches that should alert the clinician are those that wake the child up from sleep, occur on awakening in the morning, involve nausea and vomiting, cause consistent focal pain, worsen with Valsalva maneuvers, progress in severity, fail to respond to any therapy, or occur in the setting of an abnormal neurologic exam (Duffner 2007). The time from the first symptom to diagnosis is shorter in high-grade gliomas than in low-grade tumors (Mehta et al. 2002; Duffner 2007). In infants with open cranial sutures, tumors may reach a massive size with gradual increase in head circumference without signs of increased intracranial pressure. Subtle symptoms such as increased irritability, change in feeding pattern, and failure to thrive are often misinterpreted. Focal symptoms depend upon the location of the tumor and may include hemiparesis, monoparesis, hemisensory loss, dysphasia, aphasia, and impairment of recent memory. Malignant gliomas are less-frequently associated with seizures and are more likely to cause focal neurologic deficits, mainly due to infiltration of normal tissue or local mass effect.

Disseminated disease at presentation is rare, in contrast to cases involving other malignant pediatric brain tumors such as supratentorial primitive neuroectodermal tumors and medulloblastomas (Benesch et al. 2005).

2.5 Diagnostic Imaging

Magnetic resonance imaging (MRI) and computerized tomography (CT) are essential tools in the diagnosis and treatment of brain tumors. Although CT is more commonly available and can be performed quickly in children, MRI provides higher sensitivity

Table 2.1. key molecular and genetic alterations in pediatric and adult gliomas

	Occurrence in pediatric HGG (%)	Occurrence in pediatric AA (%)	Occurrence in pediatric GBM (%)	Occurrence in adult HGG (%)	Reference
EGFR amplification		10 (1/10)	11 (2/18)	30–40	Nakamura et al. (2007)
	2.9 (1/34)				Pollack et al. (2006)
		0 (0/17)	0 (0/15)		Raffel et al. (1999)
	7.4 (2/27)				Bredel et al. (1999)
	0 (0/24)				Cheng et al. (1999)
EGFR overexpression	80 (17/22)			30–40	Thorarinsdottir et al. (2008)
	58 (23/40)				Liang et al. (2008)
	28 (8/28)				Nakamura et al. (2007)
			36 (14/38)		Pollack et al (2006)
	25.9 (13/54)				Ganigi et al. (2005)
	81 (22/27)				Bredel et al. (1999)
			11 (2/19)		Sure et al. (1997)
EGFRvIII expression	2.5 (1/40)			10–67	Liang et al. (2008)
PDGFR-α amplification		0 (0/28)		10–15	Nakamura et al. (2007)
TP53 mutation		30 (3/10)	33 (6/18)	30–35	Nakamura et al. (2007)
	33 (40/121)				Pollack et al. (2002a
	38 (9/24)				Cheng et al. (1999)
		24 (4/17)	20 (3/15)		Raffel et al. (1999)
			25 (5/20)		Sure et al. (1997)
p53 overexpression	35 (14/40)				Liang et al. (2008)
	35 (41/115)				Pollack et al. (2002a
			53.7 (29/54)		Ganigi et al. (2005)
Rb mutation/loss of expression			7.4 (4/54)	70–85	Ganigi et al. (2005)
PTEN mutation/deletion/ alteration	33 (13/39)			20–30	Liang et al. (2008)
			11 (2/18)		Nakamura et al. (2007)
			28 (7/25)		Pollack et al. (2006)
MGMT methylation			40 (4/10)	45	Donson et al. (2007)

Genetic alterations in pediatric gliomas. Percentages are given for anaplastic astrocytoma (AA) and glioblastoma (GBM) separately if included in the analysis otherwise AA and GBM are grouped into high grade glioma (HGG). *EGFR* epidermal growth factor receptor; *PDGFR* platelet-derived growth factor receptor; *PTEN* phosphatase and tensin homolog; *MGMT* O^6-methylguanine–DNA methyltransferase

in differentiating tumor tissue from normal brain, allowing more detailed anatomic characterization of the lesion, and should be obtained in all children with a suspected brain tumor. A complete series should include the following sequences: T1-weighted axial and coronal (both before and after gadolinium), T2-weighted axial and coronal, and fluid attenuated inversion recovery (FLAIR). In addition, sagittal plane sequences are helpful in defining the anatomy of suprasellar and midline tumors. Other sequences such as fat suppression and MR angiography may also be required in specific situations. Contrast-enhanced neuroimaging of the entire neuraxis should be considered if there is a high index of suspicion for the presence of disseminated disease at the time of evaluation. Newer techniques, such as MR spectroscopy, functional MRI, and perfusion measurements offer the potential for obtaining biochemical and functional information noninvasively (see Chap. 13 for more details).

There is no pathognomonic appearance to differentiate high-grade gliomas from other tumors on MRI. They appear hypointense on T1-weighted images and hyperintense on T2-weighted sequences. Enhancement occurs after contrast injection, but degree of enhancement does not correlate with tumor grade (Fig. 2.1). On T1-weighted images, GBMs often demonstrate central areas of low density corresponding to necrosis and are typically poorly circumscribed. This area is surrounded by an area of high density that enhances with contrast, and corresponds to actively dividing and proliferating tumor cells. A third, low-attenuation area around the tumor is often seen representing tumor-associated vasogenic edema, but also containing infiltrating tumor cells. Peritumoral edema surrounding most high-grade astrocytomas appears as a hyperintense region of signal abnormality on T2-weighted images. The extent of peritumoral edema is underestimated on T1-weighted images. High-grade lesions demonstrate increased blood flow on perfusion studies and elevated choline:NAA ratios on MR spectroscopy (Fig. 13.1 in Chap. 13).

Thalamic tumors can present as diffuse swelling of the entire thalamus, with or without significant edema (Fig. 2.2). The differential diagnosis based on imaging appearance includes other malignant supratentorial hemispheric tumors, such as ependymomas, supratentorial primitive neuroectodermal tumors, and pleomorphic xanthoastrocytomas. Gliomatosis cerebri is usually diagnosed by widespread infiltration of tumor throughout the hemisphere. A focal lesion is usually not present, although mass effect can be substantial (Fig. 2.3).

Recurrence is an unavoidable feature of most glial neoplasms. For this reason, serial imaging over time is often the only method of determining whether tumor progression has occurred. Grade II astrocytomas often recur as higher-grade lesions. The recurrent tumors will usually have imaging features consistent with GBM. Most patients with high-grade gliomas are treated as part of a clinical trial and the frequency of screening MRIs is generally included in the study design and is frequently

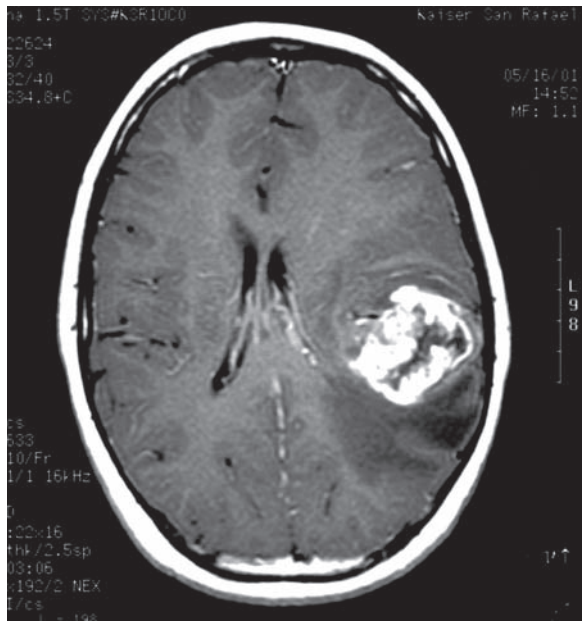

Figure 2.1

A postgadolinium T1-weighted axial magnetic resonance image of a teenage boy with a glioblastoma who presented with dysphasia. A large tumor in the left frontoparietal area is visible. The margin of the tumor enhances, a central necrotic area is visible, and the low signal region surrounding the mass represents tumor-associated edema

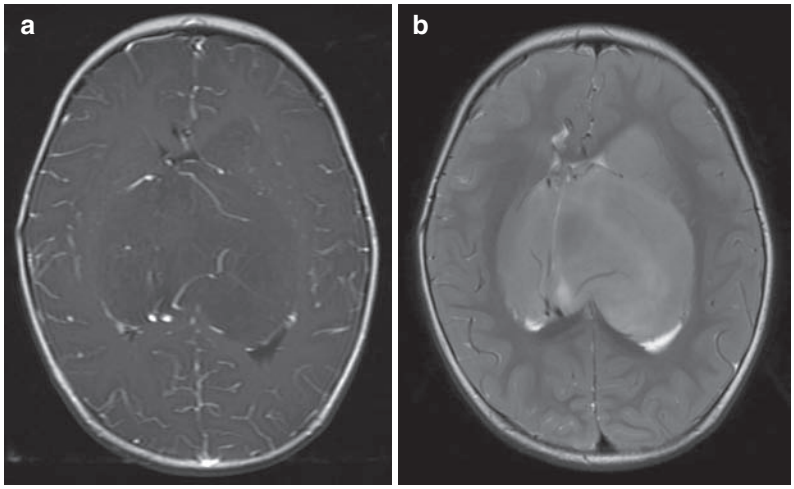

Figure 2.2
A diffusely infiltrating bilateral thalamic astrocytoma (grade III) in a 2-year-old boy. The tumor does not enhance on T1-weighted images (**a**). The extent of the tumor is better appreciated on T2-weighted images (**b**)

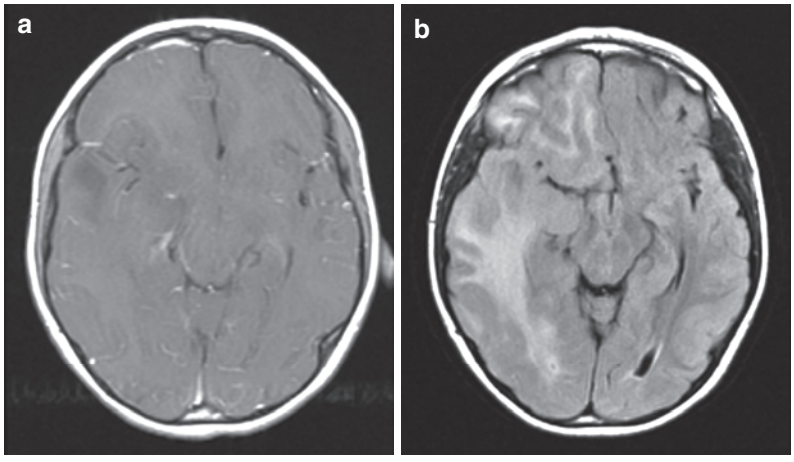

Figure 2.3
Gliomatosis cerebri. The tumor is difficult to appreciate on T1-weighted images (**a**). An axial fluid-attenuated inversion recovery (FLAIR) image (**b**), however, clearly shows diffuse involvement extending from the frontal lobe into the occipital lobe. Distortion of the cerebral peduncle is seen from the enlarged temporal lobe

performed every three months in the first year after diagnosis.

2.6 Treatment

2.6.1 Surgery

Aggressive resection, with preservation of neural function, is the cornerstone of initial management of children with high-grade astrocytomas. The primary objective is to obtain tissue for pathologic diagnosis, to relieve increased intracranial pressure if present, and to decrease tumor burden. High-grade gliomas are diffusely infiltrative lesions, and therefore it remains challenging for the neurosurgeon to define the tumor boundaries during the resection process. For deep lesions or those in eloquent cortex, a stereotactic needle biopsy may be the only surgical option. The secondary objective is to perform as extensive a resection as possible with acceptable neurologic outcome. Gross total resection (GTR) is preferred because greater extent of resection is linked to longer survival (Finlay et al. 1995; Heideman et al. 1997; Wolff et al. 2002). In the CCG 945 study,

children with high-grade gliomas who underwent GTRs (defined as >90%), had a 5-year PFS rate of 35% (±7%) compared to 17% (±4%) in the group that had subtotal resections (STR) ($p = 0.006$) (Wisoff et al. 1998). This association persisted in subgroup analyses based on histology. AA patients who underwent GTRs had a 5-year PFS rate of 44% (±11%) compared to 22% (±6%) for those who had STRs [$p = 0.055$]. GBM patients who underwent GTRs had a 5-year PFS rate of 26% (±9%) compared to 4% (±3%) for those who had STRs [$p = 0.046$] (Wisoff et al. 1998). Further analysis of the CCG 945 trial revealed that 1 patient was diagnosed by central review with an oligoastrocytoma, and 8 patients were diagnosed with anaplastic oligoastrocytomas. The 5-year event free survival rate (event defined as relapse or death from any cause) for patients with oligoastrocytomas was 37.5 ± 17% (Hyder et al. 2007).

The feasibility of an open-surgical approach depends upon several factors, the most important of which is the exact location of the tumor. Deep lesions within the basal ganglia, thalamus, motor cortex, or brainstem are not amenable to open surgical resection, while tumors in other locations can be accessed through various standard approaches. Thalamic tumors in general are considered unfavorable for resection, and therefore carry a dismal prognosis (Fig. 2.2). Other factors that modify the decision to attempt surgical resection are the patient's clinical condition, age, associated hydrocephalus, and the surgeon's assessment of risk of neurologic sequelae.

Contemporary neurosurgical methods, including ultrasonography, functional mapping, frameless navigational resection devices, and intraoperative imaging techniques, enable more extensive resections with less morbidity. These techniques and intraoperative considerations specific to the pediatric age group are discussed in detail in Chap. 14.

2.6.2 Radiation Therapy

Radiation therapy is the only adjuvant therapy proven to improve survival of children with brain tumors, and remains the standard of therapy after surgical resection for older children. Children older than 3 years are treated with 50–60 Gy of external beam radiation delivered with standard daily fractions of 1.8–2.0 Gy. Conformal techniques that allow treatment planning based on three-dimensional reconstructions using CT or MRI have dramatically advanced the area of radiation oncology over the past decade (see Chap. 16). Attempts at dose intensification by dose escalation (to a cumulative total dose of 72 Gy) in conjunction with hyperfractionation have failed to improve outcome in the setting of high-grade gliomas (Fulton et al. 1992; Packer et al. 1993). Hyperfractionated radiotherapy utilizes lower doses of radiation per fraction (usually 1–1.1 Gy) administered more than once daily. Decreasing the dose per fraction theoretically spares healthy tissue more than it spares tumor cells, allowing for higher total doses to the tumor, while limiting long-term side effects.

Long-term side effects of radiotherapy include neurocognitive decline, vasculopathies, endocrine abnormalities, as well as secondary malignancies. The effects of radiation are particularly harmful to the developing brain, and therefore the aim of post-surgical therapy has been to limit the use of radiotherapy in children less than 3 years of age. Two multi-institutional studies reported that outcome at younger age was even better without the use of radiation therapy compared to older children (Geyer, Finlay et al. 1995; Duffner et al. 1996). Children less than 2 years were treated with an "8-in-one-day" chemotherapy regimen after surgical resection without the use of radiation and had a PFS rate of 36% (±8%) and an overall survival rate of 51% (±8%) at 3 years. Analyzed by histological grade, patients with AA had the expected more favorable outcomes than those with GBMs; respective PFS rates were 44 (±11%) and 0% (Geyer, Finlay et al. 1995). Another study demonstrated that children less than 3 years of age treated for high-grade gliomas with vincristine and cyclophosphamide after surgical resection had a 3-year PFS rate of 43% (±16%) and a 5-year overall survival rate of 50% (±14%) (Duffner et al. 1996). Whether and if so, why, the younger child has a better response to chemotherapy without radiation remains to be elucidated. Currently, children less than 3 years of age are treated with chemotherapy after resection,

seeking to delay radiotherapy until at least three years of age.

2.6.3 Chemotherapy

The effectiveness of adjuvant chemotherapy in conjunction with radiation for high-grade glioma is uncertain. A Phase III randomized trial conducted by the CCG evaluated the role of chemotherapy in children with high-grade gliomas, who were randomized postoperatively to receive radiation therapy with or without chemotherapy with prednisone, lomustine, and vincristine. Children who had received postradiation chemotherapy had better PFS (46%) than those who did not receive chemotherapy (26%) (Sposto et al. 1989). Surprisingly, this benefit was most apparent in patients with GBM who had at least partial resections of their tumors. In a subsequent CCG study, patients were randomized to receive one of two chemotherapy regimens comparing an intensive "8-drugs-in-one-day" regimen to the more standard regimen of prednisone, vincristine, and lomustine. No difference in 5-year PFS was seen between these regimens (33 vs. 36%) (Finlay et al. 1995). Based on these data, adding adjuvant chemotherapy to radiation appears to provide a small survival benefit and standard agents are lomustine and vincristine, in combination with procarbazine (PCV). Since these early studies, chemotherapy has been added to radiation therapy in different schedules including "sandwich" protocol (prior and after radiation therapy), concomitant administration, and maintenance therapy. Single agents including etoposide, cyclophosphamide, irinotecan, platinum compounds, PCV, and topotecan have been studied in Phase II trials with marginal effects on overall survival. Since concomitant temozolomide (TMZ) and radiation therapy for adult GBM patients led to prolonged survival, several studies have tested the efficacy of this drug in pediatric brain tumors (Stupp et al. 2002). Multiple studies including patients with brainstem gliomas, high-grade gliomas, and recurrent gliomas have shown minimal effects of TMZ on survival (Estlin et al. 1998; Lashford et al. 2002; Nicholson et al. 2007). These studies suggest that TMZ is less effective in pediatric patients with high-grade astrocytomas than it is in adults. Ongoing trials are evaluating TMZ in combination with additional chemotherapeutic agents, including O^6-benzylguanine, an inhibitor of the DNA repair protein O^6-alkylguanine-DNA alkyltransferase.

High-dose, myeloablative chemotherapy with autologous hematopoietic stem-cell rescue (ASCR) has also been explored, and its role in the treatment of high-grade glioma remains unproven. The CCG 9922 study using thiotepa, BCNU, and etoposide followed by ASCR and focal radiation therapy resulted in a 2-year PFS rate of 46% (±14%) (Grovas et al. 1999). This study was closed early after 5 of the 11 treated patients developed significant pulmonary complications. Another study using thiotepa in patients with newly diagnosed high-grade glioma showed a 4-year survival rate of 46% (Massimino et al. 2005). The most appropriate candidates for myeloablative therapy are those with complete or near-complete resection prior to myeloablative therapy (Marachelian et al. 2008). The use of high-dose chemotherapy with ASCR may contribute to long-term disease control, but at the expense of significant morbidity and mortality as a consequence of the regimens themselves. The associated side effects and resultant poor quality of life have led many investigators to question the benefit of high-dose chemotherapy with ASCR, despite the potential for better disease control.

Currently, a combination of surgery, radiation, and chemotherapy is the standard therapy for children with high-grade gliomas who are older than three years. PCV regimen is the standard against which other chemotherapeutic protocols will be evaluated in the future, both with respect to efficacy and toxicity. For children less than three years, chemotherapy after surgical resection is the mainstay of therapy. However, the best regimen still needs to be determined, and newer strategies including targeted therapies and local delivery systems are currently under investigation.

2.7 Outcome

Overall survival for children with high-grade astrocytomas remains poor, but is generally more

favorable than in adults. It is unclear if this is due to differences in underlying pathology and molecular mechanisms leading to these tumors, therapeutic approaches, inherent tumor resectability, or other factors. Certain molecular characteristics have been associated with improved outcome as outlined above. Other factors linked to better outcome are the histological grade and extent of resection. Patients with GTRs live longer than those with STRs, who in turn, live longer than those who have only biopsies. A further consideration is that partial resection is often accompanied by significant postoperative edema surrounding residual tumor tissue along with increased neurologic morbidity. Children with anaplastic gliomas who receive GTRs followed by local radiation therapy have approximately a 40–50% 5-year survival (Sposto et al. 1989). Patients with GBMs have a 20% survival rate after GTR and adjuvant therapy. Patients with partially resected GBMs rarely survive (Finlay et al. 1995). However, the literature regarding the prognostic impact of surgery is controversial, and the controversy is mainly due to lack of randomized studies addressing the issue. An additional complicating factor is the inconsistent and subjective methodology used in determining extent of resection. The prognosis for children with recurrent high-grade glioma is dismal, and chemotherapy is often the only treatment option available. These children generally die within one year, and only very toxic chemotherapy regimens have shown some beneficial survival effects (Finlay et al. 1996).

Children treated for brain tumors have long-term consequences that they suffer from owing to their tumors and treatments. Standard use of radiation therapy is associated with well-known risks of delayed cognitive and neuropsychologic sequalae, endocrine abnormalities, as well as vasculopathies; therefore, these patients require long-term follow-up in specialized clinics. Current strategies are able to target more precisely the tumor cells while minimizing the volume of normal brain irradiated. Such novel technologies can significantly spare key structures such as the hippocampus and neural stem cell compartments, and thus will likely translate into less radiation-induced cognitive dysfunction (Barani et al. 2007; Gutierrez et al. 2007; Merchant et al. 2008). The often devastating consequences of radiation therapy in children less than 3 years of age led to substantial attention to refining strategies that either delay or avoid radiotherapy entirely in this population, by first administering an extended course of intensive chemotherapy. Children who receive treatment for a brain tumor should undergo neuropsychologic assessment and specific cognitive-behavioral training. Secondary malignancies in brain-tumor survivors have been reported. Among others, alkylating agents, etoposide, and irradiation are causative agents for further malignancies. Survivors need long-term monitoring and follow-up for early detection and intervention if needed.

2.8 Future Directions

The goal of ongoing investigations is to improve overall survival, enhance long-term quality of life, and reduce treatment-related toxicities for children with brain tumors. The role of radiation and surgery is well-established in the treatment of high-grade gliomas in children, but the optimal chemotherapy regimen still warrants further research. Current studies tackle several aspects of treatment and examine new combinations of drugs, optimal chemotherapy dose intensities, and radiosensitizing agents to enhance the efficacy of an already proven therapy, and limit side effects. Novel targeted therapies aim to interfere with the molecular pathways associated with AA and GBM. Inhibitors of EGFR or PDGFR are being tested in Phase I/II trials with and without radiation as well as in combination with conventional chemotherapy. Imatinib (PDGFR inhibitor) has been associated in a Phase I trial with increased incidence of intracranial hemorrhage, especially in patients with brainstem glioma, which requires further investigation (Pollack et al. 2007). Other agents include inhibitors of farnesyltransferase, NOTCH, and mTOR signaling pathways as well as multiple antiangiogenic agents as listed in Table 2.2. These small-molecule inhibitors are tested as single agents as well as in combination with conventional chemotherapy and radiation.

Technologies to improve local drug delivery are currently part of intensive research, and include

Table 2.2. Current clinical trials using small-molecule inhibitors for newly diagnosed or recurrent high-grade glioma in children

	Drug	Type of study	Intracellular target	Disease indication
EGFR inhibitors	Erlotinib	Phase I	EGFR	New/RE/PRO/REF
	Gefitinib	Phase I/II	EGFR	New
Farnesyltransferase inhibitors	Lonafarnib	Phase I	Farnesyltransferase	RE/PRO
	Tipifarnib	Phase I/II	Farnesyltransferase	RE/PRO
PDGFR inhibitor	Imatinib	Phase I/II	PDGFR	New/REC
mTOR inhibitors	Temsirolimus	Phase I/II	mTOR	RE/PRO/REF
	Everolimus	Phase I	mTOR	PRO/REF
Antiangiogenic agents	Cilengitide	Phase I	$\alpha_5\beta_3$ Integrin receptor	RE/PRO/REF
	Lenalidomide	Phase I	Immunmodulatory	RE/PRO/REF
	Enzastaurin	Phase I	Proteinkinase Cβ	RE
	Cediranib	Phase I	VEGFR 1,2,3	RE/PRO/REF
	Semaxanib	Phase I	VEGFR-2	RE/PRO
	Bevacizumab	Phase II	VEGF Ab	RE/PRO/REF
MGMT inhibitor	Temozolomide	Phase I/II	MGMT	New/RE/PRO/REF
NOTCH signaling inhibitor	MK0752	Phase I	NOTCH	RE/PRO/REF

Ab antibody; *EGFR* epidermal growth factor receptor; *MGMT* O^6-methylguanine–DNA methyltransferase; *mTOR* mammalian target of rapamycin; *New* newly diagnosed tumors; *PDGFR* platelet-derived growth factor receptor; *PRO* progressive disease; *RE* recurrent disease; *REF* refractory disease; *VEGF* vascular endothelial growth factor; *VEGFR* vascular endothelial growth factor receptor

convection-enhanced delivery, antibody- or ligand-mediated targeting of tumor cells, and radionuclide conjugates specifically designed to bind directly to tumor cells. Gene therapy using toxin-producing viral vector constructs to induce selective killing of rapidly proliferating tumor cells are also under current investigations.

2.9 Conclusions

Supratentorial high-grade gliomas are less common in the pediatric population compared to adults, but cause significant morbidity and mortality. In children greater than 3 years of age, high-grade tumors are treated aggressively with surgery, radiation, and adjunctive chemotherapy. For the younger child (less than 3 years of age), the goal is to delay radiation therapy with chemotherapy regimens to avoid significant side effects of radiation on the developing brain. Children with high-grade gliomas have poor prognoses and the long-term outcome remains poor. Current research focuses to elucidate the underlying molecular pathways to better direct the development of new therapies.

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Brainstem Gliomas

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Contents

3.1 Introduction

Historically, brainstem gliomas (BSGs) were regarded as a homogeneous category of central nervous system (CNS) neoplasms with a uniformly poor prognosis. With the advent of magnetic resonance imaging (MRI), BSGs are now recognized as a heterogeneous group of neoplasms with distinct subtypes that vary widely with respect to prognosis and growth patterns. They can be classified broadly into two categories: the diffuse intrinsic gliomas and the nondiffuse brainstem tumors (Table 3.1). The diffuse intrinsic gliomas, which constitute the majority of brainstem tumors and conform to the stereotype of BSGs, occur most often in the ventral pons, infiltrate throughout the brainstem, and have a uniformly poor prognosis. The nondiffuse brainstem tumors include focal midbrain, dorsally exophytic, and cervicomedullary tumors. Almost all these tumors are slow-growing, low-grade neoplasms that have a more favorable prognosis and response to treatment (specifically surgery) than the diffuse intrinsic gliomas. The management plan for these tumors is individualized to each distinct brainstem tumor type and is based strongly upon their MRI characteristics, suspected histology, and clinical presentations. It should be appreciated that nonneoplastic conditions such as brain abscess, neuroepithelial cyst, and demyelinating disorders can also present with lesions in the brainstem, but these entities are rare and will not be discussed further.

Table 3.1. Overview of the brainstem glioma subtypes[a]

Tumor type	Approximate frequency (%)	Clinical characteristics	Imaging characteristics	Predominant pathology
Diffuse intrinsic	75–85	Multiple bilateral CN deficits LTS Ataxia Short clinical history	Diffuse pontine enlargement T1 hypointensity T2 hypointensity Little contrast enhancement	Fibrillary astrocytoma (grades II–IV)
Focal mid-brain	5–10	Signs and symptoms of raised ICP Isolated CN deficit Ataxia Hemiparesis (rarer) Torticollis	Small, well-circumscribed No edema T1 hypointensity T2 hyperintensity Variable enhancement Ventriculomegaly	Low-grade astrocytoma (grades I and II) Ganglioglioma
Dorsally exophytic	10–20	Signs and symptoms of raised ICP CN dysfunction Prominent nystagmus Torticollis FTT (infants) LTS typically absent	Arise from floor of 4th ventricle T1 hypointensity T2 hyperintensity Bright enhancement	Pilocytic astrocytoma (grade I) Grade II astrocytoma
Cervico-medullary	5–10	Lower CN dysfunction LTS Apnea Sensory loss Torticollis Hydrocephalus (rarer)	Arise from lower medulla/upper cervical cord Bulges dorsally toward fourth ventricle T1 hypointensity T2 hypointensity Commonly enhances	Low-grade astrocytoma Ganglioglioma

[a] Adapted from Freeman and Farmer (1998)
CN cranial nerve; *ICP* intracranial pressure; *LTS* long tract signs; *FTT* failure to thrive

3.2 Epidemiology

Brainstem tumors account for approximately 10–20% of all intracranial tumors in children (Panitch and Berg 1970; Farwell et al. 1977; Albright et al. 1983) and 90% are glial in origin (Pierre-Kahn et al. 1993). Seventy-five percent of BSGs occur in patients before age 10 (Panitch and Berg 1970; Farwell et al. 1977). Historically, the prognosis for children with diffuse pontine gliomas has been exceedingly poor, with median survival ranging from 4 to 15 months (Fulton et al. 1981). The median time to disease progression of diffuse intrinsic gliomas is only 5–6 months, and only 6–10% of these patients survive beyond 2 years after treatment (Freeman and Perilongo 1999). The overall 5-year survival rates are in the range of 20–30% for all brainstem tumors (Freeman and Farmer 1998).

Diffuse pontine gliomas represent 80% of all pediatric BSG subtypes (Freeman and Farmer 1998). The nondiffuse brainstem tumors, including focal midbrain, dorsally exophytic, and cervicomedullary tumors, occur less frequently but have much better prognoses. One study noted a 4-year progression-free survival rate (PFS) of 94% and a total 4-year survival rate of 100% in 17 patients with focal midbrain tumors, which included tectal gliomas (Robertson et al. 1995). Pollack et al. observed that 17 of 18 patients (94%) who underwent surgical resection for dorsally exophytic brainstem tumors were alive at the conclusion of their study; follow-up periods ranged from 33 to 212 months (Pollack et al. 1993). Patients with cervicomedullary tumors have been

noted to have a 5-year PFS rate of 60% and an overall 5-year survival rate of 89% after initial resection (Weiner et al. 1997). Thus, the incidence and prognosis of BSG vary depending on the specific tumor subtype and location.

3.3 Pathology

BSGs are not designated as a specific pathological category in the World Health Organization (WHO) classification of CNS tumors. BSGs are classified by location rather than histology. For this reason, BSGs comprise tumors of varying behavior and grade. Benign and low-malignancy brainstem tumors tend to occur in the midbrain and medulla, while higher-grade gliomas occur more frequently in the pons. The major utility of examining BSGs as a separate group from other posterior fossa tumors is that distinct therapeutic and prognostic concerns are related to neoplasms in this location.

3.3.1 Histopathology

3.3.1.1 Diffuse Pontine Glioma

Similar to astrocytomas elsewhere in the CNS, most diffuse pontine gliomas are fibrillary and characterized by the presence of nuclear atypia, scant cytoplasm, and microcysts. Increased mitotic activity and nuclear pleomorphism are features of grade III (anaplastic) astrocytoma, while microvascular proliferation and necrosis are required for the diagnosis of grade IV astrocytoma (glioblastoma multiforme (GBM)). Fibrillary astrocytomas also exhibit immunohistochemical reactivity to glial fibrillary acidic protein (GFAP) and vimentin. It is difficult to accurately determine the frequency of low- vs. high-grade tumors with diffuse intrinsic gliomas, since biopsies are performed in only one-fourth to one-third of all cases. An additional complicating factor is the substantial risk of sampling error when a stereotactic biopsy is performed (Freeman and Farmer 1998). At autopsy, however, most pontine tumors are high-grade gliomas with extensive brainstem involvement, a finding that is consistent with the poor outcome associated with these tumors (Mantravadi et al. 1982; Piette et al. 2008).

3.3.1.2 Nondiffuse Brainstem Glioma

The overwhelming majority of focal midbrain tumors, either tectal or tegmental, are grade I (pilocytic) or grade II astrocytomas (Hoffman et al. 1980; Robertson et al. 1995). Anaplastic astrocytomas have been reported to occur in this region; however, they are recognized to have a more indolent course than tumors of similar histology within the cerebral hemispheres (Raffel et al. 1988). Similarly, most cervicomedullary tumors are low-grade astrocytomas. Both gangliogliomas, which contain both neoplastic glial cells and dysplastic neurons, and ependymomas have also been reported in this region (Epstein and Farmer 1993; Weiner et al. 1997). Anaplastic astrocytomas have been observed in 9–10% of patients with cervicomedullary tumors; therefore, approximately 90% of pediatric cervicomedullary tumors have low-grade histology.

Dorsally exophytic tumors are largely low-grade astrocytomas. Khatib et al. reported in their series that 11 of 12 patients (92%) with dorsally exophytic tumors had classic grade I pilocytic astrocytomas (Khatib et al. 1994). Histologically, these tumors are characterized by a biphasic pattern of compacted bipolar cells with loose-textured multipolar cells, low cellularity, and Rosenthal fibers, which are eosinophilic, hyaline, corkscrew-shaped intracytoplasmic masses. Mitoses are rare in these tumors. Long-term survival after resection of pilocytic astrocytomas of the brainstem has been observed and appears to be related to the extent of initial excision (Kestle et al. 2004).

3.3.2 Molecular Biology

Understanding the biology of BSG is limited by the relative paucity of human tissue available for molecular analysis, as few diffuse pontine glioma patients undergo biopsy. Sawyer et al. reported an extra copy of the long arm of chromosome 1 (trisomy 1q) that was translocated onto the distal end of one copy of chromosome 7 as the sole chromosomal abnormality in a patient with a high-grade pontine astrocytoma

(Sawyer et al. 1990). Analysis of 13 pontine gliomas of juvenile onset revealed a high incidence of multiple or tandem mutations of probable somatic (not germ-line) origin in the *p53* gene. These mutations appear to be characteristic for pontine gliomas, as cerebral gliomas do not usually have multiple mutations (Zhang et al. 1993). Louis et al. also reported allelic losses of chromosomes 17p (including the *p53* gene) and 10 in pediatric patients with brainstem GBM, with no epidermal growth factor receptor (EGFR) gene amplifications noted (Louis et al. 1993). This pattern of genetic alterations (i.e., *p53* mutations without EGFR amplification) is similar to that of secondary GBMs in young adults, which are believed to arise from lower-grade astrocytomas (Watanabe et al. 1996). Gilbertson and colleagues observed amplification and overexpression of *ERBB1*, the degree of which correlated with tumor grade. The significance of such findings remains unclear. More recently, efforts are underway to identify molecular epitopes specific to pediatric BSG that can be exploited by targeted therapies. IL-13 protein and mRNA, for example, are expressed at significantly higher levels in BSG than in normal brain tissue (Joshi et al. 2008). These studies, however, have not led to the development of an effective therapeutic agent.

3.4 Clinical Features

The array of clinical signs and symptoms caused by BSGs is dependent upon their exact location and the affected anatomic structures (Table 3.1). For example, focal midbrain tectal gliomas typically cause hydrocephalus and extraocular motor palsies, while hemiparesis is much less common. Dorsally exophytic tumors arise primarily within the medulla and extend posteriorly into the fourth ventricle. They often present with signs and symptoms of raised intracranial pressure, including headache, nausea, vomiting, papilledema, gait ataxia, and stupor. In infants, such tumors often present insidiously with failure to thrive (FTT). Other signs include torticollis, prominent nystagmus, and cranial nerve (CN) dysfunction (Pollack et al. 1993). Long tract signs (LTS) such as paresis, hyperreflexia, spasticity, and the Babinski reflex are typically absent in patients with these tumors. Cervicomedullary tumors originate in the lower medulla and upper cervical spinal cord, which contain the lower CN nuclei (IX to XII), medullary respiratory center, descending motor corticospinal tracts, and ascending sensory tracts. Thus, presenting signs and symptoms of cervicomedullary tumors typically include dysphagia, dysarthria, nausea, vomiting, apnea, FTT in infants, upper motor neuron dysfunction, sensory loss, and torticollis. Unlike in patients with dorsally exophytic tumors, hydrocephalus is unusual and LTS are common in patients with cervicomedullary tumors.

The pons is the largest of the three brainstem components and primarily contains motor tracts destined for the spinal cord and cerebellum. Diffuse intrinsic pontine gliomas may present with a "triad" of clinical signs: CN dysfunction (particularly CN VI and VII), LTS, and ataxia. While these three signs present simultaneously in only about 35% of diffuse pontine glioma patients (Farmer et al. 2001), the majority of patients present with at least one of these cardinal signs. These tumors typically have a short duration of symptoms prior to diagnosis (median of 1 month), and only about 10% of patients present with hydrocephalus at diagnosis (Freeman and Farmer 1998).

3.4.1 Growth Pattern

Many of the BSGs, when subclassified correctly according to clinical presentation and location, have stereotypical growth patterns. The growth and shape of these tumors, especially the benign, slow-growing neoplasms, are strongly influenced by existing anatomical structures. This was first observed by Scherer in 1938, who stated that fiber tracts and pial borders direct the growth of low-grade lesions. Focal midbrain tumors often remain circumscribed within the dorsal area of the midbrain (tegmentum and tectal plate) (Rubin et al. 1998). Diffuse pontine gliomas, in comparison, grow unhindered along the medullary axis both rostrally and caudally, without involving the fourth ventricle (Epstein and Farmer 1993). Unlike low-grade tumors, the expansion of a high-grade tumor is not contained or controlled by the surrounding tissue matrix.

Dorsally exophytic tumors originate within the substance of the medulla. Initially, the lesion causes

focal swelling of the medulla and displaces the axially-oriented fiber tracts. Because of rostral and caudal anatomic barriers, the tumor grows toward the avenue of least resistance, which in this region is the floor of the fourth ventricle, thus becoming dorsally exophytic (Fig. 3.1) (Epstein and Farmer 1993).

Cervicomedullary tumors originate within the upper cervical cord below the cervicomedullary barrier. Caudal growth is limited by the circumferential pia of the upper cord and follows a cylindrical shape, similar to spinal cord tumors. Rostral growth is limited by the crossing fibers of the low medulla, and thus directs the growth toward the least resistant area, the obex, which is the midline point of the dorsal medulla that marks the caudal angle of the fourth ventricle (Fig. 3.2) (Epstein and Farmer 1993). From there the tumor may rupture through the obex into the fourth ventricle and cause obstructive hydrocephalus.

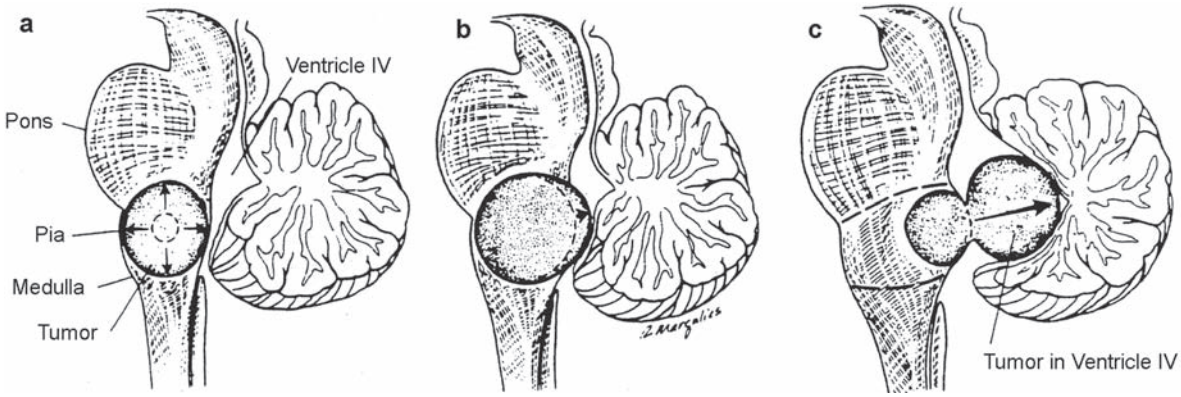
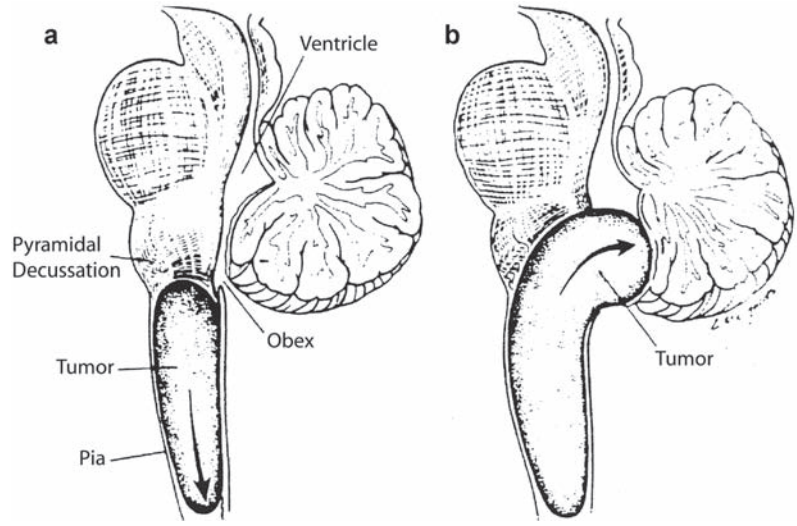


Figure 3.1

(**a–c**) Illustrations of growth patterns of benign medullary tumors. (**a**) Focal medullary tumor displaces axially oriented fibers as it grows (*arrows*). (**b**) Larger focal medullary tumor tends to grow subependymally (*arrowhead*) because its axial growth is limited by barriers. (**c**) Subependymal lesion becomes dorsally exophytic (*arrow*) because of the limited resistance to growth offered by the ependyma. (Reprinted with permission from Epstein and Farmer 1993)

Figure 3.2

(**a, b**) Illustrations of growth patterns of cervicomedullary lesions. (**a**) Caudal growth is cylindrical, as for spinal cord tumors (*arrow*). (**b**) Rostral growth is directed toward the obex (*arrow*) as a result of hindrance from pial elements and decussating fibers. (Reprinted with permission from Epstein and Farmer 1993)



3.4.2 Prognostic Factors

A number of studies have addressed the question of which factors are predictive for prognosis. Albright et al. found that early presentation of CN palsies and presence of mitoses on histologic examination were statistically significant negative prognostic factors, whereas calcification or Rosenthal fibers in the tumor histology were significantly favorable prognostic factors (Albright et al. 1986). Other studies have also found a significant correlation of early CN involvement with poor outcome. Other features associated with poor outcome include the presence of LTS (Freeman et al. 1993), young age (less than 3 years) (Broniscer et al. 2008), and short duration of signs and symptoms prior to diagnosis (Panitch and Berg 1970). Favorable outcome is associated with older age, absence of CN and LTS at presentation, longer duration of signs and symptoms, and neurofibromatosis type 1 (Kaplan et al. 1996). It is not clear why CN and LTS portend poor outcomes, but they may reflect the aggressive behavior of high-grade gliomas.

3.5 Diagnosis and Imaging

3.5.1 Computed Tomography and Magnetic Resonance Imaging

High-quality neuroimaging, specifically MRI, is the diagnostic tool of choice for BSGs. On computed tomography (CT) scans, diffuse intrinsic tumors are iso- or hypodense and enhance poorly after contrast administration. If a posterior fossa lesion is suspected, an MRI scan is mandatory; for most cases of diffuse intrinsic pontine glioma, diagnosis and prognosis is determined from appearance on MRI scans alone. On MRI, diffuse pontine gliomas are usually hypointense on T1-weighted and hyperintense on T2-weighted images (Fig. 3.3). Most do not enhance significantly with gadolinium, although some may exhibit heterogeneous enhancement. The differential diagnosis of a diffuse intrinsic pontine mass on MRI includes malignant nonglial tumors (e.g., ependymomas or primitive neuroectodermal tumors), nonmalignant tumors (e.g., gangliogliomas, hamartomas), infarction, infection, and demyelination.

Focal midbrain tumors are also iso- or hypointense on T1-weighted images and hyperintense on T2-weighted images (Fig. 3.4). Lesions that exclusively involve the midbrain tectum rarely enhance with gadolinium (Robertson et al. 1995; Bowers et al. 2000), whereas peritectal and tegmental tumors more frequently demonstrate enhancement (Robertson et al. 1995). Ventriculomegaly secondary to obstructive hydrocephalus can also be readily discerned on MRI.

Dorsally exophytic tumors appear as sharply demarcated hypointense lesions on T1-weighted images and are hyperintense on T2-weighted images (Fig. 3.5). Unlike the other BSGs, bright uniform enhancement and hydrocephalus are commonly noted findings (Khatib et al. 1994). Cervicomedullary tumors appear as solid masses within the lower medulla and upper cervical cord that frequently extend into the fourth ventricle. Like the other BSGs, they are hypointense on T1-weighted and hyperintense on T2-weighted images. They often enhance homogeneously with gadolinium (Fig. 3.6).

With the development of MR imaging, BSG subtypes could be classified by various imaging criteria. Barkovich et al. retrospectively reviewed 87 pediatric patients with BSG and noted several statistically significant prognostic factors for poor outcome, including location primarily in the pons (as opposed to the midbrain or medulla), moderate to severe brainstem enlargement, and diffuse infiltration. Focal lesions and tumors with identifiable cysts had favorable outcomes; tumor necrosis and hydrocephalus had no prognostic significance (Barkovich et al. 1990). In their review, Moghrabi et al. found that the presence of MRI enhancement of BSG gave no statistically significant prognostic information (Moghrabi et al. 1995). The value of contrast enhancement lies in the follow-up of BSG patients, as new-onset or significantly increased contrast enhancement may indicate tumor progression, particularly if noted prior to radiotherapy.

Functional MR imaging now plays an increasingly prominent role in monitoring disease burden and response to therapy. After radiotherapy, children with diffuse intrinsic pontine gliomas are followed with sequential MRI. However, since MRI changes do

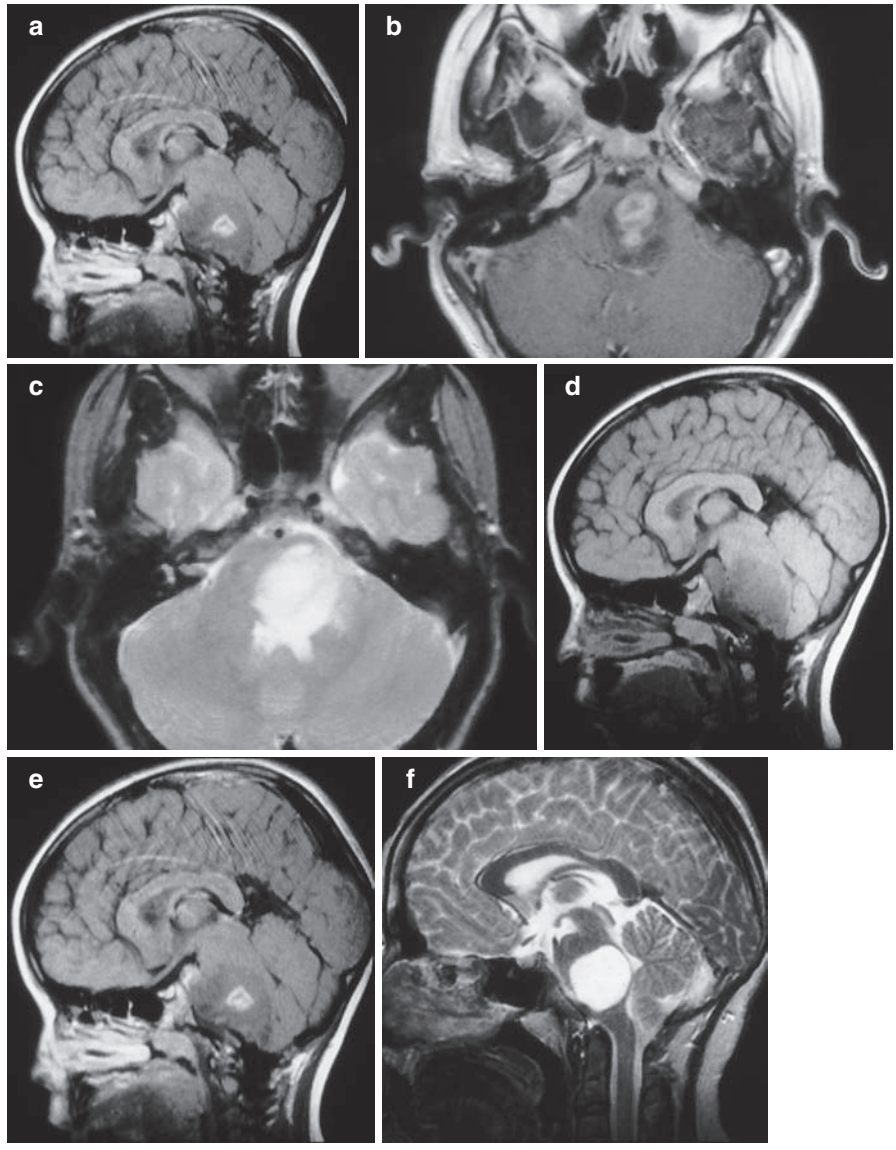


Figure 3.3

(**a**–**f**) Magnetic resonance (MR) images of diffuse pontine gliomas. (**a**) Axial T1-weighted image without contrast. The lesion is slightly hypointense compared with the normal pons. (**b**) Axial T1-weighted image following gadolinium administration. An irregular area of enhancement is seen with a hypointense center. (**c**) An axial T2-weighted image: the lesion is hyperintense, demonstrating the large area of involvement. (**d**) Sagittal T1-weighted image without contrast: the lesion is hypointense and expands the pons. (**e**) The same image as (**d**) following contrast. There is a small central area that enhances brightly with gadolinium. (**f**) Sagittal T2-weighted image: note the striking hyperintensity of the lesion and the expansion of the pons

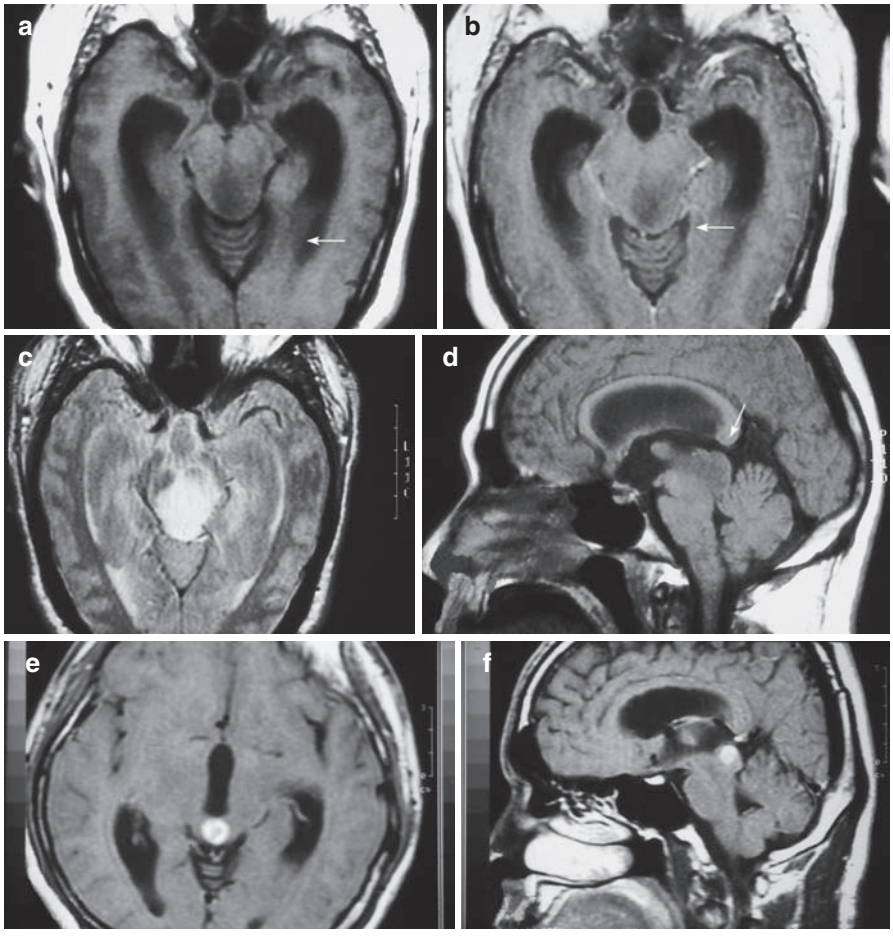


Figure 3.4

(**a–f**) Magnetic resonance (MR) images of tectal gliomas. (**a**) Axial T1-weighted image without contrast: the lesion is small, well-circumscribed, and produces no edema. (**b**) Axial T1-weighted image following contrast: note the lack of enhancement. (**c**) Axial proton density image: the lesion is notably hyperintense, which contrasts with the hypointense signal of the lesion on T1-weighted precontrast images. (**d**) Sagittal T1-weighted image without contrast: the lesion is hypointense and does not produce significant edema. (**e**) Axial T1-weighted image following contrast: this tectal glioma exhibits obvious contrast enhancement, illustrating the enhancement variability of tectal gliomas. (**f**) Sagittal T1-weighted image following contrast: the lesion is well-circumscribed and enhances brightly, which contrasts with the lesion noted in image (**b**)

not necessarily reflect tumor progression, additional noninvasive tools are now in development to improve the definition of progression vs. treatment-related changes (Laprie et al. 2005). Longitudinal multi-voxel magnetic resonance spectroscopy imaging (MRSI) measurements, for example, have potential value in assessing response to radiation or other therapies, because they offer more coverage than single-voxel techniques and provide reliable spectral data (Fig. 3.7).

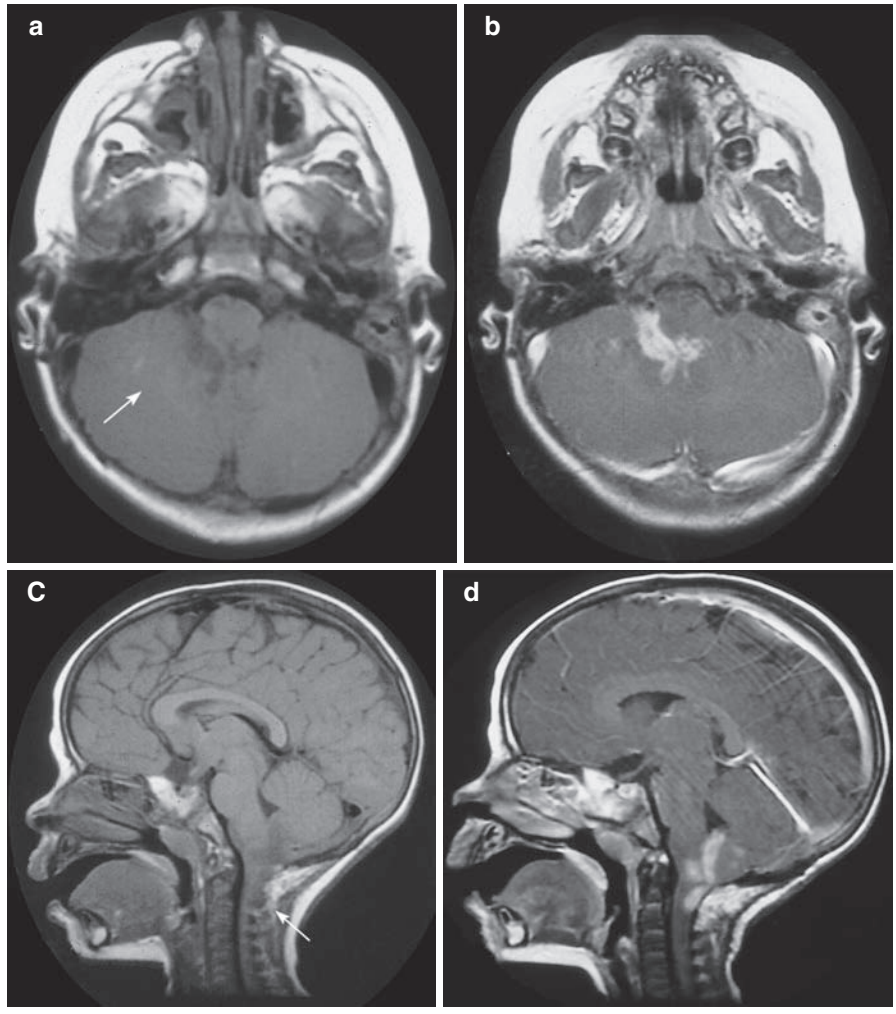


Figure 3.5

(**a–d**) Magnetic resonance (MR) images of dorsally exophytic tumors. (**a**) Axial T1-weighted image without contrast: the lesion arises from the medulla and is hypointense on T1-weighted images. (**b**) Axial T1-weighted image with contrast: the lesion enhances brightly with contrast, which is a typical characteristic for dorsally exophytic tumors. (**c**) Sagittal T1- weighted image without contrast: the lesion does not invade the intrinsic tissue of the lower brainstem. (**d**) Sagittal T1-weighted with contrast: the enhancing lesion extrinsically involves the posterior upper cervical cord, medulla, and fourth ventricle

3.5.2 Role of Diagnostic Biopsy for Diffuse Pontine Glioma

The issue of whether or not to biopsy a diffuse brainstem lesion has been a subject of controversy (Leach et al. 2008; Teo and Siu 2008; Wilkinson and Harris 2008). Prior to the general availability of MRI, brainstem biopsies were performed to confirm the diagnosis of a neoplasm and identify the histologic grade, thereby contributing to prognosis and formulation

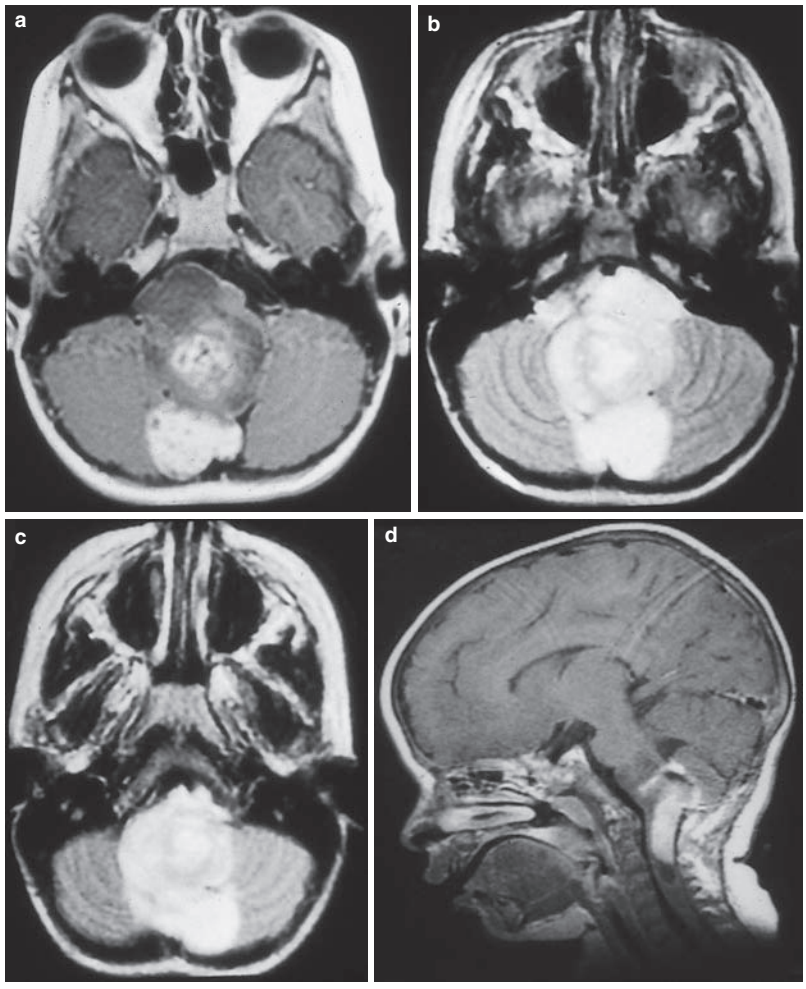


Figure 3.6

Magnetic resonance (MR) images of cervicomedullary tumors. (**a**) Axial T1-weighted image with contrast: the lesion enhances heterogeneously and arises from the upper cervical cord. (**b, c**) Axial proton density images: the lesion is hyperintense. (**d**) Sagittal T1-weighted image following contrast: the lesion bulges dorsally into the fourth ventricle

of a treatment plan. When the MRI scans and clinical features are consistent with diffuse BSG, the diagnostic information obtained from biopsy often has little impact on prognosis (Albright et al. 1993). Additionally, other lesions in the differential diagnosis, such as demyelination or encephalitis, have markedly different clinical and radiographic features than those of diffuse BSGs, and thus often do not require biopsies to distinguish them from BSG. Finally, biopsy of brainstem lesions is subject to sampling error. Cases have been documented where the biopsy revealed a low-grade glioma, yet 1 year later on autopsy the brainstem lesion was noted to be a GBM (Albright et al. 1986).

More recently, however, mounting evidence suggests that considerable pathologic heterogeneity exists among radiographically diagnosed BSGs (Pincus et al. 2006). Although the stereotactic brain biopsy procedure itself is relatively safe (mortality

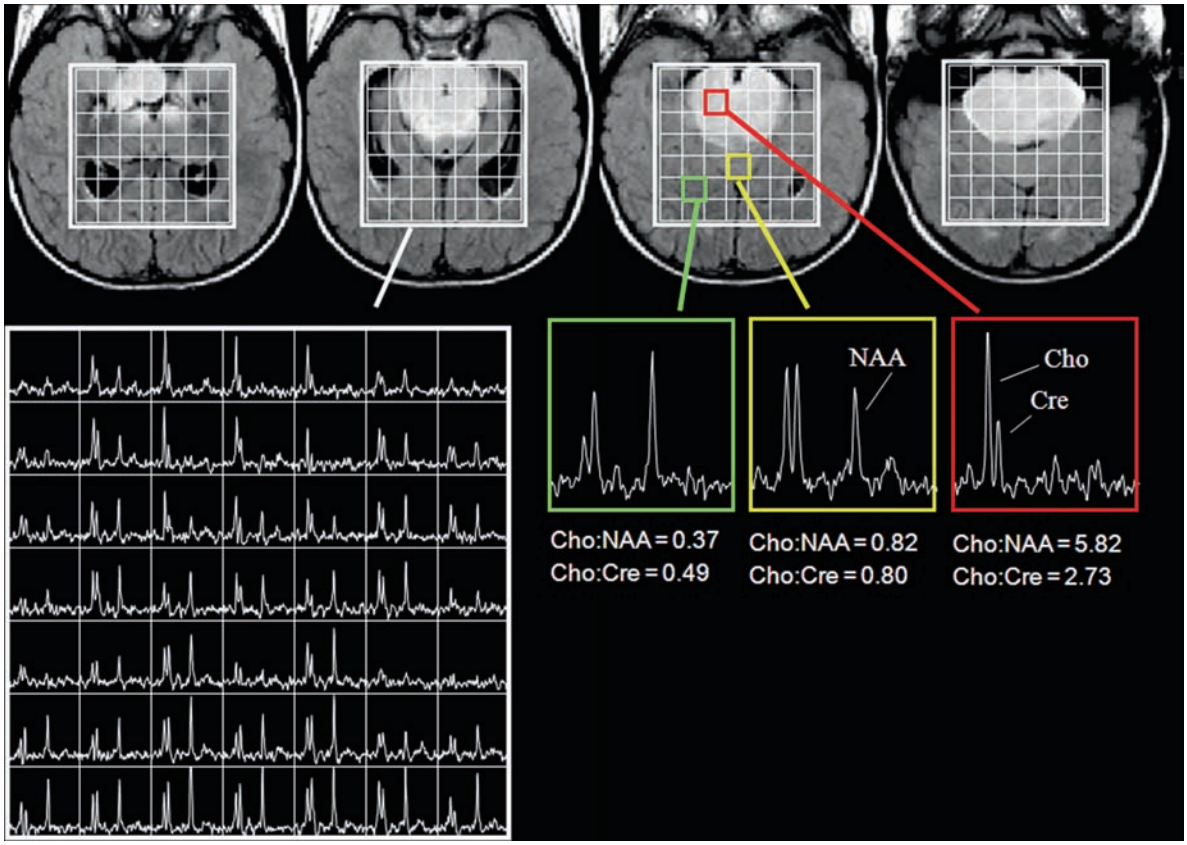


Figure 3.7

High-quality magnetic resonance spectroscopy imaging (MRSI) data that can be acquired from a child with a brainstem glioma. The four MRSI slices cover both the tumor (bright lesion on T2 MRI) and surrounding normal brain. The spectral peaks in each voxel are highly resolved with little or no artifacts. Spectra from tumor (*far right*) are distinguished from normal brain spectra (*far left*) by high choline and low N-acetylaspartate (NAA). Peritumoral spectra (*middle*) show a mixture of both normal and tumor spectral signatures

rate is less than 0.5% and morbidity is approximately 6%), risks still exist, such as hemiplegia, hemorrhage, CN deficits, and the possibility of the biopsy being nondiagnostic (Albright 1996; Sanai et al. 2008). Advances in functional imaging, such as positron emission tomography (PET), may improve the selection of biopsy targets and also reduce the risk of associate morbidity (Pirotte et al. 2007). It is clear that surgical biopsy can be performed with acceptable morbidity. Regardless, the concept of obtaining a histologic diagnosis is currently being revisited, particularly in light of advances in molecular diagnostic techniques and clinical trials requiring a tissue diagnosis.

3.6 Treatment

3.6.1 Radiotherapy

The conventional treatment for BSGs remains fractionated external beam radiotherapy. The standard radiation dose is 54–60 Gray (Gy), or 5,400–6.000 rad, delivered conformally in single, daily fractions of

1.8–2.0 Gy over approximately 6 weeks. Hyperfractionated external beam radiotherapy (HFRT) is a regimen in which total doses of 64 Gy or more are delivered in twice-daily, smaller-dose fractions (e.g., 1 Gy) over 6 weeks (Jennings et al. 1996). HFRT was originally proposed for the treatment of patients with diffuse intrinsic gliomas. However, Mandell et al. conducted a Phase III randomized study demonstrating that there were no statistically significant differences in PFS or overall survival between diffuse pontine glioma patients treated with standard radiation and those treated with HFRT; median time to death was 8.5 months for patients treated with the standard radiation dose and 8 months for those who received HFRT to 70.2 Gy (Mandell et al. 1999). Furthermore, HFRT was reported to cause significant adverse effects in long-term survivors (Freeman et al. 1996). Median survival for untreated diffuse intrinsic glioma patients is approximately 20 weeks (Langmoen et al. 1991). More recently, a hypofractionated regimen, distributed over 3 weeks as opposed to the usual 6, has been proposed as a feasible and safe means of reducing patient burden (Janssens et al. 2009), although this has not been widely accepted as a standard therapy.

3.6.2 Chemotherapy for Diffuse Pontine Glioma

The role of chemotherapy in the management of diffuse intrinsic gliomas is not clear. Numerous chemotherapy regimens have been used to treat recurrent BSG and have not demonstrated significant efficacy. These include PCNU (Allen et al. 1987), cisplatin (Sexauer et al. 1985), topotecan (Blaney et al. 1996), ifosfamide (Heideman et al. 1995), and temozolomide (Broniscer et al. 2005). Chamberlain reported that out of 12 patients with recurrent BSG treated with oral VP-16 (etoposide), 1 patient had a complete response, 3 patients had partial responses, and 2 patients had stable disease; however, 2 of the partial responders were over age 28 (Chamberlain 1993). Trials involving multiagent chemotherapy regimens for recurrent BSG have not produced better outcomes (Pendergrass et al. 1987; Rodriguez et al. 1988; van Eys et al. 1988).

Results from studies of regimens for newly diagnosed BSG patients that involve combining radiotherapy and chemotherapy, either concurrently or sequentially, have been generally underwhelming. Such regimens include radiation with high-dose tamoxifen (Broniscer et al. 2000), HFRT with carboplatin and etoposide concurrently (Walter et al. 1998), radiation followed by high-dose busulfan and thiotepa (Bouffet et al. 2000), concurrent radiation with bradykinin/carboplatin (Packer et al. 2005), etanidazole administered concurrently with hyperfractionated radiation (Marcus et al. 2003), and temozolomide after radiation therapy (Broniscer et al. 2005). The only Phase III trial evaluating chemotherapy in diffuse intrinsic glioma patients involved the randomization of patients to one of two arms: radiotherapy alone vs. radiotherapy with a concurrent chemotherapy regimen of vincristine, CCNU, and prednisone. Overall 5-year survival rate was 17% for patients who received radiotherapy alone and 23% for those who received radiotherapy and chemotherapy. These results were not statistically different, and the median survival was 9 months in both trial arms (Jenkin et al. 1987). Chemotherapy administered concurrently with radiation as a radiosensitizing agent also has not demonstrated benefit – in fact, patients who received cisplatin with HFRT had worse outcomes compared with those who received HFRT alone (Freeman et al. 2000).

Another approach to treating diffuse intrinsic gliomas involves immunotherapy, in which the goal is to heighten the patient's antitumor immune response. The interferons, a widely used class of immunotherapy agents, are glycoproteins that induce the synthesis of specific proteins, regulate immune effector cells, and inhibit mitotic activity (Packer et al. 1996). However, results of clinical trials involving interferons are conflicting. Wakabayashi et al. reported 3 patients with complete responses and 9 patients with partial responses in a group of 16 diffuse intrinsic glioma patients treated with interferon-α, ACNU, and radiation therapy (Wakabayashi et al. 1992). Median survival was 15.7 months, which was notably higher than previously reported survival rates for BSG patients. However, in a Phase I/II study by Packer et al., 30 of 32 diffuse intrinsic glioma patients treated

with escalating doses of interferon-α and HFRT to 72 Gy developed progressive disease at a median of 5 months. Median survival was only approximately 9 months (Packer et al. 1996).

Chemotherapeutic delivery remains a primary challenge in the adjuvant treatment of BSGs. Convection-enhanced delivery is a method currently in development as a means of homogeneously distributing small-molecular-weight and large-molecular-weight substances while bypassing the blood–brain barrier. Recent preclinical studies have also shown that coinfused imaging surrogate tracers can be used to monitor and control the convective distribution of therapeutic agents in vivo (Song and Lonser 2008). This technology may eventually translate into a new therapeutic modality for pediatric BSGs.

Recent clinical trials reflect interest in novel, biologically targeted therapies. Choice of agents has largely been based on evidence of preclinical activity in malignant glioma models. Recently completed trials include Phase I/II trials of the Ras-targeted, farnesyl transferase inhibitor tipifarnib (R115777) and radiation therapy in patients with newly diagnosed nondisseminated diffuse BSGs. Although the drug was well tolerated, preliminary Phase II results show no survival benefit (Haas-Kogan et al. 2008). Similarly, the EGFR inhibitor gefitinib and the platelet-derived growth factor receptor (PDGFR) inhibitor imatinib were well tolerated, but preliminary survival results were disappointing (Geyer et al. 2004; Pollack et al. 2007). Radiosensitizing strategies are also under investigation. Motexafin gadolinium (MGd) is an expanded metalloporphyrin that localizes in tumors with minimal normal tissue incorporation. In preclinical models, MGd has a radiation sensitizer enhancement ratio of approximately 2, primarily through depletion of repair enzymes, including thioredoxin reductase. In a Phase I trial, the combination of MGd administered on a Monday-to-Friday regimen at a daily dose of 4.4 mg/kg with 54 Gy radiation therapy over a 6-week period was relatively well tolerated in children with newly diagnosed BSGs (Bradley et al. 2008). Further analysis of the correlation of tumor uptake to local control and outcome will be performed in the Phase II study. The Children's Oncology Group recently completed accrual to a trial using topotecan as a radiosensitizer. Among several other important trials still underway (Hargrave et al. 2006), an examination of the VEGF inhibitor bevacizumab is ongoing.

Currently, there is little evidence to suggest that any standard chemotherapy agent or multiagent regimen has a significant impact on the outcome of pediatric patients with diffuse intrinsic gliomas. Thus, the standard of care for newly diagnosed diffuse intrinsic gliomas is conventional radiotherapy. Chemotherapy should be reserved for cases involving tumor progression. Whenever possible, patients should be given the option for enrollment into clinical research trials. Given the dismal prognosis, any treatment developed in the future that exhibits a modestly significant benefit will have a tremendous impact on the outcome of this patient group.

3.6.3 Surgery and Adjunctive Treatment for Nondiffuse Tumors

Focal midbrain tumors often have an indolent course reflective of their benign pathology and favorable prognosis (Robertson et al. 1995; Bowers et al. 2000). Small tectal tumors can be followed by serial MRI scans, while hydrocephalus can be alleviated with CSF diversion by a shunt or third ventriculostomy. Often, these tectal gliomas will remain unchanged for many years. With tumor progression, surgery is indicated to obtain tissue for diagnosis and potentially achieve a gross total resection. If a tumor happens to be surgically accessible, then gross total resection may be attempted, although the difficult location of these tumors usually precludes complete excision. Tegmental and other nontectal midbrain tumors tend to be larger and more frequently cause signs and symptoms of brainstem involvement (Robertson et al. 1995). Surgery is indicated for these midbrain tumors, and debulking or resection often leads to neurologic improvement (Pendl et al. 1990; Vandertop et al. 1992). The role of radiotherapy has not been definitively outlined, but is often used for progressive tumors not amenable to resection. Although no chemotherapy regimen has been shown to have any meaningful impact on survival in this patient subgroup, some clinicians consider it an option as

a radiation-delaying strategy in young patients with progressive or recurrent disease following surgery.

Surgery is also the treatment of choice for dorsally exophytic tumors. Despite that an optimal resection may still leave a thin layer of tumor on the floor of the fourth ventricle, several series have noted excellent results for most of these patients (Pollack et al. 1993; Khatib et al. 1994). Although routine postoperative adjuvant treatment is not indicated, the minority of patients whose tumors recurred after initial resection were noted to have their tumors controlled with repeat resections and radiotherapy (Pollack et al. 1993). Radiation should be considered for patients with high-grade tumors or for those whose tumors progress within a short time frame postoperatively (Freeman and Farmer 1998). An increasing number of pediatric patients are being treated with chemotherapy for symptomatic and recurrent low-grade tumors. Regimens include carboplatin plus vincristine, and nitrosourea-containing multiagent chemotherapy drugs. There is increasing interest in the role of antiangiogenic therapies and biologically targeted therapies for this group of low-grade gliomas. A Pediatric Brain Tumor Consortium clinical trial investigating the use of bevacizumab with irinotecan for low-grade glioma is ongoing.

Like other nondiffuse BSGs, cervicomedullary tumors are mostly of low-grade histology and associated with a favorable prognosis (Epstein and Wisoff 1987; Weiner et al. 1997). Conceptually, they should be regarded as intramedullary spinal cord tumors (Robertson et al. 1994). Thus, surgery is the mainstay of treatment when symptoms of progression arise and, if possible, should be performed prior to the occurrence of significant neurologic disability. Most of these tumors have long antecedent presentations (18–24 months) and have very slow-developing symptomatic progression (Jennings et al. 1996). Initially, asymptomatic or stable patients may be followed clinically and radiographically. If residual disease is present within the medulla or upper cervical spinal cord, careful observation is probably warranted. Routine adjuvant chemotherapy or radiotherapy is typically reserved for progressive or recurrent disease not amenable to resection. However, these treatment modalities may be used to manage the small proportion of high-grade cervicomedullary tumors, which should be treated as if they were diffuse intrinsic gliomas.

3.7 Conclusion

BSGs are a heterogeneous group of neoplasms with dissimilar natural histories and prognoses. Distinct tumor subtypes and growth patterns exist that are classified according to location within the brainstem, clinical presentation, suspected histology, and radiographic appearance. They are subdivided into diffuse intrinsic gliomas, which originate primarily in the pons and have a dismal prognosis, and the nondiffuse BSGs, of which the overwhelming majority are low-grade in histology and have more favorable outcomes. While diagnosis and management strategies for these lesions have traditionally been made on the basis of noninvasive methods – careful clinical history, physical examination, and MRI characteristics – mounting evidence supports the utility of histologic diagnosis. However, in the setting of classic neuroradiologic and clinical findings, routine biopsy for diagnosis remains typically not indicated. Developing effective treatments for diffuse intrinsic gliomas has been especially frustrating, as their infiltrative nature and brainstem location precludes surgical debulking, and chemotherapeutic agents have not demonstrated significant efficacy against them. Conventional conformal radiotherapy is the mainstay of treatment for diffuse intrinsic gliomas, while surgical resection is the treatment of choice for symptomatic or recurrent nondiffuse BSG. Radiotherapy and chemotherapy for nondiffuse BSG are reserved for recurrent or high-grade neoplasms.

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Ependymoma

Matthew D. Smyth • Joshua Rubin

Contents

4.1 Epidemiology

4.1.1 Incidence

Ependymomas are gliomas that appear to originate from the lineage of cells that give rise to the differentiated ependymal cell layer lining the ventricular system and central canal of the spinal cord. Intracranial ependymomas comprise approximately 9% of all brain tumors in patients under 20 years of age, and are the third most common primary brain tumor in children (following astrocytomas and primitive neuroectodermal tumors). Data from the SEER group (Surveillance, Spidemiology, and End Results) suggest that the annual incidence of ependymoma is 2.6 per million for the 0–14 age group, and 2.2 per million for the 0–20 age group (Linet et al. 1999; Ries et al. 1999). The Connecticut Tumor Registry reports that between 1935 and 1973, 5 spinal cord ependymomas and 44 intracranial ependymomas were identified in the Connecticut population under 20 years of age, suggesting that spinal cord ependymoma represents approximately 10% of all ependymal tumors in children and young adults (Dohrmann et al. 1976). Another large institutional series confirmed that spinal cord ependymomas are rare in children under 10 years, comprising less than 1% of all spinal tumors. After the age of 10, the incidence of spinal cord ependymoma increases and it represents the majority of intramedullary tumors in patients older than 20 years (Constantini et al. 1997).

4.1.2 Age and Sex Distribution

The incidence of intracranial ependymoma peaks in the 0–4 age group (5.2 cases per million) and

decreases thereafter to 1.5 per million in the 5–14 age group, and 0.9 per million in the 15–19 age group. Ependymomas are twice as common in males than in females. The average annual incidence is 3 per million in males and 1.5 per million in females (Linet et al. 1999; Ries et al. 1999).

4.1.3 Environmental and Viral Causes

The etiology of ependymoma formation remains obscure. In most epidemiologic studies, ependymomas are grouped with other brain tumors, thus making it impossible to identify risk factors that are specific for ependymoma. The role of polyomaviruses in the etiology of ependymoma has been well-studied. From 1955 to 1963, pools of poliovirus and adenovirus vaccines were contaminated with simian virus 40 (SV40), raising concern about possible increases in overall cancer incidence and increases in the incidence of rare tumors such as ependymoma and choroid plexus papilloma in patients inoculated with contaminated vaccines (Carbone et al. 1997).

SV40 is able to transform cells from different species, including normal human cells, into cells with a neoplastic phenotype. In one animal model, the intracerebral inoculation of rodents with SV40 induces ependymoma (Kirschstein and Gerger 1962). The transforming ability of SV40 depends on the expression of the early region gene product, large tumor antigen (Tag), which inactivates tumor-suppressor genes such as *p53*, *pRb*, *p107*, *p130*, *p300*, and *p400* (Zhen et al. 1999). The SV40 genome can be detected in a majority of ependymomas and choroid plexus carcinomas, and also in astrocytoma, meningioma, glioblastoma multiforme, and medulloblastoma (Bergsagel et al. 1992; Martini et al. 1996). Normal brain tissue is negative for SV40 Tag. Inactivation of *p53*, *pRb*, and other possible tumor supressor genes may be a mechanism in the pathogenesis of brain tumors (Zhen et al. 1999). However, large epidemiologic studies that evaluated the incidence of neoplasms in patients inoculated with contaminated vaccines, with follow-up ranging from 17 to 30 years, did not detect an increased overall incidence of ependymoma or other neoplasms (Strickler et al. 1998).

4.1.4 Genetic Predisposition

Neurofibromatosis type 2 (NF2) is the only known genetic disorder associated with a predisposition for developing ependymoma. Patients with NF2 typically develop intramedullary spinal tumors (Lee et al. 1996). NF2 mutations have been found in 25–70% of patients with sporadic intraspinal ependymomas. No NF2 mutations were found in patients with ependymomas of other locations (Birch et al. 1996; Lamszus et al. 2001). Although familial intracranial ependymoma is very rare, in a family in which four cousins developed ependymoma, a suspected tumor-suppressor gene locus was located by a segregation analysis to chromosome region 22pter-22q11.2 (Hulsebos et al. 1999). Although there is a case report of a child with a germline mutation in the *p53* gene and intracracranial ependymoma, ependymoma is usually not considered one of the cancers of the Li–Fraumeni syndrome (Hamilton and Pollack 1997).

One large population study indicated that parents of children with ependymoma might be at an increased risk of colon cancer (relative risk 3.7) (Hemminki et al. 2000). However, another large study did not identify increased risk of any cancer in families of children with brain tumors (Gold et al. 1994).

4.2 Pathology

4.2.1 Histopathology

Ependymomas arise from ependymal epithelium that lines the ventricles of the brain and central canal of the spinal cord. Therefore, the most common sites for this tumor are the fourth, third, and lateral ventricles and the lumbosacral spinal cord. Ependymomas are usually well-demarcated tumors that often display areas of calcification, hemorrhage, and cysts. Ependymomas vary from well-differentiated tumors with no anaplasia and little polymorphism to highly cellular lesions with significant anaplasia, mitotic activity, and necrosis that may resemble glioblastoma multiforme. The World Health Organization (WHO) classification of brain tumors (Louis et al. 2007) distinguishes three grades of ependymoma. Two histological entities are considered as WHO grade I

ependymoma: subependymoma and myxopapillary ependymoma.

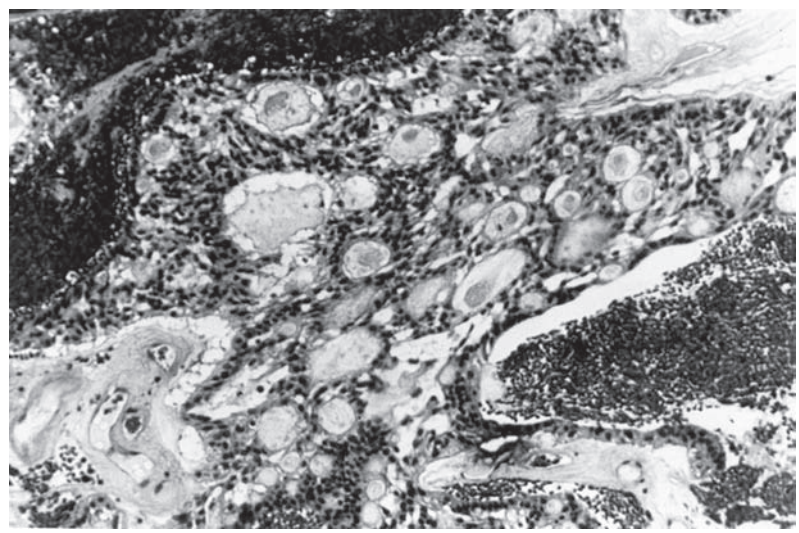
Subependymoma is a rare tumor usually located in the wall of the ventricular system. Histologically, subependymomas are characterized by clustering of monomorphic cells arranged against a fibrillary background, frequently showing the presence of focal cystic degeneration, vascular hyalinization, hemosiderin deposition, and calcifications. Subependymomas usually show strong immunopositivity for glial fibrillary acidic protein (GFAP) and S-100 antigens. Compared to other ependymal tumors, subependymomas have the lowest rate of cell proliferation, as demonstrated by MIB-1 immunostaining (Prayson and Suh 1999). Subependymomas do not show any cytogenetic changes and are considered to be hamartomatous lesions by many authors (Debiec-Rychter et al. 2000). Most subependymomas are incidental tumors discovered at autopsy, but may grow large enough to be symptomatic. Following surgical resection, these tumors rarely recur, and the long-term prognosis is excellent.

Myxopapillary ependymoma is found almost exclusively in the region of the cauda equina where it originates from the filum terminale. Myxopapillary ependymomas are slow-growing tumors that may eventually erode into the adjacent bone and soft tissues. Grossly, myxopapillary ependymomas appear as well-circumscribed masses that typically occur within the filum terminale. The microscopic features are reminiscent of the normal filum terminale. Cuboidal to columnar cells, sometimes with clear cytoplasm are arranged in a perivascular papillary pattern around central cores whose stroma is comprised of connective tissue and blood vessels (Fig. 4.1) (Louis et al. 2007). Although rare, myxopapillary ependymoma can spread along the central nervous system (CNS) axis (Woesler et al. 1998; Smyth et al. 2000), or occur outside the CNS in ectopic sites such as the sacrum and presacral tissues, where embryonically derived ependymal rests may be found (Ciraldo et al. 1986).

WHO grade II ependymomas are usually solid and well-demarcated, with limited infiltration of surrounding structures. Histological hallmarks include perivascular pseudorosettes, which consist of neoplastic cells encircling a blood vessel with cytoplasmic processes extending between their nuclei and the vessel wall (Fig. 4.2). Less commonly, true ependymal rosettes may form, which consist of neoplastic cells forming a central space reminiscent of ependymal canals. Grade II ependymomas are moderately cellular with low mitotic activity, but may demonstrate nuclear atypia, occasional mitoses, and foci of necrosis and calcification.

Figure 4.1

Myxopapillary ependymoma, WHO grade I, demonstrates cuboidal to elongated tumor cells arranged in a perivascular papillary pattern around central cores of mucinous perivascular stroma



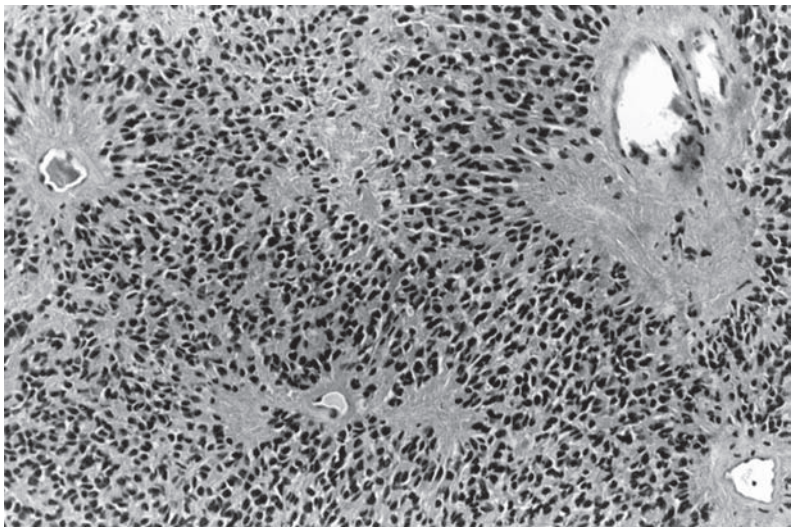


Figure 4.2
Ependymoma, WHO grade II, demonstrates moderate cellularity with low mitotic activity and pseudorosettes (neoplastic cells around a blood vessel with their cytoplasmic processes running between their nuclei and the vessel wall)

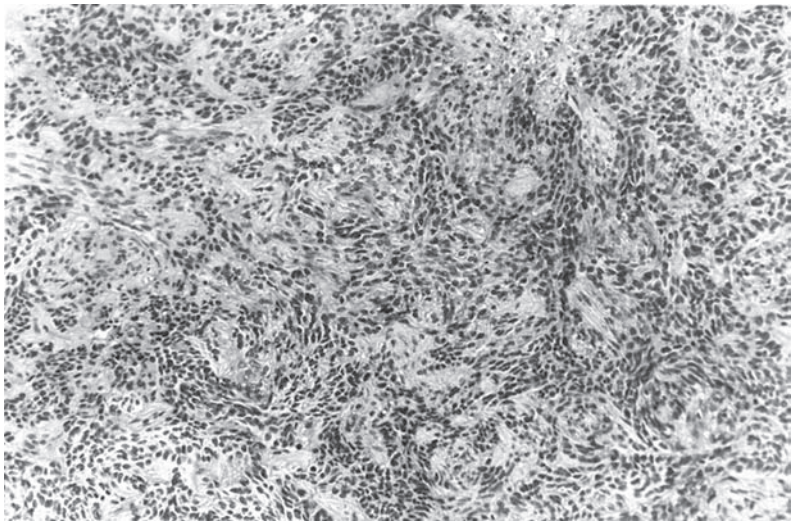


Figure 4.3
Ependymoma, WHO grade II, demonstrates high cellularity, nuclear atypia, and mitotic activity

Three subtypes of grade II ependymomas are described: (a) cellular ependymoma, a variant with conspicuous cellularity, but often less prominent pseudorosette or rosette formation; (b) papillary ependymoma, which histologically mimics the pattern of choroid plexus papilloma; and (c) clear cell ependymoma, which consists of cells with swollen, clear cytoplasm, and well-defined plasma membranes (Louis et al. 2007).

WHO grade III anaplastic (malignant) ependymoma has histological evidence of anaplasia, including high cellularity, variable nuclear atypia and hyperchromatism, and marked mitotic activity (Fig. 4.3). Vascular proliferation is often prominent, and necrosis may be widespread (Louis et al. 2007).

Ependymoblastomas are highly malignant rare tumors of embryonic origin that consist of elements

resembling primitive embryonic ependymal cells. Despite their name, these tumors are not ependymal tumors, but highly malignant primitive neuroectodermal tumors.

There is discordance among neuropathologists over the diagnosing and grading of ependymomas. The rate of misclassification can be as high as 69% (Robertson et al. 1998), and the criteria for distinction between grades II and III are not highly reproducible. Many studies, even with central review, could not confirm the correlation between histology and patients' outcomes (Ross and Rubinstein 1989; Schiffer et al. 1991; Perilongo et al. 1997; Robertson et al. 1998).

Immunohistochemistry may be difficult to interpret in ependymomas, and does not appear to add useful information to conventional histological examination. Most ependymomas express GFAP, while the expression of other antigens, such as epithelial membrane antigen (EMA), varies. Vimentin is usually found in perivascular pseudorosette expression. In a study of 22 patients with ependymoma, a DNA index did not correlate with outcomes or histology (Reyes-Mugica et al. 1994).

Electron microscopy can be useful in establishing the diagnosis of ependymoma when there is atypical appearance under light microscopy. The normal ependymoma cell bears microvilli and cilia on its apical surface (Sara et al. 1994). True rosettes are found in more than 90% of cases, while they are present in only 30–40% of cases by light microscopy. However, there are no ultrastructural features that would differentiate low-grade from anaplastic ependymomas.

4.2.2 Genetics and Molecular Biology

Genomic analyses of ependymoma have established several characteristic location- and grade-specific differences in tumor karyotype and gene expression. These studies demonstrate that recurrent chromosomal aberrations and altered expression in a relatively small number of genes can distinguish intracranial from spinal cord ependymomas, and in some cases, supratentorial from posterior fossa tumors (Table 4.1). Several of these genetic events have prognostic significance.

Table 4.1. Most frequent genetic aberrations in pediatric ependymoma, using comparative genomic hybridization

Study	Number	Chromosomal losses and frequency		Chromosomal gains and frequency	
Reardon et al. 1999	22 (intracranial)	Xy 6q 22q	6/22 4/22 4/22	1q 9	4/22 3/22
Ward et al. 2001	40 (intracranial)	22 16p 17q 20q	10/40 5/40 5/40 5/40	1q 4q 7q 6q 7p	8/40 7/40 6/40 5/40 5/40
Hirose et al. 2001	14 (intracranial) 9 (spinal cord)	9 6q 22q 1,2,10 22q	5/14 2/14 2/14 2/9 2/9	1q 7 9 20	4/14 9/9 8/9 4/9
Scheil et al. 2001	9 (intracranial)	No pattern identified		1q 17	4/9 3/9
Zheng et al. 2000	7 (intracranial)	22q 16 20q	5/8 5/8 4/8	13q 21q	3/8 2/8

Numerous chromosomal abnormalities have been described in ependymomas, including gains involving chromosomes 1, 5, 7, 9, and 12 and losses involving chromosomes 6, 9, 10, 11, 13, 17, and 22 (Modena et al. 2006; de Bont et al. 2008). Loss of chromosome 22, including monosomy 22, is the most common chromosomal abnormality in ependymoma and occurs most frequently in adults with spinal cord tumors (Park et al. 1996). While the *NF2* gene is located on chromosome 22 and there is an increased incidence of ependymoma in patients with *NF2*, the regions involved in allelic losses of chromosome 22 (22q) are distinguished from the *NF2* locus (Rubio et al. 1994). Chromosome 7 gains are more commonly found in spinal cord tumors (Jeuken et al. 2002). In contrast, gains of chromosome 1q are more common in children, especially in high-grade intracranial lesions (Hirose et al. 2001; Mendrzyk et al. 2006). Gains of chromosomes 12q and losses of 6q and 13 are also more characteristic of intracranial ependymomas (Hirose et al. 2001; Jeuken et al. 2002).

A number of candidate oncogenes and tumor-suppressor genes are localized to regions of gains and losses, respectively. The region of chromosome 22q loss involves several candidate tumor-suppressor genes, including CBX7 (Suarez-Merino et al. 2005). CBX7 is involved in silencing the p16/p14 locus, which is predicted to inactivate Rb and p53 providing dysregulated cell-cycle progression and loss of apoptotic responses. Gains of chromosome 5 involve the hTERT gene, the expression of which has negative prognostic significance (Rushing et al. 1997; Mendrzyk et al. 2006).

Gene array analyses of ependymomas also reveal region-specific recapitulation of developmental pathway activation. For example, targets of EPHRIN and Notch signaling are involved in the formation of the cortical subventrivular zone, and are also upregulated in supratentorial ependymomas (Conover et al. 2000; Hitoshi et al. 2002). Similarly, *HOX* gene expression is increased in spinal ependymoma, consistent with the high level of *HOX* expression during spine development (Taylor et al. 2005).

While the application of genomic analyses to clinical practices is not yet routine, several studies suggest that these techniques can be used for risk-stratification at the time of diagnosis. Gain of 1q25 was independently correlated with recurrence-free and overall survival in pediatric patients with grade III intracranial ependymoma (Mendrzyk et al. 2006). In addition, amplification of the epidermal growth factor receptor (EGFR)at 7p11.2 with increased EGFR protein overexpression was correlated with poor prognosis in WHO grade II ependymoma (Mendrzyk et al. 2006). Reduced expression of *NF-κB2* and *pleckstrin*, together with overexpression of LOC374491 a PTEN pseudogene, was associated with recurrent ependymoma in children (Sowar et al. 2006). Finally, Gilbertson and colleagues observed increased expression of *ErbB2* and *ErbB4* in 75% of ependymoma specimens studied, with a high level of coexpression that correlated with increased proliferative activity. These results suggest that Erb may be a relevant therapeutic target in ependymoma (Gilbertson et al. 2002).

Expression studies have also supported novel insights into the cell of origin of ependymoma. Within freshly isolated ependymoma specimens is a small fraction of cells that appear to possess tumor-initiating properties (Taylor et al. 2005). These cells, called "tumor stem cells" or "tumor-initiating cells," are distinguished from the bulk of the tumor mass by their expression of several phenotypic markers, including CD133 (Prominin) and nestin (Uchida et al. 2000; Singh et al. 2003). Tumor-initiating cells from primary ependymoma specimens expressed CD133 like other neural-stem cells, but also expressed brain-lipid binding protein (BLBP), suggesting that they were derived from radial glial cells. Radial glial cells are the normal multipotent precursors of neurons and glia. Significantly, the ependymoma-initiating cell phenotype was distinguished from the tumor-initiating cells derived from medulloblastoma, which expressed CD133, but not BLBP. These observations suggest that ependymomas derive from a primitive stage of ependymal development.

In sum, genomic techniques provide an insight into the heterogeneity of ependymoma. These studies have the potential to advance our understanding of ependymoma biology and our ability to improve outcomes by both identifying high-risk patients and by supporting improved biologically based stratification for clinical-trial enrollment.

4.3 Clinical Features

Ninety percent of all ependymomas in children occur in the brain, whereas only 10% are located in the spinal cord (Dohrmann et al. 1976). One third of intracranial ependymomas occur in a supratentorial location while two thirds are infratentorial. Approximately 35% of patients have WHO grade III histology at diagnosis. Seven to fifteen percent of patients with ependymoma have disseminated disease at diagnosis (Perilongo et al. 1997; Robertson et al. 1998). Supratentorial ependymomas grow as intraparenchymal tumors, typically adjacent to the lateral ventricles. Infratentorial ependymomas arise from the fourth ventricle and typically invade adjacent structures or extend into the aqueduct of Sylvius, foramen of Magendie, foramen of Luschka, or to the upper cervical cord. Extraneural ependymomas have been rarely described, usually after progression of intracranial disease. The sites of extraneural spread include peritoneum, lymph nodes, lungs, pleura, bone, and liver (Newton et al. 1992). Chang's staging system for posterior fossa tumors (Table 4.2) can be applied to categorize ependymomas, although this is less commonly used in clinical practice.

Posterior fossa ependymomas typically present with signs and symptoms of obstructive hydrocephalus including vomiting, headache, and ataxia (Ilgren et al. 1984; Nazar et al. 1990). Infiltration into the brainstem and growth through the foramina of Luschka or central canal may result in cranial nerve palsies, torticollis, or meningismus. Children less than two years of age tend to present with nonspecific signs such as irritability, vomiting, lethargy, macrocephaly, or gait disturbance (Nazar et al. 1990). The duration of symptoms is usually less than 6 months at the time of diagnosis (Coulon and Till 1977), with 50% of children presenting with duration of symptoms of 1 month or less (Horn et al. 1999). Symptoms of spinal cord ependymoma from an adult series included pain in 75% of patients, sensory changes in 71%, and weakness in 68%. The average duration of symptoms was 13 months prior to diagnosis (Waldron et al. 1993). Ependymomas of the cauda equina present with limited spinal motion in 50% of patients, paravertebral spasm in 32%, and motor deficits and abolition of reflexes in 34% of patients (Wager et al. 2000).

4.4 Natural History and Risk Factors

In a small retrospective series of 11 untreated intracranial ependymomas, all patients died within 3 years

Table 4.2. Modified Chang's staging system for posterior fossa tumors

		Definition
Tumor	T1	Tumor confined to the fourth ventricle
	T2	Tumor of the fourth ventricle with contiguous extension inferiorly through the foramen Magendie and extending to the upper cervical canal
	T3	Tumor of the fourth ventricle with lateral extension through the foramen of Luscka into the cerebellomedullary or cerebellopontine cistern
	T4	Tumor of the fourth ventricle with invasion of other structures such as the cerebellar peduncle, medulla, pons, midbrain, etc.
Metastases	M0	No evidence of metastases
	M1	Microscopic tumor found in cerebrospinal fluid
	M2	Gross nodule seedings in the cerebellar or cerebral subarachnoid space or in the third or lateral ventricles
	M3	Gross nodule seedings in the spinal subarachnoid space
	M4	Extraneuroaxial metastases

of symptom onset (Mork and Loken 1977). In an older series, surgery alone was shown to be curative only in a small proportion of patients. For example, in one pediatric series of patients diagnosed between 1935 and 1973, 4/12 patients with intracranial ependymomas, and 3/3 of patients with spinal cord ependymomas were alive 5 years after surgery (Dohrmann et al. 1976). In another series of patients diagnosed between 1953 and 1974, 2/12 patients with intracranial ependymomas treated with surgery alone were alive 5 years after the surgery, and 10/17 patients with intramedullary ependymomas were alive 10 years after the surgery (Mork and Loken 1977). Another series using better diagnostic imaging indicated that if complete resection was achieved, surgery alone might be curative in a subgroup of children with low-grade intracranial ependymoma. In that study, 5/7 patients treated with gross total resection (GTR) alone remained in remission 24–70 months following surgery (Awaad et al. 1996). Similarly, Hukin, et al. reported 10 cases of ependymoma treated with complete resection alone. Seven out of ten patients were free of disease and 3 recurred, with median follow-up of 48 months. Two of the recurrences were salvaged with repeat surgery and radiation therapy (Hukin et al. 1998). Notably, a longer period of observation of patients with ependymoma is necessary, since recurrences continue even after 5 years from diagnosis.

While most studies agree that achievement of GTR of intracranial and intramedullary spinal cord ependymoma correlates with superior outcomes, other risk factors, including location of tumor, histology, and use of adjuvant chemotherapy have not been unequivocally confirmed to predict outcome (Cervoni et al. 1994; Rousseau et al. 1994; Perilongo et al. 1997; Robertson et al. 1998). Younger children with ependymoma historically have had worse outcomes. It is not clear if age alone, or a combination of risk factors such as unfavorable location, which may preclude GTR, and withholding radiation therapy, may have contributed to poor outcomes in younger age groups. Current therapeutic studies use age, histology, and location of ependymoma for stratification of treatment, despite conflicting literature reports on their validity as prognostic factors.

4.5 Diagnosis

Evaluation of a patient with ependymoma should include a comprehensive history and physical examination, pre- and postoperative magnetic resonance imaging (MRI) of the brain, MRI of the spine, and cerebrospinal fluid evaluation. The spine MRI should ideally be performed prior to surgery, because postoperatively, blood in the spinal subarachnoid space may be confused with drop metastases.

Radiographically, supratentorial ependymomas appear as large, heterogeneous, periventricular, or, less commonly, intraventricular masses. Calcifications are present in approximately 50% of tumors examined by computerized tomography. Most supratentorial ependymomas have cystic components and enhance after the administration of intravenous contrast (Furie and Provenzale 1995). Infratentorial ependymomas appear as heterogeneous lesions that grow into the fourth ventricle and cause dilation of its upper part. Usually, the tumor is separated from the vermis by a cleavage plane. In most cases, the solid part of the tumor is intense with gray matter on T1- and T2-weighted MR images, and this enhances with contrast (Tortori-Donati et al. 1995) (Figs. 4.4–4.6).

The typical picture of an intramedullary ependymoma on MRI consists of segmental or diffuse cord expansion with intramedullary intensity abnormalities and prominent nodular gadolinium enhancement (see Chap. 10, Fig. 10.2). Intramedullary cysts and hydrosyringomyelia are common, particularly in childhood cases. Gadolinium enhancement may distinguish solid tumor from cord edema and from cyst or syrinx (Slasky et al. 1987). Cauda equina ependymomas usually demonstrate homogeneous hypointense signal on T1-weighted MRI sequences, hyperintense signal on T2-weighted sequences, and homogeneous enhancement after gadolinium injection (Wager et al. 2000).

4.6 Treatment

4.6.1 Surgery

The goals of surgery are to make a definitive tissue diagnosis, achieve a GTR of the tumor, and

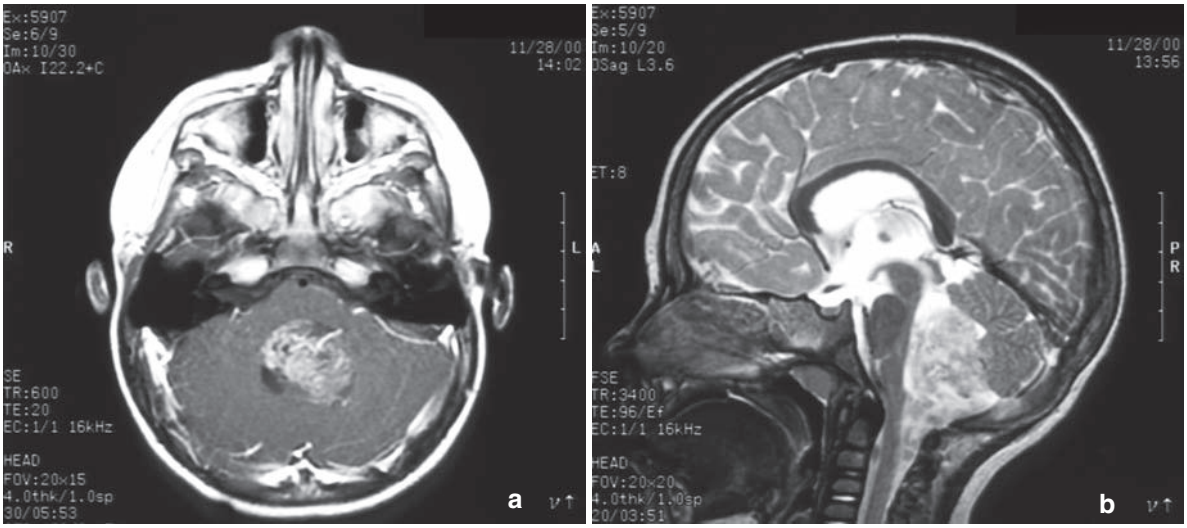


Figure 4.4

Typical imaging features of a posterior fossa grade II ependymoma showing heterogeneous enhancement following gadolinium administration (**a**). The T2-weighted image (**b**) shows the typical extension of the tumor through the foramen magnum into the upper cervical spinal canal

reestablish cerebrospinal fluid flow. Tumor invasion of surrounding tissues and proximity of posterior fossa tumors to midbrain structures can preclude complete removal in a subgroup of patients.

Based on retrospective studies, the extent of surgery is considered as the most important prognostic factor. Several recent prospective studies have confirmed this finding. In a retrospective analysis of 96 pediatric posterior fossa ependymomas from the Children's Oncology Group, extent of resection and older age were significantly correlated with better overall survival. They went on to review 1444 patients from 32 manuscripts from 1990 to 2005, and determined that extent of resection was a significant factor in 21 studies, age in 12, and histological grading in 9 of the studies (Tihan et al. 2008). In a study of 55 patients with anaplastic ependymoma, patients with a complete surgical resection followed by other treatments had an 83% disease-free survival after 3 years of follow-up, compared with 38% for those without complete resection (Timmermann et al. 2000). In a similar study of 32 children with ependymoma between 2 and 18 years of age, 66% of patients with complete resection had 5-year progression-free survival, compared with 11% of those without complete resection (Robertson et al. 1998).

Some investigators have used surgery alone to treat ependymoma. In one study of 10 selected patients with intracranial ependymoma (8 supratentorial and 2 posterior fossa tumors), 7 remained free of disease without any other interventions at a median follow-up of 48 months (Hukin et al. 1998). Investigators at St. Jude Children's Research Hospital have found that 10/16 patients with residual disease after the first surgery achieved GTR after a "second-look" surgery (Osterdock et al. 2000). The Children Oncology Group has completed a study in which a second-look surgery was performed in patients with residual local disease, following adjuvant chemotherapy.

Posterior fossa ependymomas frequently arise from the floor of the fourth ventricle or the region of the foramina of Luschka, extending out to the cerebellopontine angle (Fig. 4.6). Cranial nerves

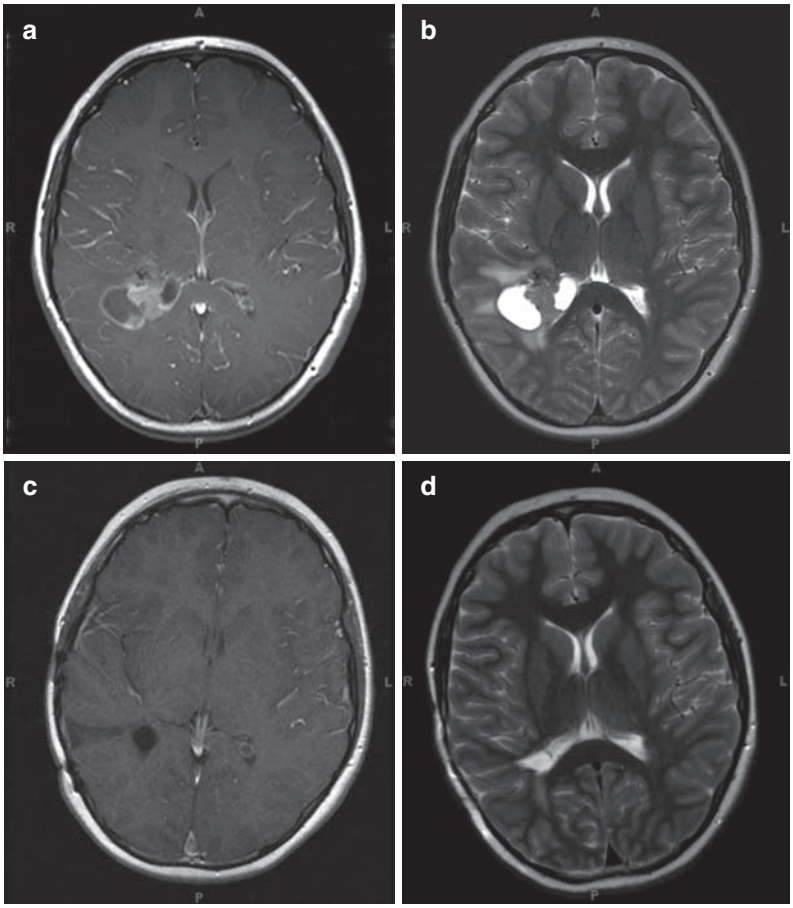


Figure 4.5

Preoperative T1- (**a**) and T2-weighted (**b**) MR images of a supratentorial ependymoma in a 9-year-old boy arising adjacent to the right trigone and periventricular area. The grade 3 ependymoma was grossly resected, and after external beam radiation therapy he remains progression free for 3 years. The postoperative T1-weighted image with contrast (**c**) and T2-weighted image (**d**) show no evidence of tumor recurrence

and vascular structures are frequently encased or displaced by the tumor, making surgical excision difficult. Sequelae of an aggressive surgical approach often includes cranial neuropathy, bulbar dysfunction, and the risk of posterior circulation infarction. Surgical results have improved through technical advances, such as intraoperative electromyographic monitoring of cranial nerves, computer-assisted navigation, and the operating microscope. Due to the strong prognostic impact of the degree of surgical resection, all children with suspected ependymoma should be referred to a center that can provide the expertise required for optimal management of these tumors.

4.6.2 Radiation Therapy

Radiation therapy is considered the standard adjuvant treatment of intracranial ependymomas in older children, with different definitions of lower age limit in different studies. The approach to radiation therapy of ependymoma, in particular the radiation field, has changed over a period. In the 1960s and 1970s, local field radiation was used, as improved outcomes were noted in irradiated patients, when compared to historical controls. In 1975, Salazar recommended extending the radiation field to include the whole brain in patients with low-grade ependymomas and the entire craniospinal axis in patients with high-grade

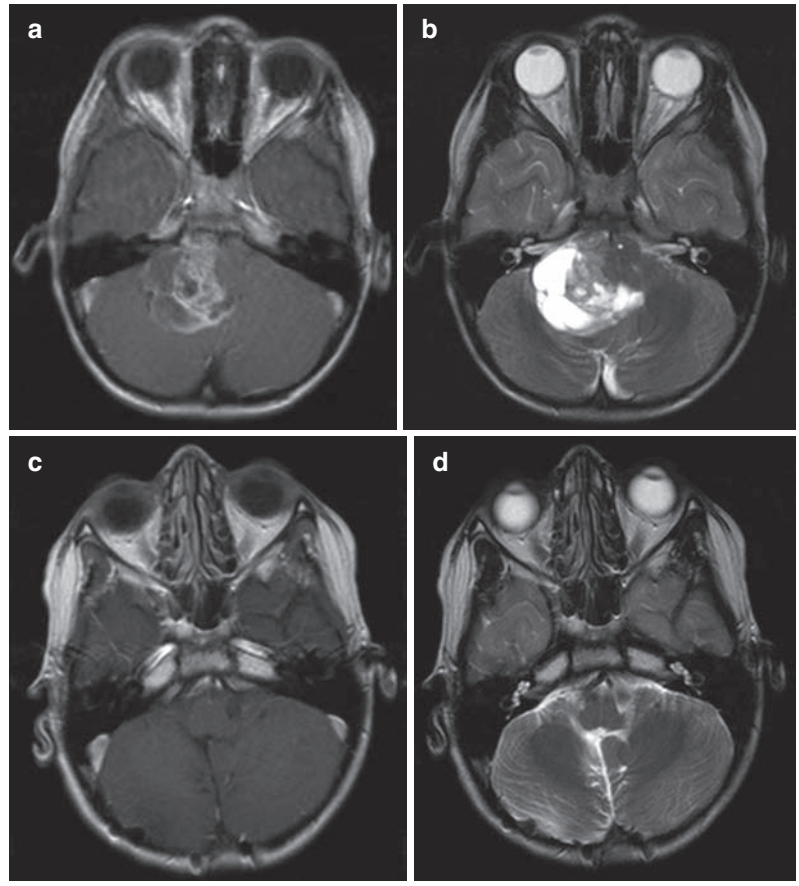


Figure 4.6

A preoperative T1-weighted MR image with contrast (**a**) and T2-weighted image (**b**) from a 7-year-old boy with a right cerebellopontine angle grade 2 ependymoma. After resection and external beam radiation therapy he remains progression free for 5 years. The postoperative T1-weighted image with contrast (**c**) and T2-weighted image (**d**) shows no evidence of tumor recurrence

ependymomas (Salazar et al. 1975). These recommendations were based on an overestimated risk of dissemination from autopsy findings, and on poor distinction between ependymomas and ependymoblastomas. In the late 1980s and early 1990s, multiple studies questioned the role of craniospinal radiation (Shaw et al. 1987; Goldwein et al. 1991; Vanuytsel and Brada 1991), as there was no difference in failure rates between patients undergoing localized versus craniospinal radiation. Local relapse was confirmed to be the most significant component of failure, and a local radiation dose of more than 4500 cGy was recommended (Goldwein et al. 1991).

In the late 1980s, cooperative pediatric cancer groups initiated studies of postoperative chemotherapy in infant brain tumors with the goal to delay, and possibly avoid radiation in young patients for whom large radiation fields would cause significant morbidity (Duffner et al. 1993; Geyer et al. 1994). Young children with ependymomas were treated in these studies together with patients with primitive neuroectodermal tumors. In the 1990s, attempts were made to replace radiation therapy with high-dose chemotherapy consolidation in children less than 6 years of age with malignant brain tumors (Mason et al. 1998), or to replace radiation with postoperative chemotherapy in children under 5 years of age (Grill et al. 2001). However, radiation was avoided in only 23% of patients in the later study, and after progression of tumor, only those children who underwent a second

complete resection remained in remission following radiation therapy.

Hyperfractionated radiation therapy was investigated by the Society for Pediatric Oncology. They reported on 24 children over the age of 5 years, treated with either 60 Gy (for patients with complete resection) or 66 Gy (for patients with incomplete resection), given in two daily fractions. Five-year overall survival was 74% and progression-free survival was 54%. The study concluded that although the treatment was well-tolerated, the survival figures were comparable to those for more conventional treatment regimens, and hence hyperfractionated therapy did not warrant further investigation (Conter et al. 2009). Other investigators have focused on reducing the radiation field by using conformal radiotherapy. In one such study, 36 children with localized ependymoma underwent conformal radiotherapy with an anatomically defined clinical target volume margin of 10 mm surrounding the postoperative residual tumor and tumor bed. Two failures occurred after a median follow-up period of 15 months. It is of significance that 30/36 children in this preliminary report had complete surgical resection (Merchant et al. 2000). More recently, the authors have published a follow-up study of 153 pediatric patients with ependymoma (median age 2.9 years). Patients received conformal, focal radiation to a dose of 54–55.9 Gy following definitive surgery. Thirty-five subjects had prior chemotherapy. Seven-year local control, event-free survival, and overall survival were 87, 69, and 81%. Survival was affected by tumor grade and extent of resection (Merchant et al. 2009). Radiosurgery has also been used in patients with ependymoma, usually at the time of recurrence, and it can be used safely without significant risk of radionecrosis (Hodgson et al. 2001). In another study, tumor control was achieved in 3/5 patients undergoing radiosurgery for residual localized ependymoma (Aggarwal et al. 1997). It is possible that radiosurgery will have a significant role in local control of ependymoma in the future; however, more studies comparing radiosurgery to standard radiation are necessary.

Given the limited effectiveness of chemotherapy in avoiding radiation (see section 4.6.3) and concerns about radiation-induced neurocognitive deficits, 88 patients at St Jude's between the ages of 2.85 and 4.5 years were treated with conformal radiation therapy (54 or 59 Gy) to gross tumor volume plus a margin of 1 mm (Merchant et al. 2004). Median follow-up was more than 3 years. The 3-year progression-free survival rate in this study was nearly 75%, with a cumulative incidence of local failure as a component of failure (distant +- local) at 3 years being14.8%. Serial neurocognitive evaluations performed until patients were 24 months postcompletion of radiation therapy revealed stable IQs. This significant study has prompted continued evaluation of conformal radiotherapy in patients older than 12 months of age, including a Pediatric Brain Tumor Consortium study for children <3 years of age, which uses intrathecal chemotherapy, systemic chemotherapy, and conformal radiotherapy; and a Children's Oncology Group proposal to use conformal radiation therapy in a subgroup of patients older than one year of age with higher-risk localized ependymomas. Craniospinal radiation is still to be used alone, or in combination with chemotherapy for older patients with disseminated ependymoma.

In summary, although the role of radiation therapy has not been confirmed in randomized studies, the high risk of relapse in younger children treated with chemotherapy only, even after GTR, warrants using this modality. Studies are underway to confirm the role of conformal field radiation in local control of ependymoma.

4.6.3 Chemotherapy

Ependymomas are sensitive to chemotherapy. In multiple studies involving adults with relapsed ependymoma, cisplatin-containing regimens have yielded superior response rates to alternate approaches. Complete and partial responses have been observed at rates that range between 30 (Walker and Allen 1988; Brandes et al. 2005) and 60% (Gornet et al. 1999). Despite these high rates of response, no chemotherapy regimens have yet been demonstrated to improve overall survival of adults with recurrent ependymoma.

In newly diagnosed patients with ependymoma, chemotherapy has been evaluated for the treatment of children with residual disease or to avoid radiotherapy

in young children (< 3 years old). In 8 children under the age of 4 with residual ependymoma, an 86% response rate to VETOPEC therapy (vincristine, etoposide, cyclophosphamide, cisplatin, carboplatin) was reported (White et al. 1998). The Children's Cancer Group protocol (CCG-9942) investigated the role of preirradiation chemotherapy with vincristine, etoposide, cisplatin, and cyclophosphamide in children older than three years of age with residual disease. In a preliminary report from this study, the event-free survival did not differ between patients without residual disease whose postoperative treatment consisted of radiation therapy alone (62 ± 8%) and patients with residual disease who received chemotherapy and irradiation (55 ± 9%). The chemotherapy objective response rate was 58 and 14% of patients experienced tumor progression while receiving chemotherapy prior to irradiation (Garvin et al. 2004).

The role of chemotherapy in delaying or avoiding radiation in young children with ependymoma has been well-studied (Table 4.3). The outcomes are difficult to compare due to differences in the use of radiation. In the earlier studies, though radiation was planned, it was not always given (Duffner et al. 1993; Geyer et al. 1994). While in later studies, radiation was used only after tumor progression, and its use indicated chemotherapy failure (Mason et al. 1998; Grill et al. 2001; Grundy et al. 2007). These issues notwithstanding, several valuable observations regarding the effectiveness of chemotherapy can be made. In the most recently published study, Grundy et al. report the most favorable outcome data with chemotherapy (vincristine, carboplatin, cisplatin, cyclcophosphamide, and methotrexate) in the treatment of 80 children less than 3 years old with nonmetastatic intracranial ependymoma (Grundy et al. 2007). The 5-year cumulative incidence for freedom from radiotherapy was 42% in this group of patients. Further, with a median follow-up of 6 years, this group achieved an overall survival rate of approximately 80% at 3 years and 60% at 5 years. While the study is limited by lack of radiographic data and neurocognitive follow-up (Bouffet et al. 2007), it does suggest that intensive chemotherapy, particularly the addition of methotrexate, may have benefit in the treatment of young children with ependymoma. An improvement in survival was also seen in young children (<3 years old) with medulloblastoma who had been treated with methotrexate

Table 4.3. Progression-free survival of young children with ependymoma treated with chemotherapy

Study	Duffner et al. 1993[a]	Geyer et al. 1994	Mason et al. 1998	Grill et al. 2001	Grundy et al. 2007[b]
Age group	<36 months	<18 months	<6 years	< 5-years	<3 years
Chemotherapy regimen	7 cycles VCR/CTX alternating with cisplatin/VP-16	8 courses of 8-drugs-in-1-day	5-cycles of induction VCR/CTX/cisplatin/VP-16; consolidation with high dose carbo/thiotepa/VP-16 and stem cell rescue	7-cycles alternating 3 regimens Procarbazine/carboplatin VP-16/cisplatin VCR/CTX	7 cycles containing 4 courses of therapy VCR/Carboplatin VCR/Methotrexate VCR/Cyclophosphamide Cisplatin
Complete resection	19	15 patients total, degree of resection not availalbe	4	46	41
Incomplete resection	27		6	27	36
Progression -free survival	42% at 2-years 27% at 5-years	26% at 3 years	30% at 2-years	22% PFS at 4-yeras	47% at 3 years 42% at 5 years

[a] Most patients in this study underwent irradiation following chemotherapy

[b] 42/89 total patients, 36/80 nonmetastatic patients received radiation therapy upon relapse or progression. Table entried refer to the nonmetatstaic group only

(Rutkowski et al. 2005). While response in this recent study is promising, there are no data to suggest that the neurocognitive outcome for these patients will be superior to that observed with conformal radiotherapy (Merchant et al. 2004). Thus, concerns about response and outcome have resulted in a reexamination of local radiation in all but the youngest patients in several ongoing clinical trials for ependymoma.

High-dose chemotherapy followed by autologous bone marrow rescue has been used in the setting of recurrent or progressive disease with dismal results. In a study using a thiotepa, etoposide, and carboplatinum-conditioning regimen in addition to autologous bone marrow rescue, 5 out of 15 children with recurrent ependymoma died of treatment complications and all other patients sustained disease recurrence (Mason et al. 1998). In another study using busulfan and thiotepa as a conditioning regimen, 1 out of 16 patients died from treatment-related toxicity, and only 3 were alive at follow-up times of 15–25 months. All three surviving patients received additional radiation (one patient) or surgery and radiation (two patients) after transplant (Grill et al. 1996). In two additional studies, involving similar conditioning regimens only 1 of 4 patients with relapsed ependymoma responded, and survived to 37 months (Thorarinsdottir et al. 2007; Shih et al. 2008). Because of the poor outcomes in these small studies, high-dose therapy is not recommended in patients with relapsed or progressive disease. Zacharoulis et al. reported on the Headstart protocol experience for young children with newly diagnosed ependymoma (Zacharoulis et al. 2007). Patients with metastatic disease underwent five cycles of chemotherapy with vincristine, cisplatin, cyclophosphamide, etoposide, and high-dose methotrexate. This was followed by a single myeloablative cycle of thiotepa, carboplatin, and etoposide, with autologous stem-cell rescue. Five-year event-free and overall survival rates were 12 and 38%, and the study concluded that the regimen showed no advantage over nonmyeloablative regimens.

Conventional chemotherapy for relapsed ependymoma typically has low response rates (Bouffet et al. 2009). Novel strategies such as small-molecule targeted therapy and antiangiogenic chemotherapy are of great interest. Kieran et al. reported on the toxicity and progression-free survival rate following an antiangiogenic, metronomic chemotherapy regimen (Kieran et al. 2005). Twelve patients with relapsed brain tumors were treated with a cocktail of oral antiangiogenic agents including thalidomide, celecoxib, and low-dose oral etoposide, and cyclophosphamide. Four of the twelve patients had relapsed ependymoma. While 1 patient progressed during the first 3-week treatment cycle, the remaining 3 patients continued to receive therapy for 58–83 weeks, and had progression-free survival ranging from 58 weeks to longer than 157 weeks. Currently, fenofibrate in combination with oral thalidomide, celecoxib, low-dose oral etoposide, and cyclophosphamide, and the combination of bevacizumab and irinotecan are being studied. Several biologically targeted therapies have been investigated in Phase I settings in small groups of patients, but definitive response rates are not established (Bouffet et al. 2009).

Currently, chemotherapy is used as an adjuvant treatment in patients with postoperative residual disease, with a goal of achieving a response that would make a second look surgery and conformal radiation therapy more feasible. Chemotherapy may also control microscopic disseminated disease, but it rarely results in complete response of macroscopic disease.

4.6.4 Spinal Cord Ependymomas

Spinal cord ependymoma has a more favorable prognosis than its intracranial counterpart. Surgery remains the primary mode of therapy for spinal cord ependymomas, and complete resection is usually curative. Current treatment recommendations are that another resection must be attempted, if residual tumor is unexpectedly found on the postoperative scan, or in the case of recurrence (Nadkarni and Rekate 1999). Radiation therapy is used when complete resection is not possible. In some studies, excellent control rates of residual tumor were achieved with radiation therapy (80% progression-free survival at 5 years after diagnosis) (Garrett and Simpson 1983; Waldron et al. 1993); while others report higher postradiation relapse rates (37–89%) (Whitaker et al. 1991; Cervoni et al. 1994). More information regarding spinal cord tumors is presented in Chapter 10.

4.6.5 Recurrent Disease

Depending on the completeness of surgical resection and patient age, disease recurs in 25–80% of patients. In a retrospective series of 52 relapsed pediatric patients, the majority of progressions occurred at the original tumor site (73%), the original and a new site were involved in 16%, and a new site alone in 11%. Thirteen percent of patients with previously localized disease recurred with disseminated disease (Horn et al. 1999). A similar distribution of site of relapse was observed in another retrospective study of 37 relapsed patients (Goldwein et al. 1990). Very similar results were obtained in a prospective study of young children. Eighty-seven percent of relapses in that study were local and 13% were at a distant site (Grill et al. 2001). Merchant reported substantially improved local control rates following treatment with focal conformal radiation (cumulative incidence of local failure was 12%) (Merchant et al. 2009). A variety of treatments were used after relapse including second surgery, radiation, radiosurgery, chemotherapy, and high-dose chemotherapy. Twenty to twenty-eight percent of patients achieved a second complete remission (Goldwein et al. 1990; Grill et al. 2001). Children under 5 years of age who did not receive irradiation upfront and who underwent a second complete resection followed by irradiation therapy had the best chance of second complete remission (28%). However, there was no benefit of irradiation for recurrent disease if a second complete resection was not achieved (Grill et al. 2001).

Although recurrent ependymoma carries a poor prognosis, routine neuroimaging surveillance is recommended as patients with asymptomatic recurrences, discovered on routine imaging scans, had longer survival than patients who were symptomatic at the time of tumor recurrence (60 vs. 30% at 2 years postrecurrence) (Good et al. 2001).

4.7 Outcome

4.7.1 Neurologic Function

With long-term remission rates of at least 50% at 5 years after diagnosis, long-term effects of tumor and its treatment on neurologic functioning have become increasingly more important. Long-term sequelae most commonly include cranial nerve deficits, abnormal gait, and difficulties with fine motor functioning (Table 4.4). Of note, 30% of children

Table 4.4. Results of neurologic exam in children with intracranial ependymoma (Horn et al. 1999)

Neurologic finding	Percentage of children with normal findings, 1 month after surgery ($n = 84$)	Percentage of surviving children with normal findings, 6 years after diagnosis ($n = 39$)
Consciousness	92	100
Speech	80	82
Memory	98	80
Visual acuity	86	90
Visual fields	80	90
Cranial nerves	49	67
Fine motor function	64	74
Sensory function	97	97
Gait	43	67
Swallowing	84	95
Posterior-fossa mutism[a]	79	93

[a] Only patients with posterior fossa tumors included

with supratentorial ependymomas and 50% of those with infratentorial tumors required placement of a ventriculoperitoneal shunt (Horn et al. 1999). Brannon Morris et al. described a cohort of 96 patients >1 year of age with posterior fossa ependymoma (Brannon Morris et al. 2009). They were treated with surgery and radiation in a Phase II trial. Late neurologic effects included limb dysmetria, cranial nerve VI and VII deficits, limb paresis, dysphagia, truncal ataxia, and hypotonia. Oculomotor deficits, facial paresis, dysphagia, and gait disturbances improved with time.

Long-term cognitive impairment occurs in most of the patients with posterior fossa tumors, even after posterior fossa irradiation only. The impairment correlates well with the dose of craniospinal irradiation (Grill et al. 1999). The mean full-scale IQ score was found to be 85 in 12 patients with posterior fossa ependymoma who underwent posterior fossa irradiation as a part of their treatment. This was significantly better than in patients with medulloblastoma who underwent craniospinal irradiation, whose mean full-scale IQ score was 70. Ninety-two percent of children who underwent posterior fossa irradiation alone were able to pursue normal schooling (Grill et al. 1999).

4.7.2 Progression-Free Survival

In one retrospective series, a group of 84 children with ependymoma (all ages and treatment modalities) treated between 1987 and 1991 had close to 50% overall long-term survival, and somewhat lower progression-free survival (Fig. 4.7) (Horn et al. 1999). These observations are consistent with those published from the Children's Hospital of Philadelphia (Shu et al. 2007), and the 5-year overall survival rates obtained from SEER registry, which indicate 56% survival for children with ependymoma treated between 1985 and 1994 (Linet et al. 1999; Ries et al. 1999). With current treatment approaches, low-risk patients (older patients with complete surgical resection) treated with observation or conformal field radiation can expect 75% progression-free survival. Older patients with postoperative residual disease may achieve 30–50% progression-free survival when treated with radiation with or without chemotherapy and second-look surgery. In addition, up to 20% of patients whose disease progresses or recurs may achieve a prolonged second complete remission. Up to 50% of young children treated with upfront surgery and chemotherapy and rescue surgery and irradiation are alive, and in first or second complete remission at 4 years after diagnosis (Grill et al. 2001). Expectations are that current treatment of infants with chemotherapy and conformal field radiation can sustain similar results.

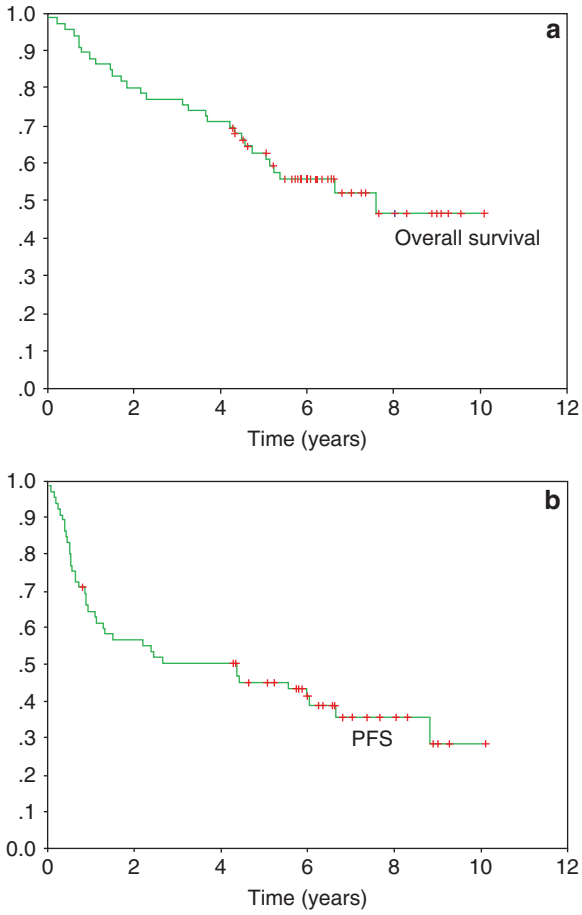


Figure 4.7
Kaplan-Meier curves for 84 children with ependymoma treated between 1987 and 1991: (a) overall survival and (b) progression-free survival (PFS). (Horn et al. 1999)

4.8 Conclusions

In summary, ependymoma affects 2.6 per million children annually. Children under 4 years of age have the highest incidence of this disease. Two-thirds of the patients with intracranial ependymomas present with posterior fossa tumors, and more than 85% present with localized disease. Complete surgical resection is the most important predictor of good outcome. Conformal field radiation is recommended as adjuvant therapy in most patients, and chemotherapy is used in control of microscopic dissemination. Currently, overall survival of all children with ependymoma is in the range of 50–60%. Most children undergoing posterior fossa irradiation for this tumor are able to pursue normal schooling.

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Embryonal Tumors

Sonia Partap • Paul Graham Fisher

Contents

5.1 Introduction

Embryonal tumors comprise a large fraction of pediatric brain tumors. Their cell of origin, histopathologic classification, and treatment are all areas of controversy. The prognosis for these tumors was at one time exceedingly poor, but therapeutic advances have led to substantial improvement in survival. Nevertheless, current treatment protocols often lead to debilitating and severe late effects.

Historically, all embryonal tumors, regardless of their site of origin in the central nervous system (CNS), were grouped under the umbrella term *primitive neuroectodermal tumor* (PNET) (Rorke 1983). These tumors were distinguished by a relatively homogeneous histological appearance consisting of poorly cohesive, undifferentiated neuroepithelial cells, often with a high mitotic rate. These small, monomorphic, round cells sometimes demonstrate neuroblastic differentiation. All embryonal tumors were conjectured to arise from a common precursor cell of the subependymal matrix in the CNS. The tendency for these neoplasms to disseminate through cerebrospinal fluid (CSF) pathways was believed to contribute to their poor outcome. Medulloblastoma, thought by Bailey and Cushing to originate from "medulloblasts," was sometimes referred to as infratentorial PNET. However, the distinct biologic nature of medulloblastoma now has become apparent.

Evidence suggests that rather than being one uniform group of tumors, PNETs are a heterogeneous group of neoplasms. Indeed, gene-expression profiling favors the older concept of a site-specific origin for distinct embryonal tumors (Gilbertson 2002;

Pomeroy et al. 2002). Embryonal tumors are better identified by their more classic descriptions, based on tumor location, divergent histopathology, and patterns of differentiation. These embryonal neoplasms include medulloblastoma, atypical teratoid/rhabdoid tumor (ATRT), pineoblastoma, ependymoblastoma, cerebral neuroblastoma, ganglioneuroblastoma, medulloepithelioma, and supratentorial PNET. Children with average risk medulloblastoma have significantly higher survival rates than those with other embryonal neoplasms (McNeil et al. 2002). In this chapter, we consider and discuss separately the entities of medulloblastoma, ATRT, pineoblastoma, and other embryonal tumors, as recognized by the current World Health Organization (WHO) classification of tumors (Louis et al. 2007).

5.2 Medulloblastoma

5.2.1 Epidemiology

The incidence of pediatric CNS neoplasms is approximately 3.5 per 100,000 children per year. Medulloblastoma accounts for about 20% of cases (Gurney et al. 1999). By the 1990s, multimodal therapies were associated with increasing survival from medulloblastoma (Gurney et al. 1999; McNeil et al. 2002), while incidence was considered to be decreasing slightly (Thorne et al. 1994; Morland and Parkes 1995). Regardless, medulloblastoma remains the second most common pediatric brain tumor, following pilocytic astrocytoma. Peak occurrence is around the age of four years (Thorne et al. 1994; Gurney et al. 1999). Thirty percent or more of cases occur in patients over 15 years of age (Roberts et al. 1991; Peterson and Walker 1995; Prados et al. 1995). Males are affected 1.5 times more frequently than females, except among infants, for whom incidence by gender is nearly equal. As far as survival is concerned, gender does not appear to have an effect upon the outcome until after the age of three, when girls fare better (Weil et al. 1998; Gurney et al. 1999; McNeil et al. 2002; Curran et al. 2009).

The etiology for this tumor is unclear, except for a small fraction of children who harbor a germline mutation of a tumor-suppressor gene, such as in Gorlin syndrome or, even more rarely, Turcot syndrome (Hamilton et al. 1995), Li–Fraumeni syndrome (Pearson et al. 1982), ataxia telangectasia (Shuster et al. 1966), or Coffin–Siris syndrome (Rogers et al. 1988). Gorlin syndrome is identified by nevoid basal-cell carcinoma, jaw cysts, palmar and plantar pits, rib anomalies, hyporesponsiveness to parathyroid hormone, and medulloblastoma (Gorlin and Goltz 1960; Gorlin et al. 1965). Environmental exposures such as JC virus and SV40 virus have been described as putative causes for medulloblastoma, but epidemiological studies are inconclusive (Fine 2002). Maternal consumption of cured meats and exposure to *N*-nitroso compounds have been posited as risk factors for childhood brain tumors, yet evidence is inconsistent (Gurney et al. 1999).

5.2.2 Pathology

5.2.2.1 Grading and Histopathology

Most clinicians and neuropathologists now agree that medulloblastoma is a distinct, cerebellar cancer. The WHO classifies medulloblastoma as a malignant, invasive embryonal neoplasm of the cerebellum with predominantly neuronal differentiation, distinct from other embryonal tumors, and a tendency to metastasize via CSF pathways (Louis et al. 2007). All tumors are classified as grade IV because of their highly malignant phenotype. However, some data suggest that this grading system may be an oversimplification. Lesser differentiation and increasing anaplasia are associated with a significantly worse outcome (Eberhart et al. 2002; McManamy et al. 2003). Severe anaplasia appears to be indicative of high relapse risk and poor survival, especially in the presence of a high apoptotic rate (Giangaspero et al. 2006).

Histologically, classic medulloblastoma is a small, round-cell embryonal tumor, composed of tightly packed and poorly differentiated cells with scanty cytoplasm and dense basophilic nuclei, as well as a number of mitotic figures (Fig. 5.1). Glial or neuronal differentiation may be present. Perivascular pseudorosettes or Homer-Wright rosettes, that is, neuroblastic rosettes of nuclei in a circle around tangled cytoplasmic processes may be present in a minority

Figure 5.1

Hematoxylin and eosin micrograph of classic medulloblastoma. There are dense sheets of small cells with scant cytoplasm. This appearance has been described as typical for "small round blue cell tumors"

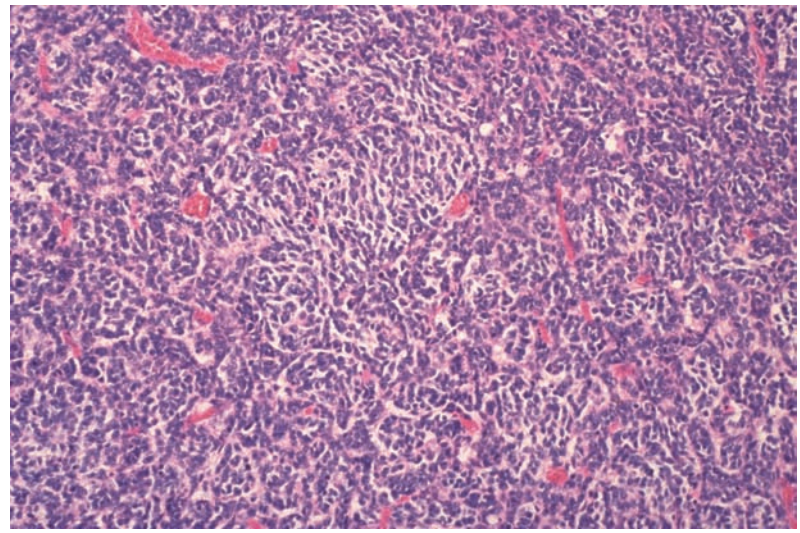
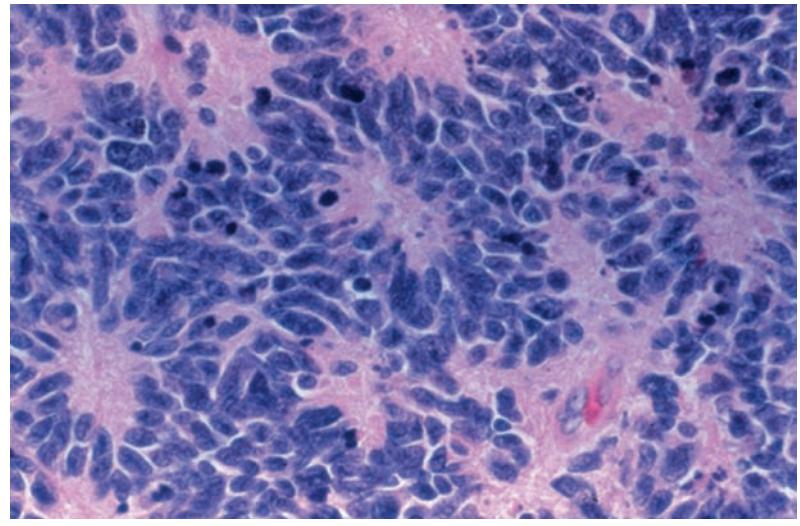


Figure 5.2

Hematoxylin and eosin micrograph of Homer-Wright rosettes in medulloblastoma



of cases (Fig. 5.2). Vascular proliferation and hemorrhage are seldom noted. Grossly, the tumor often sits at the cerebellar vermis or within the fourth ventricle as a several-centimeter, circumscribed, yet friable, tan-to-pink mass (Fig. 5.3).

A variety of histological variants of medulloblastoma have been identified to date. Desmoplastic and nodular medulloblastomas have better outcomes than the distinctly different subtypes of large cell and anaplastic medulloblastomas. While exceedingly rare, medullomyoblastoma, with striated muscle or muscle antigen, and melanotic medulloblastoma, with a minor component of melanin-forming neuroepithelial cells, were described decades ago (Marinesco and Goldstein 1933; Fowler and Simpson 1962). Both these subtypes may carry a worse prognosis than classic medulloblastoma. Previously misclassified as medulloblastoma, ATRT is a separate entity.

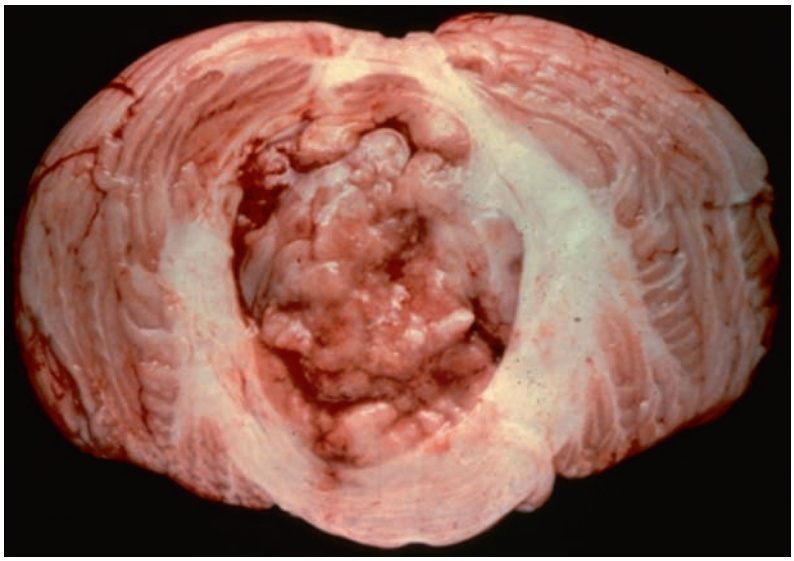


Figure 5.3
Gross specimen of circumscribed medulloblastoma at the level of the cerebellar vermis and fourth ventricle

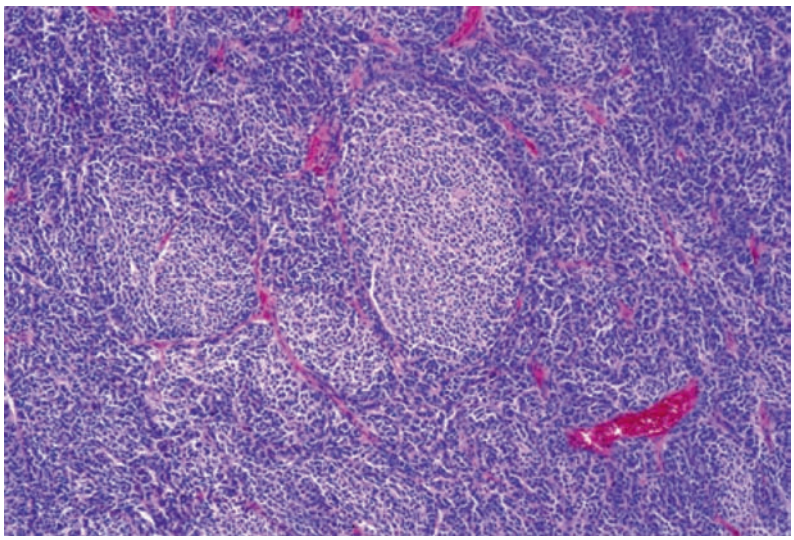


Figure 5.4
Hematoxylin and eosin micrograph of desmoplastic medulloblastoma with pale islands of tumor cells and intervening dense reticulin

Desmoplastic medulloblastoma is characterized microscopically by an abundant stromal component of dense reticulin surrounding nodular foci of tumor, so-called pale islands (Fig. 5.4). Macroscopically, this variant often appears as a mass at the superficial edge of a cerebellar hemisphere (Fig. 5.5), occurring perhaps more often in an adolescent or young adult (Levy et al. 1997). There may be extensive infiltration of the overlying meninges. There is also recent work to indicate that desmoplastic medulloblastoma may be more common and have a more favorable outcome in infants (McManamy et al. 2007).

Large-cell medulloblastoma is identified histologically by pleomorphic, large round-to-irregular nuclei

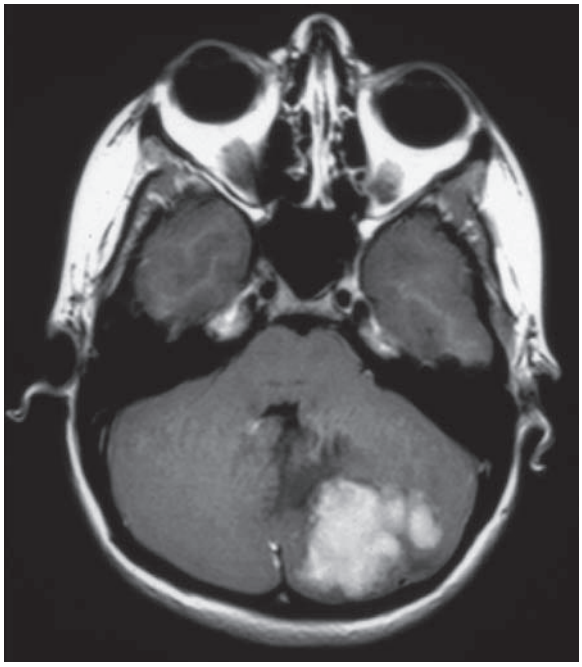


Figure 5.5
Transverse T1-weighted axial magnetic resonance image following contrast administration demonstrating a superficial left cerebellar desmoplastic medulloblastoma in a 16-year-old girl

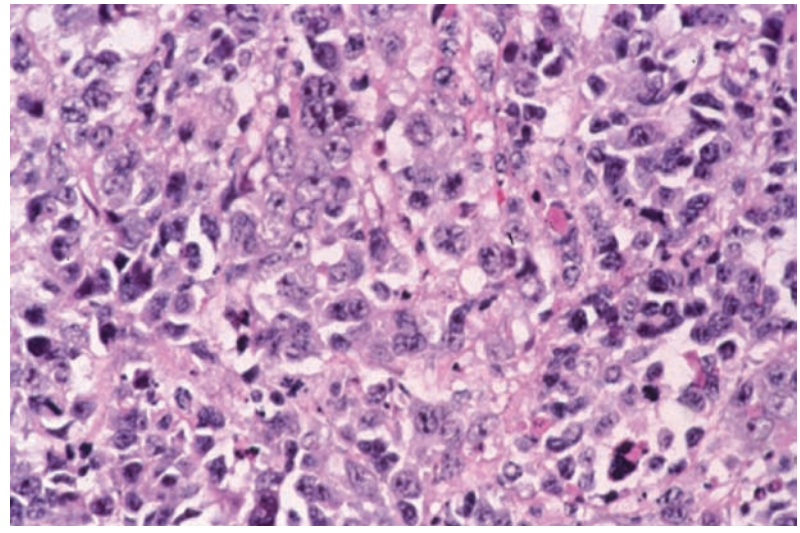
with a prominent nucleoli and a more abundant cytoplasm than classic medulloblastoma (Fig. 5.6) (Giangaspero et al. 1992). Numerous mitoses and a high apoptotic rate are common. Large-cell tumors stain uniformly for synaptophysin, and may stain for chromogranin. These tumors may constitute up to 4% of medulloblastomas, and are frequently associated with bulky spinal metastases at diagnosis (Fig. 5.7) and an aggressive disease course (Brown et al. 2000). Overall survival at 5 years from diagnosis may be as low as 10%.

Similarly, anaplastic medulloblastoma has marked nuclear pleopmorphism with nuclear molding, a high mitotic rate, and prominent apoptosis. Though these changes can be seen focally in all medulloblastomas, these histological findings are widespread throughout this subtype. Since anaplastic regions are frequently seen in large-cell tumors, a combined category of large-cell/anaplastic medulloblastoma has been suggested (McManamy et al. 2003).

5.2.2.2 Molecular Biology and Cytogenetics

Improved characterization of the histologic variants of medulloblastoma has also led to an improved understanding of the underlying biologic features. Better knowledge of the molecular and cytogenetic changes associated with outcome in medulloblastoma

Figure 5.6
Hematoxylin and eosin micrograph of large-cell medulloblastoma with cells having abundant cytoplasm, irregular nuclei, and prominent nucleoli



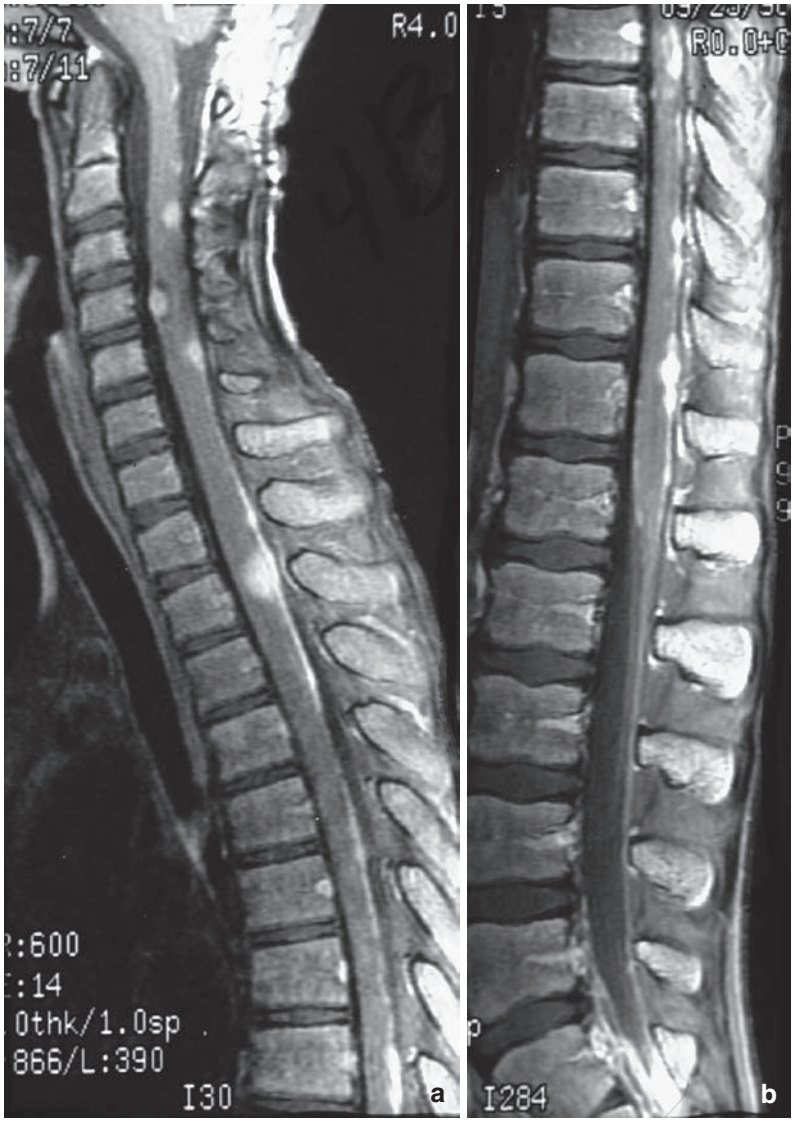


Figure 5.7

T1-weighted sagittal post-gadolinium images of the thoracic (**a**) and lumbar spine (**b**) of 10-year-old with widely metastatic large-cell medulloblastoma just after resection of a vermian primary mass. Widespread tumor dissemination is visualized on the surface of the cerebellum and spinal cord

(Table 5.1) will be necessary to refine stratification of disease risk, which, at present, is based solely on clinical features (see later). In the future, ascertainment of molecular variations may allow for individually tailored therapy using specific or novel targets.

In the 1970s and 1980s, the descriptive histopathologic features such as desmoplasia and increased cellular differentiation were correlated with improved survival (Chatty and Earle 1971; Caputy et al. 1987), although one report suggested that patients with differentiating neoplasms fare worse (Packer et al. 1984). More recently, a low proliferative index (determined by Ki-67 antigen/MIB-1 antibody identification) of cycling, non G_0/G_1 phase cells has been found to predict a better outcome (Grotzer et al. 2001). A high rate of apoptosis also predicts an improved outcome (Haslam et al. 1998).

Table 5.1. Cytogenetic and molecular features associated with medulloblastoma outcome

Good prognosis
Hyperdiploidy (Gajjar et al. 1993)
High *trkC* expression (Kim et al. 1999; Grotzer et al. 2000)
β-catenin nuclear immunoreactivity (Ellison et al. 2005)
Poor prognosis
Isolated 17p loss of heterozygosity (Gilbertson et al. 2001)
Elevated *erbB2* expression (Gilbertson et al. 2001; Gajjar et al. 2004)
Elevated c-*myc* expression (Scheurlen et al. 1998; Eberhart et al. 2004)
Overexpression of calbindin-D_{28k} (Pelc et al. 2002)

Cytogenetic studies over the last 10 years have yielded a number of findings. Isochromosome 17q is seen in about half of the cases of medulloblastoma (Bigner et al. 1988), and is associated with large-cell medulloblastoma (Brown et al. 2000). Loss of heterozygosity of 17p may be seen with isochromosome 17q. Isolated 17p loss appears to be associated with poor prognosis (Gilbertson et al. 2001). Chromosome 1 rearrangements and 1q loss have been inconsistently noted in medulloblastoma (Bigner et al. 1988). Hyperdiploidy appears to be associated with a better outcome than diploidy (Gajjar et al. 1993), yet one study found diploidy to fare better than aneuploidy (Zerbini et al. 1993). Comparative genomic hybridization has revealed that high-level chromosomal gain at 8q24 (the locus of c-*myc*, see below) may be associated with large-cell medulloblastoma (Brown et al. 2000).

Molecular markers recently associated with medulloblastoma have thus far included the genetic loci c-*myc*, *trkC,* and *erbB2*. In a study of 55 patients, elevated expression of *erbB2*, a gene for Class I receptor tyrosine kinases was associated with lower patient survival (Gilbertson et al. 2001). Gajjar and colleagues found that patients with tumors that expressed the erbB2 receptor had worse overall and progression-free survival (PFS). For patients with erbB2-negative tumors ($n=49$), 5-year PFS was 72% compared to 42% for those with erbB2-positive tumors ($n=32$) (Gajjar et al. 2004). High expression of *trkC*, a neurotrophin receptor gene that promotes apoptosis in medulloblastoma, has consistently predicted a favorable clinical outcome (Kim et al. 1999; Grotzer et al. 2000). Children with medulloblastoma that revealed nucleopositivity for β-catenin also had significantly better overall and event-free survival than those with tumors without the nuclear immunophenotype (Ellison et al. 2005).

Amplification of the c-*myc* proto-oncogene has been linked to a very poor prognosis and was found in 8 of 32 medulloblastomas (Scheurlen et al. 1998). This proto-oncogene has been found to be amplified in large-cell medulloblastomas and is associated with tumor anaplasia (Brown et al. 2000; Eberhart et al. 2004). The significance of the N-*myc* proto-oncogene has not yet been conclusive. A recent report found medulloblastoma patients with high c-*myc* levels in conjunction with LDHB and CCNDB1 oncogenes had a 5-year survival of only 16% compared to 57% for patients whose tumors only had c-*myc* amplification. The presence of LDHB and CCNDB1 without c-*myc* amplification was not correlative with the outcome (de Haas et al. 2008). Overexpression of the calcium-binding protein calbindin-D_{28k} is also associated with a high risk of medulloblastoma relapse (Pelc et al. 2002). This protein protects cells from calcium overload and perhaps prevents apoptosis.

Recent laboratory reports have implicated a key role of the human homolog of the Drosophila gene *patched* (*PTCH*). Mutations in this gene occur in some medulloblastoma tumors (Pietsch et al. 1997; Raffel et al. 1997; Wolter et al. 1997; Xie et al. 1997). The PTCH protein product serves as a transmembrane receptor, where the antagonist ligand sonic hedgehog protein (Shh) binds. This is a key ligand-receptor signal transduction pathway in cerebellar development (Gilbertson 2002). The mechanism by which PTCH signal dysregulation leads to tumorigenesis is unclear, but appears to stem from a principal defect in PTCH. Overexpression of *PTCH* and two other Shh downstream target genes – *GLI* and N-*myc* – is highly correlated with desmoplastic medulloblastoma (Pomeroy et al. 2002). Patients with Gorlin syndrome have germline mutations in the *PTCH* gene at chromosome 9q31, and their medulloblastomas are often desmoplastic (Pietsch et al. 1997). Mutations in other genes in the Shh pathway, such as the human *suppressor of fused* (*SUFU*), have

also been identified as leading to medulloblastoma (Taylor et al. 2002).

Further research is being carried out by the use of transgenic mice models of medulloblastoma. Inactivation of one *PTCH* allele in the mouse leads to a 14% incidence of medulloblastoma (Wetmore et al. 2000). These tumors demonstrate features of both glial and neuronal differentiation, which is also observed in human tumors. An additional genetic mutation in a critical tumor-suppressor gene, such as *p53*, leads to virtually all mice developing medulloblastoma (Wetmore et al. 2001). Interestingly, transgenic mice deficient for both DNA ligase IV (Lig4), a component of the DNA repair machinery, and p53 also develop medulloblastoma (Lee and McKinnon 2002). A confounding variable in the interpretation of these results is that *p53* mutations are not commonly observed in human tumors. Nonetheless, these animal studies suggest that alterations in multiple genetic pathways may result in medulloblastoma.

5.2.3 Clinical Features

Since medulloblastoma occurs most often in the midline cerebellum at the level of the fourth ventricle, children present frequently with symptoms and signs of obstructive hydrocephalus and cerebellar dysfunction over 2–6 months. Early symptoms may include irritability, behavioral changes, and declining school performance. The child may go on to experience emesis, particularly upon awakening, horizontal diplopia, head tilt, clumsiness, and occipital or frontal headaches. Within six months of headache onset, virtually all children will have associated neurologic signs, such as papilledema, strabismus, ataxia, or weakness (Honig and Charney 1982). Infants may display macrocephaly, splitting of the cranial sutures, or a bulging anterior fontanelle.

5.2.4 Natural History

Among all childhood brain tumors, medulloblastoma has the greatest tendency for subarachnoid space seeding and extraneural spread. At diagnosis, 14–43% of patients are reported to have microscopic or nodular seeding in the subarachnoid space of the spine or brain (Deutsch and Reigel 1980; Tarbell et al. 1991). In less than 5% of cases, spread outside the CNS occurs at any point in the course of the disease (Kleinman et al. 1981).

More than half of all children with medulloblastoma are now cured of their disease. Relapse occurs most often at the primary tumor site or elsewhere within the cerebellum, with or without neuraxis spread (Halberg et al. 1991). Median time to recurrence is 14 months from diagnosis, although for infants the time to progression is just 6 months (Duffner et al. 1993; Minn et al. 2001). Subarachnoid tumor spread has been noted in many patients at autopsy. These data on tumor relapse derive from children treated with 36 Gy of craniospinal irradiation (CSI), or infants treated without radiotherapy. As the dose of prophylactic neuraxis irradiation is decreased and systemic and intrathecal chemotherapies are added or altered, these patterns of relapse may change.

The relationship of age at diagnosis to natural history has been debated. Children less than 3 years of age have significantly worse survival than older children have, but there do not appear to be significant differences between age groups 4–9 years, 10–14 years, and 15–19 years (McNeil et al. 2002). Thus, the adverse effect of very young age on outcome may be confounded by the absence of irradiation during treatment. Outcome is unaffected by race (McNeil et al. 2002).

5.2.5 Diagnostic Imaging

A child presenting with the clinical features described above should be immediately evaluated by a brain imaging study. Initially, this will be a computed tomography (CT) scan of the head because of its simplicity, speed, and availability in most communities. A high-quality CT scan will almost always detect a posterior fossa mass. Because of its high cellular density, a medulloblastoma will be hyperdense, relative to normal brain on a noncontrast CT scan (Fig. 5.8). Nonetheless, anatomic definition and preoperative planning requires a high-quality MRI scan. If possible, a full spine MRI should be obtained to determine if there is leptomeningeal dissemination, the presence of which markedly affects long-term outcome.

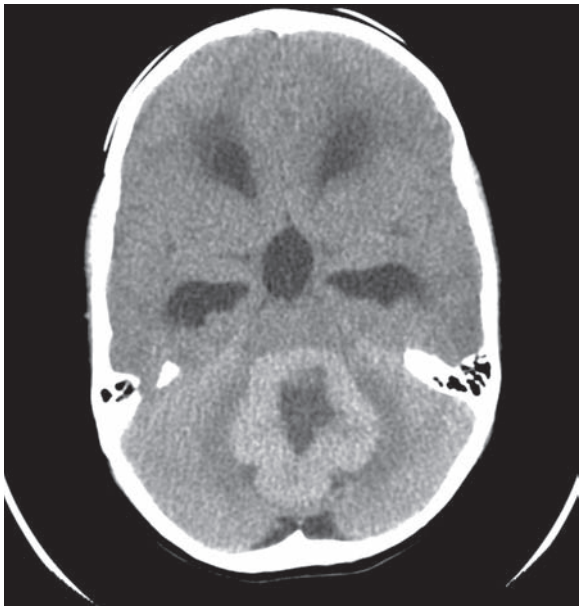


Figure 5.8
Axial noncontrast CT scan of a patient with a medulloblastoma. The tumor is hyperdense relative to the brain

On magnetic resonance imaging (MRI), the appearance can be varied. The mass can be either homogenous or heterogeneous in consistency. It is low to isointense on T1-weighted images, and intermediate or, rarely, hyperintense on T2-weighted images. Enhancement with gadolinium may be patchy or dense (Fig. 5.9). A minority of patients will present with diffuse leptomeningeal dissemination which is described as "sugar coating" of the brain on postcontrast T1-weighted MR images (Fig. 5.10).

5.2.6 Treatment

5.2.6.1 Surgery

A child with a large posterior fossa mass might have obstructive hydrocephalus, and is at risk for deterioration from transient increases in intracranial pressure (ICP) while supine or sedated during a prolonged MRI screening. Although a VP shunt can be placed prior to definitive surgery, ICP cannot be measured, and there is risk of shunt failure due to blood products remaining in the ventricles after

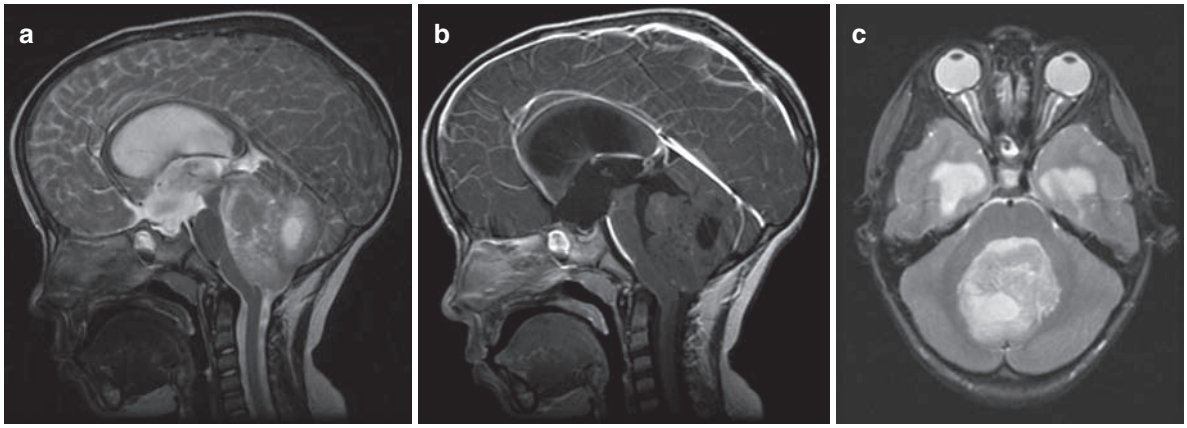


Figure 5.9
(**a–c**) Magnetic resonance images of a 5-year-old boy with a typical posterior fossa medulloblastoma. (**a**) T2-weighted sagittal image showing a large heterogeneous partially cystic mass arising within the cerebellar vermis, displacing the brainstem anteriorly and with associated ventricular enlagement. (**b**) T1-weighted image with contrast demonstrates minimal enhancement, which is a common finding. (**c**) T2-weighted axial image showing that the tumor extends to the floor of the fourth ventricle but does not invade the brainstem. This tumor was resected completely

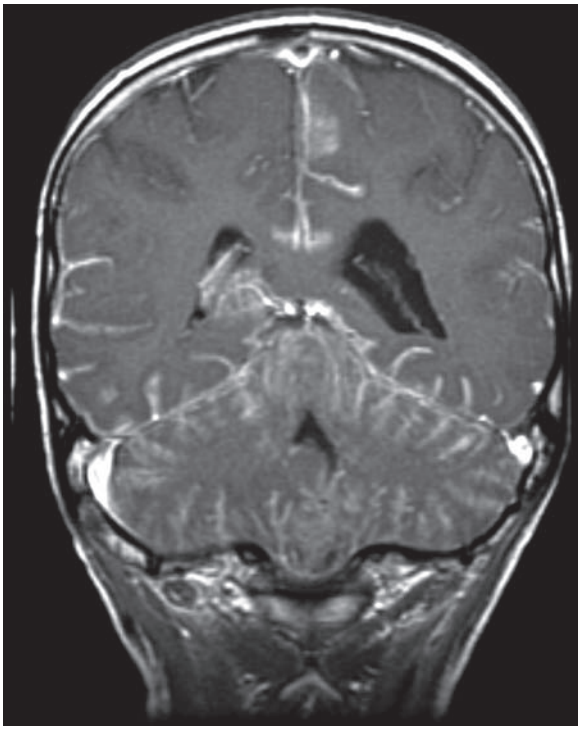


Figure 5.10

A coronal T1-weighted magnetic resonance image following contrast. Disseminated leptomeningeal tumor is clearly seen as a bright layer of tissue "sugar coating" the brain

surgery. For these reasons, an external ventriculostomy is usually preferred in the setting of hydrocephalus prior to surgery.

Virtually all children with a posterior fossa mass undergo a craniotomy. The goals of surgery are relief of mass effect, tissue diagnosis, and cytoreduction to facilitate further treatment. In general, there is no indication for stereotactic or open biopsy, unless the cerebellar tumor is diffuse or there is extensive leptomeningeal seeding. An effort should be made for a near total or gross total resection. (More details are provided in Chap. 14, Sect. 14.3). Children who are left with less than 1.5 cm^2 of residual disease on postoperative imaging have an improved prognosis for long-term, relapse-free survival (Zeltzer et al. 1999). Preoperative tumor infiltration to the brainstem does not affect prognosis (Zeltzer et al. 1999). Thus, removal of tiny components of medulloblastoma invading the brainstem or lying at the floor or exit of the fourth ventricle is not warranted, and should be avoided in order to minimize neurologic injury. A postoperative brain MRI scan should be obtained 48–72 h following surgery, before gliosis and blood product evolution obscure the ability to identify residual tumor.

A ventriculostomy placed preoperatively or intraoperatively is usually weaned over the first week or 10 days by either gradually elevating the external drain, or clamping the drain. This is usually done in an intensive care setting. If ICP rises, or if ventricular enlargement occurs with weaning of the ventriculostomy, the presence of hydrocephalus must be presumed and a permanent ventriculoperitoneal shunt should be placed. Shunt placement does not appear to increase the risk of systemic tumor spread (Berger et al. 1991). If the ventriculostomy can be removed successfully, ventricular size and clinical symptoms must continue to be observed carefully as delayed hydrocephalus can still occur.

5.2.6.2 Staging

Following surgery, the child requires staging to determine if there is evidence of tumor spread. If not already done, a full spine MRI with and without gadolinium is mandatory. Spine imaging should be delayed for at least 10–14 days following surgery, as blood products in the subarachnoid space can be misinterpreted as metastatic tumor. A lumbar puncture should be obtained in the same time period to assess cytology for microscopic tumor spread. Ventricular sampling of CSF for cytology has inferior sensitivity and should not be used, unless a lumbar sample absolutely cannot be obtained (Gajjar et al. 1999). If there is evidence of disseminated disease, a bone scan is often obtained to search for extraneural spread; bone-marrow biopsy is no longer recommended.

With these findings from staging, children over age 3 years are stratified into two risk groups, based upon resection extent and Chang metastasis staging (Tables 5.2 and 5.3) (Chang et al. 1969). Average

Table 5.2. Chang metastasis staging system for medulloblastoma (Chang et al. 1969)

M0	No evidence of gross subarachnoid or hematogenous metastasis
M1	Microscopic tumor cells found in cerebrospinal fluid
M2	Gross nodular seeding demonstrated in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles
M3	Gross nodular seeding in spinal subarachnoid space
M4	Extraneural metastasis

Table 5.3. Risk stratification for medulloblastoma in children ≥3 years

Average risk
<1.5 cm^2 postoperative residual tumor and Stage M0
High risk
>1.5 cm^2 postoperative residual tumor or Stage M1-4

risk includes children with less than 1.5 cm^2 residual and no metastasis. High risk is defined by more than 1.5 cm^2 residual or M+ disease. However, the impact of M1 disease on survival remains debatable. In two trials, Children's Cancer Group (CCG) 921 and HIT '91, overall survival was not significantly different in children staged as M1 or M0 (Zeltzer et al. 1999; Kortmann et al. 2000). Histological variants, such as large-cell medulloblastoma may portend a poor outcome. Recently, medulloblastomas with a significant degree of anaplasia are being considered high-risk, and therefore are not eligible in some average-risk studies. This trend will likely become more common in future trials.

Earlier, brainstem invasion (described as Chang stage T3b) was another indication for stratification as high-risk, but this does not appear to affect prognosis (Duffner et al. 1993). The older term low-risk, indicating less than 1.5 cm^2 residual, M0, and no brainstem invasion, has been abandoned.

Radiotherapy or chemotherapy does not usually commence until 3–4 weeks from surgery because of time required for wound healing, neurologic recovery, and staging. Baseline assessment of endocrine and cognitive function should be performed in the postoperative period, as CSI may adversely affect the pituitary and thyroid glands along with the cerebrum.

5.2.6.3 Radiotherapy

At present, a radiation dose of 23.4 Gy to the craniospinal axis plus a boost to 54 Gy to the posterior fossa followed by chemotherapy is the standard of care for average-risk disease and has resulted in 5-year survival of 80% or better (Packer et al. 2006). Areas of active investigation for average-risk disease include lowering of the craniospinal dose to 18 Gy, a conformal radiotherapy boost to the tumor volume rather than the entire prosterior fossa, and/or intensification of chemotherapy with autologous peripheral blood stem-cell support (Gajjar et al. 2006). In high-risk disease, 36 Gy to the craniospinal axis plus a boost at the posterior fossa to 54 Gy, followed by chemotherapy is the standard therapy and results in 5-year survival rates of 50–70%.

Since most patients requiring CSI are children, special considerations are necessary, such as proper stabilization during treatment and assistive anesthesia. In addition, many children have neurologic deficits impairing their ability to lie motionless for any length of time. The field arrangement consists of opposed lateral brain portals and a posterior spinal axis field, all of which are matched in the region of the cervical spine. This set-up usually requires that patients be placed in the prone position.

The usual radiation fields for medulloblastoma and other lesions of the posterior fossa include the contents of the posterior fossa, with at least a 1 cm margin and the inferior border at C2. A volume that includes the entire posterior fossa also delivers a significant dose to the parietal, occipital, and temporal lobes. Hearing, endocrine function, and cognitive ability may all be protected to some degree by a reduction in the overall area treated. Therefore, ongoing cooperative studies are evaluating whether the target volume for the primary site tumor boost in average-risk medulloblastoma can be reduced from

whole-posterior fossa to the tumor volume plus margin without compromising disease control.

In addition to reducing the volume and dose of radiation, alternative radiation modalities such as proton-beam radiotherapy have been suggested in an effort to mitigate potential long-term side effects of radiation. Although outcome data with use of proton beam for CNS tumors is limited and advocated mostly on theoretical grounds, benefits of proton-beam radiotherapy in children may be best exemplified by its use for CSI. Comparisons of proton beam, conventional 3D radiation, and IMRT for treatment of the posterior fossa and spinal column suggest superior sparing of normal structures by protons. In particular, protons are likely to mitigate long-term toxicities related to hearing, endocrine, and cardiac functions. (St Clair et al. 2004).

5.2.6.4 Chemotherapy

Attempts to omit CSI in children less than 3 years or exclusion of the entire neuraxis from the radiation field has resulted in reduced survival (Bouffet et al. 1992; Duffner et al. 1993). The cognitive and endocrinologic sequelae (see later) of craniospinal radiotherapy, along with the poor survival of children with high-risk medulloblastoma, has led to sustained efforts by cooperative groups to introduce chemotherapy in order to reduce radiation dosage, improve survival, or delay radiation.

In the late 1970s, the International Society of Pediatric Oncology (SIOP I), CCG (CCG 942), and the Pediatric Oncology Group (POG 7909) each performed prospective randomized trials of CSI alone versus postirradiation chemotherapy, heavily based in alkylators (lomustine or nitrogen mustard/procarbazine) plus vincristine, with or without prednisone (Evans et al. 1990; Tait et al. 1990; Krischer et al. 1991). An improvement in overall survival from chemotherapy was not apparent for all children, but a benefit did appear in those who had bulky residual disease or metastatic disease, that is, high-risk disease. These experiences and a series of subsequent trials demonstrated that medulloblastoma is one of the most chemotherapy-sensitive of all brain tumors. Alkylators and platinum compounds have remained the foundation of adjuvant chemotherapy, particularly lomustine and cisplatin, and sometimes procarbazine, cyclophosphamide, ifosfamide, or carboplatin. The mitotic inhibitor vincristine is often administered weekly during irradiation and then during adjuvant chemotherapy. In addition, the topoisomerase II inhibitor etoposide has shown promising activity in disseminated medulloblastoma and infant medulloblastoma, and its use is increasing (Duffner et al. 1993; Ashley et al. 1996). The antimetabolite methotrexate has been used in European trials, particularly before irradiation, but there remains concern in the United States about its potential for causing leukoencephalopathy.

In average-risk medulloblastoma, a series of trials from SIOP, the French Society of Pediatric Oncology (SFOP), POG and CCG (now merged into the Children's Oncology Group [COG]), and the German Society of Pediatric Oncology (GPO and the HIT trials) have attempted to reduce CSI by adding either preirradiation "neoadjuvant" chemotherapy or, more commonly, postirradiation chemotherapy (Table 5.4) (Bailey et al. 1995; Gentet et al. 1995; Kuhl et al. 1998; Packer et al. 1999; Kortmann et al. 2000; Thomas et al. 2000; Taylor et al. 2001; Gajjar et al. 2006; Packer et al. 2006). The study POG 8631/CCG 923 compared 23.4 and 36 Gy CSI, without any chemotherapy in either group. This study was suspended in 1990 when an interim statistical analysis revealed an increased rate of relapse in the reduced-dosage radiotherapy group (Thomas et al. 2000). Regardless, follow-up of this cohort over time has provided highly important data. First, the children receiving 36 Gy experienced an event-free survival of 67% at 5 years and 60% at 8 years. These results serve as a benchmark for average-risk disease. Second, event-free survival was marginally inferior for the 23.4 Gy group, at 52% at 5 years ($p = 0.077$). There was an increased rate of early relapse and increased risk of isolated exoprimary recurrence, contrary to earlier limited institutional experiences (Halberg et al. 1991; Deutsch et al. 1996). In contrast, the subsequent single-arm study CCG 9892, employing 23.4 Gy CSI plus a boost to the posterior fossa totaling 55.2 Gy with concurrent weekly vincristine, followed thereafter by eight courses of lomustine, cisplatin, and vincristine, attained a 5-year

Table 5.4. Cooperative group studies for average-risk medulloblastoma, age ≥3 years

Study	Years of accrual	Number of eligible patients	Pre-irradiation chemotherapy × cycles	Craniospinal radiotherapy[a]	Post-irradiation chemotherapy × cycles	Percent event-free survival at 5 years	Comments
SIOP II[b,c] (Bailey et al. 1995)	1984–1989	40 36 38 36	None None PCZ/VCR/MTX×1 PCZ/VCR/MTX×1	35 Gy 25 Gy 35 Gy 25 Gy	None None None None	60±8 69±8 75±7 42±8	No significant benefit from "sandwich" chemotherapy, but negative interaction between "sandwich" chemotherapy and reduced irradiation
SFOP M7[b,d] (Gentet et al. 1995)	1985–1988	31	"8-in-1"[e] ×2, HD MTX×2	30–37.5 Gy[f]	None	74	
POG 8631/ CCG 923[b] (Thomas et al. 2000)	1986–1990	44 44	None None	36 Gy 23.4 Gy	None None	67±7 52±11	Increased incidence of early, exoprimary neuraxis relapse
HIT '88/'89 (Kuhl et al. 1998)	1987–1991	55	PCZ/IFOS/VP16/ MTX/CDDP/ARAC x 2	35.2 Gy ($n=34$) <30 Gy ($n=21$)	None	61±7	Results compiled for all patients together
CCG 9892[g] (Packer et al. 1999)	1990–1994	65	None	23.4 Gy + weekly VCR	CCNU/CDDP/VCR×8	78±5	23% completed CDDP only with dose reduction and 36% did not complete CDDP because of ototoxicity
HIT '91[h] (Kortmann et al. 2000)	1991–1997	64 94	None IFOS/CDDP/ HD MTX/VP16/ ARAC×2	35.2 Gy + weekly VCR 35.2 Gy	CCNU/CDDP/VCR×8 CCNU/CBDCA/VCR×8 *if incomplete remission or progressive disease*		78±6% 3-year PFS 65±5% 3-year PFS Nonrandomized patients included
PNET-3[i](Taylor et al. 2001)	1992–2000	89 90	None VP16/VCR/ CBDCA/CPM×3	35 Gy 35 Gy	None None	72 59	EFS statistically significant, $p=0.05$
COG A9961[f](Packer et al. 2006)	1996–2000	193 186	None	23.4 Gy CSI 23.4 Gy CSI	CCNU/CDDP/VCR×8, or CPM/CDDP/VCR×8	81±2 86±9	EFS and OS not significant in two arms. Electrolyte disturbance more common in CCNU arm and infections more frequent in CPM arm
SJMB-96[j] (Gajjar et al. 2006)	1996–2003	86	None	23.4 Gy CSI	CPM/CDDP/VCR followed by stem cell rescue×4	83±10	Classic histology had better EFS than desmoplastic and large-cell anaplastic tumors

PCZ procarbazine; *VCR* vincristine; *MTX* methotrexate; *HD* high dose; *IFOS* ifosfamide; *VP16* etoposide; *CDDP* cisplatin; *ARAC* cytarabine; *CCNU* lomustine; *VCR* vincristine; *PFS* progression-free survival; *CBDCA* carboplatin; *CPM* cyclophosphamide

[a] Posterior fossa boost totaling 50–55.2 Gy
[b] Patients classified as low-risk
[c] Children 0–3 years included
[d] Children 24–35 months included and received 20 Gy to cranium
[e] "8-in-1" = methylprednisolone/VCR/CCNU/PCZ/hydroxurea/CDDP/ARAC/CPM;[f]23–35 Gy to cranium
[g] Children 3–10 years only
[h] Patients with and without residual disease, M1 patients included, and not all patients were randomized to therapy
[i] M0 and M1 patients only
[j] M0 only patients

event-free survival of 78%, statistically no different than the POG 8631/CCG 923 benchmark with 36 Gy. While this study accrued just 65 eligible patients, it appeared that chemotherapy could be substituted for at least some amount of CSI. The COG A9961 study randomized average risk medulloblastoma patients to receive either lomustine or cyclophosphamide in combination with cisplatin and vincristine following radiation treatment with 23.4 Gy CSI and whole posterior fossa boost to 54 Gy. Both groups had >80% event-free survival at 5 years with more infections in the cyclophosphamide arm (Packer et al. 2006).

To reduce overall treatment time, a prospective St. Jude study (SJMB-96) effectively treated medulloblastoma in a risk-adapted method with incorporated lower-dose radiation and a truncated chemotherapy regimen. Children with average-risk medulloblastoma were treated with 23.4 Gy, while children with high-risk medullobalstoma were given 36–39.6 Gy. After craniospinal radiotherapy, patients received four cycles of cisplatin, vincristine, and cyclophosphamide, followed by stem-cell rescue. Of the 134 patients enrolled, 89% completed treatment. Event-free survival was 85% in the average-risk group and 70% in the high-risk group. Of interest, histological subtype correlated with outcome, where 5-year event-free survival for classic histology was 84% compared to 77 and 57% in desmoplastic and large-cell anaplastic, respectively. In a current COG study, patients with average-risk medulloblastoma from ages 3–7 will be randomized to either 18 or 23.4 Gy to further reduce the potential side effects of radiation without compromising outcome (Gajjar et al. 2006). Whether greater experience with this approach will demonstrate a change in relapse patterns, for example, increased isolated exoprimary relapses, is uncertain. In high-risk medulloblastoma studies and even in some of the average-risk studies, there has been a consistent effort to deliver neoadjuvant chemotherapy, and sometimes postirradiation chemotherapy (Table 5.5) (Chang et al. 1969; Mosijczuk et al. 1993; Bailey et al. 1995; Gentet et al. 1995; Kuhl et al. 1998; Zeltzer et al. 1999; Tarbell et al. 2000; Taylor et al. 2005; Gajjar et al. 2006). The rationale for neoadjuvant chemotherapy is unencumbered treatment before radiation, when tolerance may be better and toxicity is less, and perhaps even disease control is increased. To date, there is less data to support such hypothetical advantages. In fact, myelosuppression in some instances has led to delays in initiation of radiotherapy or early disease progression (Mosijczuk et al. 1993; Kortmann et al. 2000). The risk of distant neuraxis relapse also appears to increase with preirradiation chemotherapy (Hartsell et al. 1997). It does seem clear that postirradiation chemotherapy improves survival in patients with high-risk medulloblastoma (Packer et al. 1994). At present, based on all studies, 5-year event-free survival appears to be at least 50% for high-risk patients.

In very young children, the challenge remains to reduce or eliminate the need for radiotherapy. An array of other studies has attempted to treat young children with postoperative chemotherapy alone to avoid the effects of radiotherapy. In 2005, three trials were published that conducted chemotherapy-only protocols in COG, SFOP, and the German HIT study. The COG 9921 trial treated 92 children with medulloblastoma, and resulted in 32% event-free survival at 5 years (Geyer et al. 2005). The French trial, BBSFOP, enrolled 79 patients <5 years of age with slightly better outcomes (Grill et al. 2005). The German HIT-SKK '92 methotrexate-based trial proved most promising with 50% survival in those with complete resection (Rutkowski et al. 2005). In patients from 8 months to 3 years of age with nonmetastatic medulloblastoma, preliminary results of COG P9934 found an improved outcome with the use of systemic chemotherapy, second-look surgery, and conformal radiation therapy limited to the posterior fossa. The study enrolled 78 patients from 2000 to 2006 with a 3-year event-free survival of 50% (Ashley et al. 2008).

5.2.7 Outcome

Data from multiple prospective studies conducted by the international community suggests that overall survival for all children with medulloblastoma now approaches 60% at 5 years and at least 40–50% at 10 years (Evans et al. 1990; Tait et al. 1990). In a review of 620 children treated on COG studies, relapse in

Table 5.5. Cooperative group studies for high-risk medulloblastoma, age ≥3 years

Study	Years of accrual	Number of eligible patients	Pre-irradiation chemotherapy × cycles	Craniospinal radiotherapy[a]	Post-irradiation chemotherapy × cycles	Percent event-free survival	Comments
SFOP M7[b,c] (Gentet et al. 1995)	1985–1988	37	"8-in-1"[d] × 2, HD MTX × 2	30–37.5 Gy[e]	"8-in-1" × 4	57 at 5 years	
POG 8695[f] (Mosijczuk et al. 1993)	1986–1990	36	CDDP/VCR × 3; CPM × 2	36 Gy	None		PFS 40% at 2 years Only 22 of 36 completed therapy, secondary to toxicity; start of radiotherapy delayed in most patients because of myelosuppression
SIOP II[g] (Bailey et al. 1995)	1984–1989	62 71	PCZ/VCR/MTX × 1 None	35 Gy 35 Gy	CCNU/VCR × 6 CCNU/VCR × 6	56 ± 7 at 5 years 53 ± 6 at 5 years	
CCG 921[h] (Zeltzer et al. 1999)	1986–1992	101 102	None "8-in-1" × 2	36 Gy + weekly VCR 36 Gv	CCNU/VCR/PCZ × 8 "8-in-1" × 8		63 ± 5% PFS at 5 years 45 ± 5% PFS at 5 years
HIT '88/'89 (Kuhl et al. 1998)	1987–1991	39	PCZ/IFOS/VP16/MTX/CDDP/ARAC × 2	35.2 Gy	CCNU/PCZ	33 ± 8 at 5 years	
POG 9031[c] (Tarbell et al. 2000)	1990–1996	114 112	CDDP/VP16 × 3 None	35.2 M0-1; 40 Gy M2-3 35.2 M0-1; 40 Gy M2-3	CPM/VCR × 8 CDDP/VP16 × 3, then CPM/VCR × 8	78 ± 4 at 2 years 80 ± 4 at 2 years	Response to chemotherapy correlated with outcome
HIT '91 (Kortmann et al. 2000)	1991–1997	40[i]	None IFOS/CDDP/HD MTX/VP16/ARAC × 2	35.2 Gy + weekly VCR 35.2 Gy	CCNU/CDDP/VCR × 8 CCNU/CBDCA/VCR × 8 *if incomplete remission or progressive disease*		For all patients 65 ± 12% PFS for M1, and 30 ± 15% for M2-3
PNET-3[j] (Taylor et al. 2005)	1992–2000	68	VCR/VP16/CBDCA × 4 alternating with VIN/VP16/CPM × 4	35 Gy	None	35 ± 11.5 at 5 years	Seven patients treated with chemotherapy did not receive RT; 24 patients given boost to metastatic areas
SJMB-96[k] (Gajjar et al. 2006)	1996–2003	48	None	36–39.6 Gy	TPT/CPM/CDDP/VCR followed by stem cell rescue × 4[l]	70 ± 15 at 5 years ±	No significant difference in those who received TPT. 54% had classic histology

HD MTX high-dose methotrexate; *CDDP* cisplatin; *VCR* vincristine; *CPM* cyclophosphamide; *PFS* progression-free survival; *PCZ* procarbazine; *CCNU* lomustine; *IFOS* ifosfamide; *VP16* etoposide; *ARAC* cytarabine; *CBDCA* carboplatin; *TPT* topotecan

[a] Posterior fossa boost to 54–55.8 Gy

[b] Children >10–35 months included and received 20 Gy to cranium

[c] Brainstem invasion used as a criterion for high-risk

[d] "8-in-1" = methylprednisolone/ VCR/CCNU/PCZ/hydroxurea/CDDP/ARAC/CPM; [e]22–35 Gy to cranium

[f] Children ≥4 years, and brainstem invasion used as additional criterion for high-risk

[g] Children 0–3 years included, and brainstem invasion but not M1 used as criteria for high-risk

[h] Children ≥1.5 years included and brainstem invasion used as additional criterion for high-risk

[i] Details of which regimen 21 nonrandomized M1 and 19 randomized M2-3 patients not provided

[j] M1 randomized, M2-M3 treated on experimental arm only

[k] M1-M3 patients and M0 patients with assessable disease on MRI after radiation. M0-1 treated with 36 Gy and M2-3 with 39.6 Gy

[l] 31 out of 48 received TPT prior to radiotherapy

high-risk patients was more likely in the first 2 years (85%) than it was in average-risk (65%) patients (Packer et al. 2008a). Relapse beyond 8 years from diagnosis appears unlikely (Belza et al. 1991). While some satisfaction can be derived from these modest improvements in survival, the growing number of children cured of their disease has led to a sobering recognition of the severity of late effects, namely cognitive decline, growth failure, endocrinopathies, hearing loss, CNS vascular disease, and secondary malignancies.

Cranial irradiation has been linked to cognitive decline, with intelligence quotient (IQ) used as a surrogate marker. Cognitive decline appears to be most notable in attention, short-term memory, visual-motor processing, spatial relations, and quantitative skills. Whether the additional radiotherapy boost to the posterior fossa, with exposure beyond the clinoid processes anteriorly to the hippocampus and forebrain, exacerbates this damage is unknown. While data are very limited, in children less than the age of 9 at diagnosis of medulloblastoma who receive 36 Gy CSI, full-scale IQ approximates 70, 6 to 9 years later; for those receiving 23.4 Gy, IQ averages 85 (Mulhern et al. 1998). Indeed, in children less than 7 years of age treated with 24–36 Gy CSI, 100% go on to require special education services (Radcliffe et al. 1992). For children older than 3 years treated with 23.4 Gy and infants salvaged with a median dosage of 35.2 Gy following relapse after chemotherapy, a striking (and worrying) finding is an approximate four-point decline in IQ every year following diagnosis (Walter et al. 1999; Ris et al. 2001). It is unclear when the IQ decline reaches a plateau. As survivors are increasing in number, long-term effects of radiation on cerebrovasculature continue to rise. Vascular malformations and ischemic events have become increasingly common, emphasizing the need for consistent follow-up and detailed neuroimaging (see Chapter 13).

Growth failure appears to be a nearly universal phenomenon in patients with medulloblastoma, secondary to radiation exposure to the pituitary gland and the spinal cord and vertebral column. Hypothyroidism and gonadal dysfunction are also common. High-frequency hearing loss from both radiation exposure to the cochlea and damage to its hair cells from cisplatin is also quite common. A detailed discussion of these late effects is provided in Chap. 17 and other sources (Blaney et al. 2006). As long-term survival continues to rise, the incidence of secondary malignancies from chemotherapy and radiation is also being increasingly recognized. The 8-year cumulative incidence of secondary malignancies in the average-risk protocol COG-A9961 was 3.5% (Packer et al. 2008b). Children with Gorlin syndrome are also at a particularly high risk for secondary cancers (Stavrou et al. 2001).

5.2.8 Future Directions

Future investigation in medulloblastoma will focus on both the optimal dosage and delivery method for radiotherapy. A single pilot study using 18 Gy CSI followed by lomustine, cisplatin, and vincristine in 10 patients less than age 5 at diagnosis of average-risk medulloblastoma produced 7 long-term survivors 4 years later with no significant change from baseline IQ (Goldwein et al. 1993). A multi-institutional pilot study of this approach is underway, and a COG-sponsored clinical trial is in the developmental stage to study this dosage in younger children. As far as delivery is concerned, technological improvements now allow for "conformal" radiotherapy to limit radiation scatter from the posterior fossa boost or even to limit the clinical target volume of the boost to the original tumor volume rather than the entire posterior fossa (Freeman et al. 2002). A prospective trial of 86 average-risk medulloblastoma patients from the ages of 3–21 years reduced the radiation volume in the posterior fossa by 13% after 23.4 Gy CSI without demonstrating a change in disease control after 5 years. The overall radiation dose to the temporal lobes, cochleae, and hypothalamus was significantly reduced compared to other trials, which should improve the overall long-term outcome (Merchant et al. 2008). Conformal techniques continue to promise to limit exposure to the cochlea, hippocampus, forebrain, hypothalamus, and pituitary gland, but may carry a possible risk of increased local recurrence as survival improves.

5.3 Atypical Teratoid/Rhabdoid Tumor

5.3.1 Epidemiology

Since ATRT was first described as a distinct entity in the 1980s, measurement of the true incidence is difficult. ATRT constitutes 1–2% of pediatric brain tumors (Louis et al. 2007). Some reports have suggested that ATRT accounts for 10% of CNS tumors in infants (Biegel 2006). The tumor has a striking predilection for infants, and mean age at diagnosis is 1–7 months. Ninety-four percent of children diagnosed are less than 5 years of age (Packer et al. 2002; Louis et al. 2007). Boys outnumber girls almost 2 to 1 (Hilden et al. 2004; Tekautz et al. 2005; Louis et al. 2007).

5.3.2 Pathology

ATRT is a malignant (WHO grade IV) (WHO grade IV) embryonal tumor containing rhabdoid cells and often additional, disparate components of small embryonal, mesenchymal, and epithelial cells (Fig. 5.11). There are sheets of rhabdoid cells, which appear as medium-sized, ovoid cells with eccentric sometimes reniform nuclei, prominent nucleoli, and fine granular homogeneous cytoplasm. These cells almost always express epithelial membrane antigen and vimentin (Burger et al. 1998). Mitoses are abundant. The labeling index, defined by positive staining for MIB-1, can be as high as 80% (Louis et al. 2007). Only 10% of tumors are composed strictly of rhabdoid cells, and one-third to one-quarter exhibit an epithelial and/or mesenchymal component (Packer et al. 2002). Epithelial cells may appear adenomatous or squamous, or occur in nests. The epithelial and mesenchymal cells can misleadingly suggest a teratoma, but ATRT is negative for germ-cell markers (Packer et al. 2002). Two thirds of tumors possess a small cell component, masquerading as medulloblastoma or other embryonal tumors (Louis et al. 2007).

ATRT appears grossly as a soft, pinkish, bulky mass demarcated from the brain parenchyma, often with necrosis or sometimes with dystrophic calcification, cysts, or hemorrhage. Over half of these tumors are located in the posterior fossa, with the remainder situated mostly in the supratentorial compartment, sometimes at the pineal region. On MRI, the tumor may appear similar to medulloblastoma, with hypointensity on T1-weighted images and isointensity on T2-weighted images (Fig. 5.12). Enhancement with gadolinium can be heterogeneous.

Cytogenetic and molecular findings are required to establish the diagnosis of ATRT. Ninety percent of tumors demonstrate monosomy or a deletion of chromosome 22 by fluorescence in situ hybridization or loss of heterozygosity studies (Burger et al. 1998; Biegel et al. 1999). Chromosome 22 abnormalities can be seen in other tumors, and hence this finding is neither sufficient nor necessary for diagnosis. More specifically, it is believed that all ATRTs demonstrate homozygous deletions or mutations of the *hSNF5/INI1* gene, which maps to chromosome 22q11.2 (Biegel et al. 1999). While its role in malignant transformation is unknown, *INI1* does appear to be a tumor-suppressor gene involved in rhabdoid tumors of the brain, as well as the kidney and other extraneural sites. A fraction of children have germline mutations of *INI1*, and such can rarely be transmitted in an autosomal dominant fashion with incomplete penetrance (Biegel et al. 1999; Taylor et al. 2000).

5.3.3 Treatment

The prognosis for this tumor is dismal and thus optimal therapy is unknown. Median survival is less than 10 months, and most children die within a year of diagnosis (Olson et al. 1995; Burger et al. 1998; Hilden et al. 1998; Biegel et al. 1999). Staging studies similar to those in medulloblastoma are reasonable, although ATRT has not been reported to disseminate to bone. Incidence of neuraxis dissemination is uncertain, and reports range from 15 to 40% at diagnosis (Burger et al. 1998; Hilden et al. 1998; Packer et al. 2002). ATRT does not appear to spread outside the neuraxis, and renal rhabdoid tumors do not appear to invade the CNS; thus, abdominal or chest staging is not necessary.

There have been case reports of prolonged survival using high-dose chemotherapy with hematopoietic stem-cell rescue or multimodality treatment with CSI, multiagent chemotherapy, and triple intrathecal

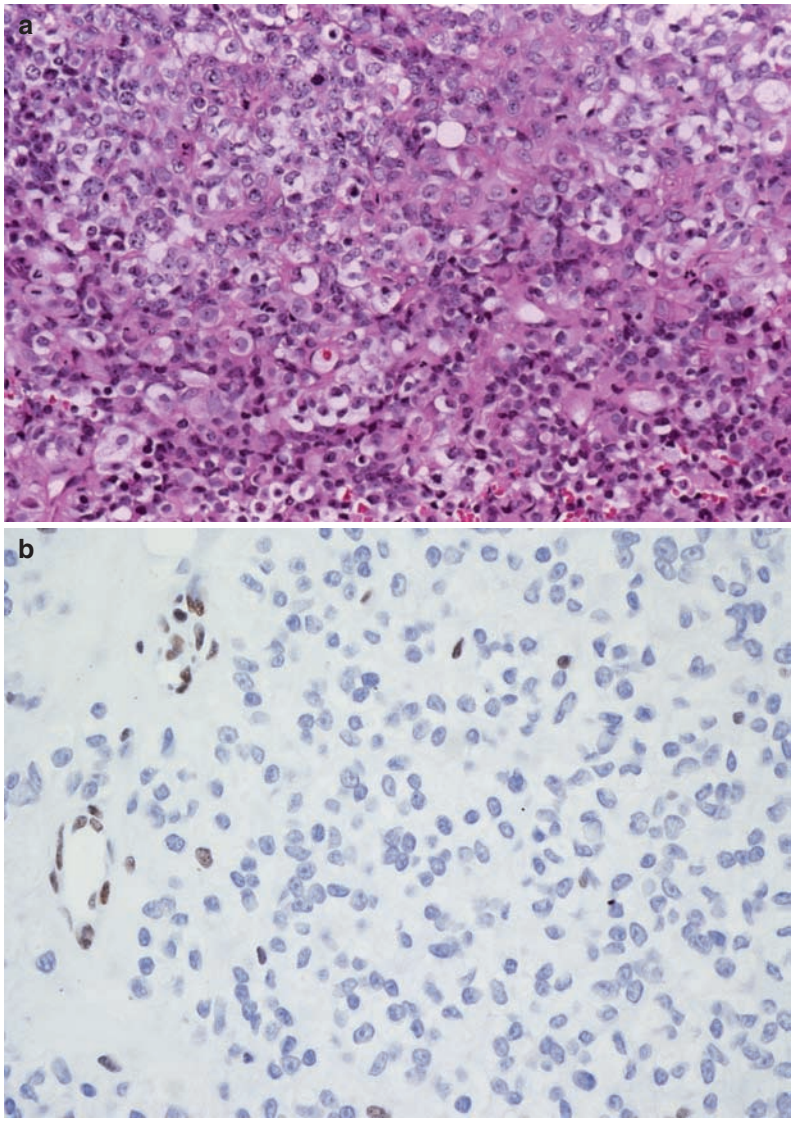


Figure 5.11
Atypical teratoid/rhabdoid tumor. (**a**) Hematoxylin and eosin micrograph, with its disparate small embryonal cell and epithelial and mesenchymal cell components. (**b**) BAF47 immunostain showing lack of reactivity for the vast majority of tumor cells. There is some scattered positive reactivity adjacent to blood vessels which is not significant

chemotherapy, similar to Intergroup Rhabdomyosarcoma Study III guidelines (Olson et al. 1995; Hilden et al. 1998). Other attempts using infant brain tumor chemotherapy regimens with cyclophosphamide, vincristine, cisplatin, and etoposide have led to tumor reduction, but responses do not appear to be sustained (Packer et al. 2002). Early incorporation of radiation therapy with intensive combination chemotherapy may be of benefit, when feasible (Chi et al. 2009).

5.4 Other Embryonal Tumors

5.4.1 Pineoblastoma

Pineoblastomas are WHO grade IV malignant tumors of the pineal region, composed of patternless sheets of densely packed small cells. Homer-Wright rosettes and Flexner-Wintersteiner rosettes, indicating retinoblastic differentiation, may be seen. These tumors comprise half of pineal parenchymal tumors, which

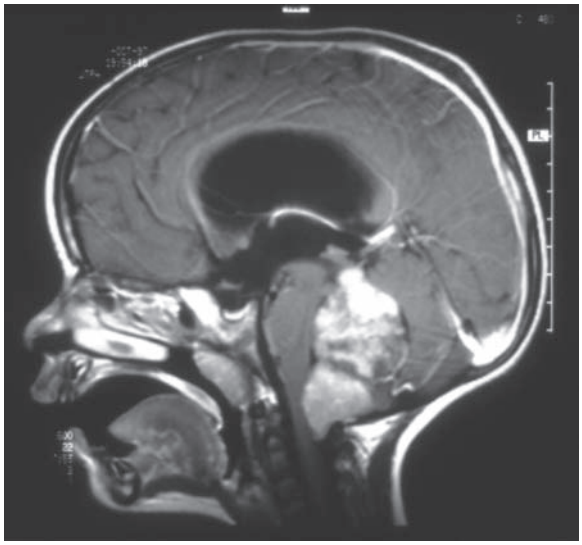


Figure 5.12
T1-weighted postcontrast sagittal magnetic resonance image of a large posterior foss a ATRT in a 3-month-old boy presenting with a facial palsy

occur in the first two decades of life, and are slightly more common in males (Schild et al. 1993; Louis et al. 2007). Like other embryonal tumors, these too have a tendency for neuraxis metastasis. Pineoblastoma can occur with bilateral/ familial retinoblastoma, termed "trilateral retinoblastoma," and in such instances, mean survival is just 11 months (De Potter et al. 1994). Pineoblastoma has also been reported with Turcot syndrome (Ikeda et al. 1998). Pineoblastoma should be distinguished from pineocytoma or a benign pineal cyst.

The mainstay of treatment for pineoblastomas has been irradiation, typically craniospinal, yielding 1-, 3-, and 5-year overall survival rates in older children and adults of 88, 78, and 58%, respectively (Schild et al. 1993). Patients with pineoblastomas fare significantly better than those with other supratentorial embryonal tumors (Cohen et al. 1995), and limited prospective data suggest that CSI plus chemotherapy, such as vincristine, lomustine, and prednisone as in CCG 921, may improve overall and PFS in children older than 3 years to 73 and 61%, respectively (Jakacki et al. 1995). In a single-institution cohort of 11 patients, gross-total resection correlated with improved survival, as did combined radiation and chemotherapy, in the 7 surviving patients (Gilheeney et al. 2008). Chemotherapy alone is insufficient for managing these tumors, especially among infants (Duffner et al. 1995; Jakacki et al. 1995; Jakacki 1999). High-dose chemotherapy with autologous stem-cell rescue in a cohort of 12 adults and children resulted in 4-year PFS and overall survival rates of 69 and 71%, respectively, with no difference in 4-year PFS in localized versus metastatic disease (Gururangan et al. 2003). A residual enhancing mass persisting for as long as 5 years before resolving is not uncommon in pineoblastomas following radiotherapy and chemotherapy, and does not indicate treatment failure (Jakacki et al. 1995).

5.4.2 Other Nonpineal Embryonal Tumors

Outcome for nonpineal supratentorial embryonal tumors has historically been worse than that for pineoblastoma or medulloblastoma, with a 3-year PFS of 33% following CSI and chemotherapy (Cohen et al. 1995). The large European prospective study PNET-3 enrolled 68 patients (54 nonpineal region tumors) and randomized patients to chemotherapy followed by radiation therapy or radiation therapy alone, with both groups receiving chemotherapy after radiation therapy. No statistically significant difference was noted in the two groups overall, but overall and event-free survival were significantly better for pineal-region patients. In patients with nonpineal region tumors, event-free survival survival at 3 and 5 years was 41%, while patients with pineal region tumors had event-free survival rates of 93 and 71%, respectively (Pizer et al. 2006).

CSI of 35 Gy with additional boost to at least 54 Gy to the tumor region is necessary (Timmermann et al. 2002). Incomplete resection, tumor dissemination, and younger age appear to be adverse prognostic factors (Albright et al. 1995; Reddy et al. 2000).

Very small numbers of the nonpineal embryonal tumors limit execution of trials aimed specifically at these entities. Additionally, their biologic characterization is incomplete. Analysis

by comparative genomic hybridization shows that supratentorial PNET and medulloblastoma have distinctly different patterns of chromosomal gains and losses, suggesting different biologic entities (Russo et al. 1999). Nevertheless, the distinct natural history and comparably poorer prognosis of PNET merit experimental, innovative treatments different from those for medulloblastoma. The reader can refer elsewhere for fuller descriptions of the uncommon tumors ependymoblastoma (Mork and Rubinstein 1985; Dorsay et al. 1995; Robertson et al. 1998; Gerber et al. 2008), cerebral neuroblastoma (Horten and Rubinstein 1976; Berger et al. 1983; Bennett and Rubinstein 1984), ganglioneuroblastoma, and medulloepithelioma (Molloy et al. 1996).

5.5 Conclusions

Pediatric embryonal malignancies are a clinically and biologically heterogenous group of tumors. Therapeutic advances in surgery, radiation therapy, and chemotherapy have not only resulted in improved survival of patients with medulloblastoma, but are also associated with increased treatment-related toxicity and secondary malignancies. Improved understanding of pathologic and biologic features have allowed for identification of ATRT as a distinct tumor type and better treatment stratification for medulloblastoma. Although standard-risk medulloblastoma is curable in many patients, most embryonal pediatric CNS tumors have high relapse rates with current treatment strategies. Ongoing investigation is required to better characterize high-risk tumor subtypes, and identify better treatment strategies.

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Intracranial Germ Cell Tumors

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Contents

6.1 Introduction

Intracranial germ cell tumors (GCT) are a group of relatively uncommon tumors that have histological, genetic, biochemical, diagnostic, and therapeutic similarities to GCTs that occur outside the central nervous system (CNS). Both types have extra-embryonic origins in the fetal yolk sac, which accounts for their numerous similarities, while subsequent migratory paths in early fetal development are responsible for the difference in location. There are two distinct histological groups within the larger group of intracranial GCTs: germinomas and nongerminomatous GCTs (NGGCTs). Germinomas are more common, accounting for 50–70% of the total number (Jooma and Kendall 1983; Oi and Matsumoto 1992). NGGCTs represent one third of intracranial GCTs and consist of embryonal carcinoma, endodermal sinus (yolk sac) tumor, choriocarcinoma, teratoma, and GCTs of mixed cellular origin. Jennings et al. found that germinomas accounted for 65% of intracranial GCTs, followed by teratomas (18%), endodermal sinus tumors (7%), embryonal carcinomas (5%), and choriocarcinomas (5%) (Jennings et al. 1985b). Other studies show a higher incidence of mixed tumors ranging from 21 to 32% (Matsutani et al. 1997; Salzman et al. 1997). Although most of these tumors are malignant, some are defined as benign (Table 6.1).

Intracranial GCTs most commonly arise from the pineal or suprasellar region, deep locations that have historically reduced the likelihood of gross total resection. For this reason, radiation alone, frequently encompassing a large treatment volume, was considered the preferred treatment standard. In the last two

Table 6.1. Classification of GCTs according to benign vs. malignant tumors

Benign germ cell tumors	Malignant germ cell tumors
Immature teratoma[a]	Germinoma
Mature teratoma	Embryonal carcinoma
	Endodermal sinus tumor (yolk sac tumor)
	Choriocarcinoma
	Mixed germ cell tumor

[a]May indicate rare malignant germ cell elements

decades, effective chemotherapy in combination with improved neurosurgical procedures and radiation techniques have resulted in dramatic improvements in survival. However, in children, the morbidity caused by radiation therapy, particularly craniospinal irradiation (CSI) has prompted many investigators to explore approaches that reduce the volume and dose of radiotherapy, while preserving high cure rates for patients with only focal disease (Shirato et al. 1997; Choi et al. 1998; Matsutani et al. 1998; Aoyama et al. 2002).

In this chapter, we review the epidemiology of intracranial GCTs, the pathologic features of both benign and malignant GCTs, and their molecular and cytogenetic characteristics. We discuss the clinical features of intracranial GCTs and the role of imaging and laboratory investigations in diagnosis. In broaching the controversy surrounding diagnostic biopsy, we delineate the arguments for and against mandatory biopsy prior to treatment. Finally, we discuss risk stratification to intensify treatment in patients with intracranial GCTs that have a poor prognosis.

6.2 Epidemiology

6.2.1 Location

Intracranial GCTs account for less than 4% of pediatric brain tumors in North America. Most intracranial GCTs originate near the third ventricle, extending from the suprasellar cistern to the pineal gland. Pineal region GCTs outnumber those in the suprasellar region by a ratio of 2:1, but in 5–10% of cases, the tumor is found in both regions (Jennings et al. 1985b). Whether this is due to bifocal disease or tumor spread remains unknown. Intracranial GCTs occur less commonly in other midline locations such as basal ganglia, thalamus, and ventricles, particularly the fourth ventricle. Intracranial GCTs have also been reported in the cerebellum (Nakase et al. 1994), medulla oblongata (Nakajima et al. 2000), and optic nerves (Iizuka et al. 1996). By GCT sub type, germinomas are more frequent in the suprasellar region and in females, while NGGCTs are more common in the pineal region and in males.

6.2.2 Age, Sex, and Geographic Variation

In western countries, intracranial GCTs account for 0.4–3.4% of all intracranial tumors, whereas in Japan and Taiwan, intracranial GCTs are more common and account for 2.1–11.1% of brain tumors (Jellinger 1973; Jennings et al. 1985b; Hoffman et al. 1991; Lin et al. 1997). This phenomenon is also seen in testicular GCTs for which the incidence in Japan is far greater than that seen in the United States (Packer et al. 2000). Most intracranial GCTs occur in adolescents and young adults (68%), with peak incidence occurring at 10–12 years of age. However, these lesions can be seen in newborns as well as in older adults. In particular, NGGCTs preferentially arise in younger children, whereas germinomas are most common in teenagers (Jennings et al. 1985b).

Intracranial GCTs are not distributed equally by gender. In the United States, between 1986 and 1995, incidence rates were 2.3 per million for males and 0.9 per million for females, representing a male predominance of 2.5:1. When examined by histology, NGGCTs demonstrate a male:female ratio of 3.2:1, while germinomas reveal a male:female ratio of only 1.8:1 (Jennings et al. 1985b). In females, 75% of intracranial GCTs develop in the suprasellar region, whereas in males 70% are found in the pineal area. The reason for these gender differences is unclear. Between the 1970s and the 1990s, the incidence of intracranial GCTs increased in the United States from 0.6 per million between 1975 and 1979 to 1.9 per million between 1990 and 1995 (Bernstein et al. 1999).

6.3 Pathology

6.3.1 Etiology

GCTs can be divided into extragonadal tumors and gonadal tumors, the latter encompassing half of all such tumors. Among extragonadal sites, half are sacrococcygeal and 40% arise intracranially. Rare sites of extragonadal GCTs include midline regions such as the retroperitoneal and nasopharynx. Their sites of origin notwithstanding, the features of GCTs, whether by light microscopy, electron microscopy, or enzyme or immunohistochemical assays, are identical (Jennings et al. 1985b; Felix and Becker 1990).

The pathogenesis of intracranial GCTs remains elusive. Although gonadotropins have been implicated in the pathogenesis of gonadal GCTs, such evidence for intracranial GCTs is lacking. One hypothesis is that GCTs arise most commonly near centers of gonadotropin regulation because such regions serve as sanctuary sites for undifferentiated germ cells (Jennings et al. 1985b). An additional role for the pineal gland in the neuroendocrine regulation of neoplastic growth has also been suggested (Lapin and Ebels 1981).

The etiology of intracranial GCTs is thought to be mismigration of primordial germ cells during embryonic development, followed by malignant transformation. According to the "germ-cell theory," primordial germ cells normally develop from the extra-embryonic yolk sac endoderm and migrate to the gonadal folds. Germinomas as well as embryonal carcinomas can develop by further differentiation and transformation of the original primordial germ cells. Embryonal carcinomas are composed of pluripotent cells that develop into endodermal sinus tumors, choriocarcinomas, or teratomas depending on the developmental pathway the cells undertake (Teilum 1976). Others have suggested that primordial germ cells can differentiate to yield either embryonal carcinomas or teratomas by differentiation through embryonic pathways, or endodermal sinus tumors or choriocarcinomas by extra-embryonic pathways (Takei and Pearl 1981).

The "germ-cell theory" is supported by the fact that interaction of the C-kit receptor with its ligand, steel factor (SLF), mediates the migration of primordial germ cells. Lack of C-kit in animal models prevents germ-cell migration. The gradient of SLF found from the yolk sac to the gonadal ridge is thought to guide the migration of primordial germ cells, and extragonadal GCTs are thought to arise from such mismigration. The protooncogene *c-kit* encodes a cell-surface receptor that carries an intrinsic tyrosine kinase activity in its cytoplasmic portion. The interaction of Kit with SLF leads to receptor dimerization, kinase activation, and tyrosine phosphorylation of specific cytoplasmic proteins. Mutations in Kit and SLF that result in a defective signaling pathway leading to infertility have been identified (Loveland and Schlatt 1997; Cushing et al. 2002).

An alternative theory, the "embryonic-cell theory," suggests that a pluripotent embryonic cell escapes normal developmental signals and gives rise to GCTs. A third hypothesis contends that germinoma is the only neoplasm arising from germ cells, and other GCTs arise from misfolding and misplacement of embryonic cells into the lateral mesoderm early in embryogenesis, leading to the entrapment of these cells into a variety of different brain regions (Sano et al. 1989). And finally, a more recent hypothesis argues that neural stem cells, because of their pluripotent potential in vitro, may be the initiating cell for intracranial germ-cell lesions (Scotting 2006).

6.3.2 Classification

The current World Health Organization (WHO) classification of GCTs is based on histology and tumor markers such as alpha-fetoprotein (AFP) and beta-human chorionic gonadotrophin (β-HCG) that have become important in diagnosis as well as prognosis. As mentioned above, different GCTs may represent the malignant forms of distinct stages of normal embryonic development. For example, primordial germ cells result in germinomas, embryonic differentiation gives rise to teratomas and embryonal carcinomas, and extra-embryonic derivatives of the yolk sac and trophoblast give rise to endodermal sinus tumors and choriocarcinomas, respectively. Intracranial GCTs can also be classified based on tumor markers found in serum or cerebrospinal fluid (CSF), which can influence diagnoses and prognoses

of patients with intracranial GCTs. Typically, germinomas are nonsecreting tumors, whereas NGGCTs usually secrete AFP and/or β-HCG. Germinomas are associated with better prognoses than NGGCTs.

6.3.3 Histopathology

Intracranial germinomas are histologically identical to dysgerminomas of the ovary and seminomas of the testis (Beeley et al. 1973). Microscopically, they are large monomorphic cells with abundant clear cytoplasm, arranged in nests separated by bands of connective tissue. The differential diagnosis includes lymphoma and endodermal sinus tumor. Germinomas can be identified by either positive placental alkaline phosphatase (PLAP) staining or positive OCT4 staining, with the latter being superior; whereas endodermal sinus tumors stain positive for AFP (Hattab et al. 2005).

Among NGGCTs, teratomas are designated as mature or immature, based on the absence or presence of differentiated tissues. Mature teratomas contain mature tissues from all three embryonic layers (ectoderm, mesoderm, and endoderm). Immature teratomas are distinguished from mature teratomas by the presence of immature tissues, usually neuroepithelium. Embryonal carcinomas arise from pluripotent embryonic cells and are characterized by large cells with large nuclei and nucleoli with varying amounts of central necrosis. Embryonal carcinomas can produce both AFP and β-HCG. Unlike other GCTs, CD30 (Ki-1 antigen) immunohistochemical staining is positive in embryonal carcinomas. Endodermal sinus tumors arise from differentiated extra-embryonic tissue, which usually occur as part of mixed GCTs, and produce AFP. Choriocarcinomas arise from placental trophoblastic tissue, which also generally occur as part of mixed GCTs, and are characterized by the presence of syncytiotrophoblasts that secrete β-HCG (Felix and Becker 1990; Hawkins 1990; Cushing et al. 2002).

6.3.4 Molecular Biology and Cytogenetics

Multiple complex karyotypes have been reported for intracranial GCTs including loss of chromosomes 4, 9p, 11, 13, and 17p as well as gain of chromosomes 8q, 21, and 1q. In addition, whereas, isochromosome 12p seems to be important in the development of testicular tumors, it is less common in extragonadal tumors (de Bruin et al. 1994; Yu et al. 1995; Lemos et al. 1998). A recent study, using comparative genomic hybridization to analyze pineal region GCTs, reported various abnormalities including gains on 12p (40%), 8q (27%), and 1q (20%), as well as losses on 13q (47%), 18q (33%), 9q, and 11q (20% each). The authors also noted different cytogenetic abnormalities based on histology. For example, the most common chromosomal changes in germinomas were −13q and −18q (38% each), whereas in mixed teratomas–germinomas frequent abnormalities included +8q (100%), +12p (75%), −13q (75%), and −9q (50%) (Rickert et al. 2000). Okada et al. examined 25 intracranial GCTs and found an increased number of X chromosomes in 23/25 cases and noted hypomethylation of the additional X chromosome in 81% of the tumors. Only 20% of cases had increased copy number of 12p and 12% had loss of 13q. They concluded that along with the increased incidence of intracranial GCTs in males as well as predisposition in patients with Kleinfelter syndrome, sex chromosome aberrations might have an important role in the development of GCTs (Okada et al. 2002).

In addition to cytogenetic changes, some of the genes that may be important in the development of GCTs have been defined. Recently, alterations in the *mdm-2* gene, often amplified in sarcomas, have been implicated in tumorigenesis of some testicular and intracranial GCTs. Mdm-2 is a negative regulator of the p53 tumor-suppressor gene product and is, in turn, induced by p53. Iwato et al. searched for *p53* mutations and *mdm-2* amplifications in intracranial GCTs and found *mdm-2* amplifications in 19% of intracranial GCTs. Theoretically, increases in mdm-2 protein level would antagonize p53 function (Iwato et al. 2000b).

Iwato et al. examined the *INK4a/ARF* locus for alterations in intracranial GCTs and found alterations in 71% of 21 tumors. The *INK4a/ARF* genes are tumor-suppressor genes and the INK4a protein inhibits its cyclin-dependent kinases and decreases phosphorylation of the retinoblastoma protein, resulting

in cell-cycle arrest. The ARF protein interacts with mdm-2 and stimulates the latter's degradation. Interestingly, alterations in *INK4a/ARF* were more common in germinomas (90%) than in NGGCTs (55%) (Iwato et al. 2000a).

6.4 Clinical Features: Signs and Symptoms

Presenting symptoms of pineal region tumors are directly related to tumor location. Pineal region tumors usually present with symptoms of eye-movement disorders or symptoms caused by increased intracranial pressure due to obstructive hydrocephalus. Headache, nausea, and vomiting are the most common symptoms, seen in 56–93% of patients. Blurred vision and somnolence are seen in 20–54% of patients, while ataxia, seizures, and behavioral disturbances are seen in 10–28% of patients (Saitoh et al. 1991; Drummond and Rosenfeld 1999; Steinbok and Cochrane 2001). Involvement of adjacent midbrain structures can result in visual disturbances, such as Perinaud's syndrome, which are seen in 25–50% of pineal region GCTs. Perinaud's syndrome is an impairment of upward gaze in combination with dilated pupils that are nonreactive to light, but responsive to accommodation. Upward gaze may in addition elicit rhythmic convergence of the eyes followed by retraction of the eyes into the orbits.

On examination, papilledema is present in about half of the patients. In patients with pineal region GCTs, approximately 80% present with symptoms of increased intracranial pressure, whereas less than 10% of patients with suprasellar GCTs present with increased intracranial pressure. Endocrinopathies such as diabetes insipidus or precocious puberty occur in patients with intracranial GCTs and account for approximately 6–12% of presenting symptoms. In fact, patients with suprasellar GCTs most commonly present with endocrinopathies such as diabetes insipidus and manifestations of anterior pituitary dysfunction such as growth failure. These symptoms were seen in 87% of patients versus only 8% of patients with pineal region GCT (Jooma and Kendall 1983; Edwards et al. 1988; Hoffman et al. 1991; Saitoh et al. 1991; Kang et al. 1998; Steinbok and Cochrane 2001). Intracranial GCTs may infiltrate adjacent structures such as the hypothalamus (11%) and third ventricle (22%), or disseminate throughout the CSF (10%). For endodermal sinus tumors and choriocarcinomas, dissemination is more common, and third ventricular involvement is present in over 40% of cases. Extracranial spread to the lungs and bones has also been reported in approximately 3% of patients (Gay et al. 1985; Jennings et al. 1985a, b).

6.5 Diagnosis and Staging

Operative morbidity and mortality prior to the 1980s were high, and impeded histological diagnoses of many intracranial GCTs. Therefore, radiodiagnostic trials of 20 Gy historically functioned as surrogates for a histological diagnosis of germinoma, since these tumors were characteristically radioresponsive. Poor response to 20 Gy indicated an alternate diagnosis such as NGGCT or glioma. A robust response to 20 Gy suggested a diagnosis of germinoma and treatment was continued to 50 Gy for definitive treatment. In light of the advances in neurosurgical techniques as well as the ability to differentially treat with chemotherapy, surgical biopsy in the modern era is generally much safer and usually recommended prior to treatment. However, some controversy remains whether biopsy is indicated for these tumors, and this decision determines the management plan.

Regardless of the ultimate histology, all GCTs are staged in a similar manner using magnetic resonance imaging (MRI) scans of the brain and spine in addition to CSF examination. Local lesions are categorized as M0. M1 disease is defined by microscopic dissemination in the CSF, while M2/M3 disease shows disseminated macroscopic lesions in the spinal region or cranial subarachnoid space visible on imaging.

6.5.1 Laboratory Investigations

AFP is normally expressed during embryonic development. It is the earliest serum-binding protein in the fetus, which reaches peak concentration at 12–14 weeks of gestation, then gradually falls to reach adult

levels of 10 ng/dL at 1–2 years of age. As AFP levels decline during fetal development, albumin becomes the predominant binding protein. The presence of AFP (>25 ng/mL) indicates that there are malignant components in the tumor consisting of yolk sac elements or embryonal carcinoma. The half life of AFP is 5–7 days and is a useful marker to follow, with one caveat: due to the variable rates of AFP levels in infants, AFP levels are less informative in this very young age group. Of note is the phenomenon of increasing AFP levels due to chemotherapy-induced tumor lysis and not necessarily due to disease progression. β-HCG is produced by syncytiotrophoblasts during pregnancy to maintain the corpus luteum, and minute amounts are found in normal adults. Pathologic elevations of β-HCG (>50 IU/L) are found when there is a clonal disorder of syncytiotrophoblasts, such as in choriocarcinoma or when syncytiotrophoblastic giant cells are found in germinomas or embryonal carcinomas. Therefore, when an elevation of one of these tumor markers is present, it is highly suggestive of GCT.

Embryonal carcinomas secrete both AFP and β-HCG, while endodermal sinus tumors secrete only AFP, and choriocarcinomas secrete only β-HCG. However, in as many as 30% of GCTs, more than one histological subtype is found (Matsutani et al. 1997). The most useful laboratory values for the diagnosis of GCTs are elevations of AFP and/or β-HCG in serum or CSF. It is important to sample both serum and CSF, as serum levels can be normal in the presence of elevated CSF levels and vice versa. If present, the protein levels can serve as useful tumor markers since they decrease as tumor burden decreases. GCTs that have elevations of these tumor markers show worse prognosis when matched with patients with identical histological diagnoses, but normal marker levels (Itoyama et al. 1995; Nishizaki et al. 2001). AFP can be used as a tumor marker in endodermal sinus tumors and β-HCG is useful in choriocarcinoma.

Another helpful tumor marker is PLAP, which is a fetal isoenzyme of alkaline phosphatase, and is almost always elevated in germinomas (Cushing et al. 2002). Therefore, one controversial option in patients with elevated PLAP, but normal β-HCG and AFP would be to assume the diagnosis is germinoma and treat accordingly (Steinbok 2001) (Table 6.2). However, PLAP is not readily available as a test in many institutions, and such empiric diagnoses are extraordinarily rare. Another marker for germinoma that has recently been investigated is the soluble isoform of C-kit (s-kit). Elevations of s-kit were found in the CSF of patients with germinoma and also correlated with the patients' clinical courses. Moreover, the level of s-kit was remarkably higher in patients with tumor dissemination and suggests that s-kit may be another useful tumor marker (Miyanohara et al. 2002). Finally, immunohistochemical staining for OCT4, an 18-kDa POU-domain transcription factor encoded by the POU5F1 gene, has been shown to be a highly specific and sensitive test for germinomas.

Table 6.2. GCTs according to tumor markers

Tumor type	AFP	β-HCG	PLAP
Mature teratoma	–	–	–
Immature teratoma	±	±	–
Pure germinoma	–	–	+
Endodermal sinus tumor	+	–	–
Choriocarcinoma	–	+	–
Embryonal carcinoma	+	+	–
Mixed germ cell tumor	±	±	±

6.5.2 Diagnostic Imaging

Like other brain tumors, computed tomography (CT) and MRI are the most common modalities used to diagnose intracranial GCTs. Of historic interest only, pineal region tumors can be detected on plain skull films by the presence of calcifications. MRI is the study of choice, although CT has an advantage over MRI in identifying calcifications. The identification of calcification in the pineal gland in a child younger than 6 years old is an indication for an MRI, even when no mass is apparent on CT (Zimmerman and Bilaniuk 1982; Steinbok 2001).

Findings on CT or MRI are almost never sufficient for the diagnosis of GCTs. Germinomas are usually diffusely enhancing on CT and MRI, whereas

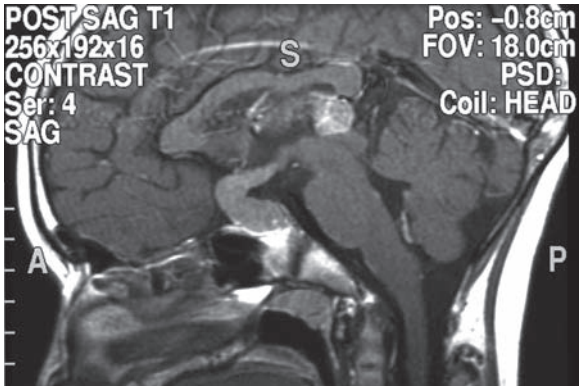


Figure 6.1

A sagittal T1-weighted MR image following contrast administration shows an anterior third ventricle mass and a pineal region mass that both enhance relative to the normal brain. After biopsy, this tumor was diagnosed as a germinoma

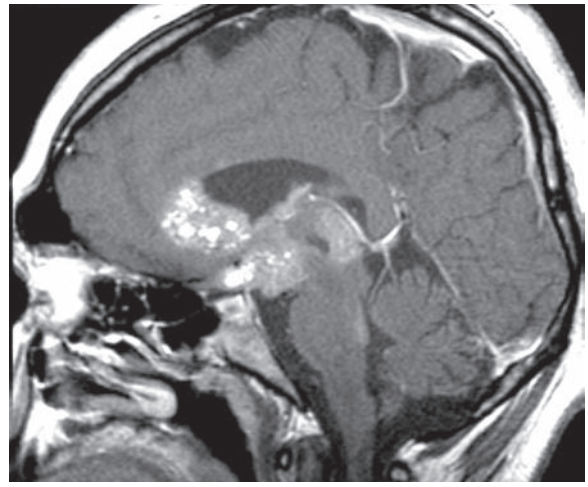


Figure 6.2

A sagittal T2-weighted image shows an extensive heterogeneous suprasellar germinoma with multiple cysts. The tumor fills the anterior portion of the third ventricle and extends posteriorly into the pineal region

NGGCTs are more likely to be heterogeneous in part due to hemorrhage. A tumor in the suprasellar region in association with a pineal tumor is usually a GCT, most likely a germinoma (Fig. 6.1). Larger germinomas can have a heterogeneous appearance and fill the third ventricle (Fig. 6.2). A bifocal location is not guaranteed to be a germinoma as GCTs with mixed elements can also appear in two locations (Fig. 6.3). A recent or old hemorrhage seen in the tumor suggests a NGGCT, particularly common with choriocarcinoma (Fig. 6.4). Intracranial teratomas tend to be well-circumscribed and have large cysts and calcifications within the tumor, which can be helpful in distinguishing them from germinomas (Fig. 6.5). Immature teratomas tend to have fewer cysts and calcifications, and may secrete tumor markers (Fujimaki et al. 1994).

In addition to GCT, the differential diagnosis of a pineal lesion includes pineoblastoma, trilateral retinoblastoma in a patient with bilateral retinoblastoma, pineocytoma, glioma, meningioma, lymphoma, or a benign lesion such as a cyst. Benign cysts can generally be distinguished from malignant cystic neoplasms by the lack of enhancement, or a very thin rim of enhancement surrounding a hypointense center (Steinbok 2001).

6.5.3 Obtaining Tissue Diagnosis

There is geographic variation in management strategies. In 1992, Oi and Matsumoto noted that the majority (84%) of Japanese neurosurgeons were comfortable using a radiodiagnostic trial of 20 Gy in lieu of histological confirmation of a germinoma. In contrast, the majority (78%) in western countries recommended histological diagnosis as the initial management of pineal region tumors. This discrepancy may be due to the fact that pineal region tumors are much more common in Japan, and the incidence of germinomas in particular is higher (Oi and Matsumoto 1992). A follow-up study showed that by 1998, radical resection of the tumor was recommended as the initial procedure by only 22% of Japanese neurosurgeons, while 39% recommended biopsy, and 39% recommended radiation therapy. The authors

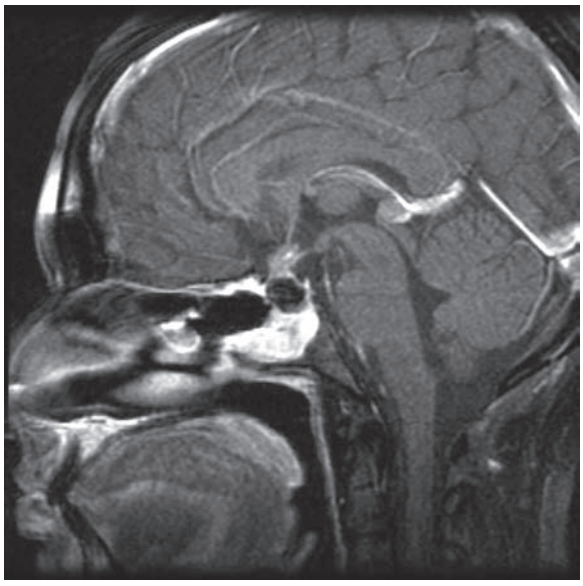


Figure 6.3

A sagittal T1-weighted image following contrast shows an unusual case of a mixed germ cell tumor containing both germinoma and teratoma located in the suprasellar, sellar, and pineal regions. The sellar component was biopsied through a transsphenoidal approach. The area of low signal intensity within the sella represents a fat patch to prevent postoperative CSF leak

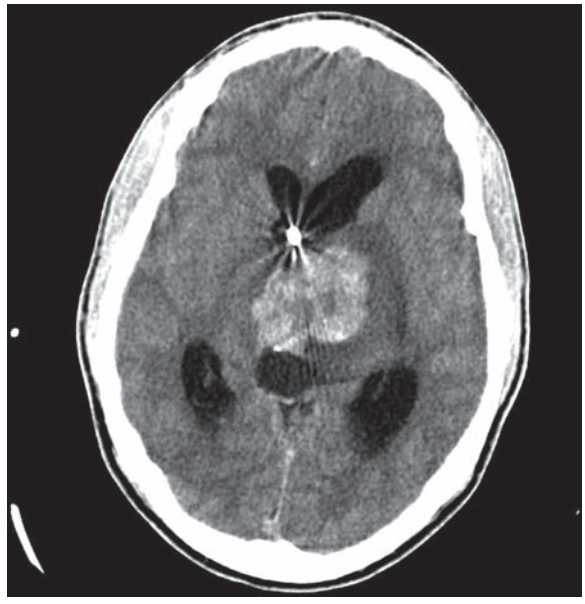


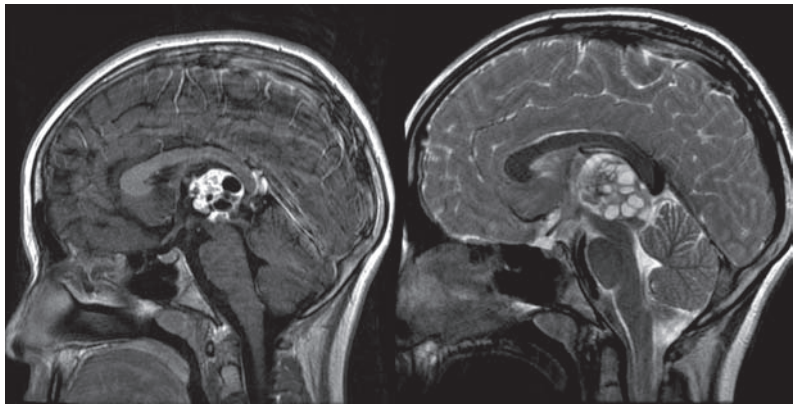
Figure 6.4

An axial CT image from a teenage boy who presented with headaches and a change in his mental status. A large partially hemorrhagic tumor is seen extending into the lateral ventricles. An endoscopic biopsy was consistent with choriocarcinoma. β-HCG as measured in the CSF was 88,767 IU/L (normal: <1.5). Hydrocephalus is present and an external ventricular catheter has been inserted into the anterior portion of the ventricle

suggested tissue diagnosis by ventriculoscopic or stereotactic approach as the most appropriate initial step for the treatment planning of pineal region tumors (Oi et al. 1998).

Because histology influences the choice of treatment, and is coincident with improved surgical techniques, the need for obtaining tumor histology is now recognized (Aydin et al. 1992; Sawamura et al. 1997). Although a definitive conclusion cannot be reached, a prudent strategy would be to utilize a safe and minimally invasive technique to obtain tissue for histological analysis. Such techniques would include endoscopic biopsy at the time of third ventriculostomy or aqueductoplasty, or stereotactic biopsy. A review of 370 cases of stereotactic biopsies in France, reported only 1.3% mortality and 1% major morbidity rates (Regis et al. 1996). Despite these relatively low rates, most surgeons are more comfortable with open biopsy in this region due to the close proximity of deep cerebral veins. One of the advantages of open biopsy is that sampling error can be minimized by taking several biopsies. This is particularly important since mixed GCTs are commonly encountered. Advances in surgical techniques allow open procedures to access the pineal region without major morbidity.

As results from intracranial GCT studies have emerged, stratification into "intermediate"- and "high"-risk prognostic groups has refined the role of biopsy. Specifically, serum and/or CSF β-HCG levels greater than 1000 IU/L and AFP levels greater than 1000 ng/mL nearly uniformly indicate the



Figuer 6.5

A sagittal T1-weighted image following contrast (*left*) and a T2-weighted image (*right*) demonstrate the typical appearance of a mixed GCT; in this case a teratoma with germinoma. The tumor is heterogeneous with robust enhancement of the solid component although there are also multiple cysts within the tumor

diagnosis of pure or predominant choriocarcinoma and yolk sac tumor, respectively (Matsutani et al. 1997; Kretschmar et al. 2007). Such conspicuous marker elevations may obviate the need for biopsy since they denote pure and/or predominant malignant elements, and thus should be treated within the highest risk group.

6.6 Treatment

6.6.1 Role of Surgery

Prior to 1970, surgery resulted in 25–70% morbidity and mortality rates and led to radiotherapy becoming the treatment of choice with a modern 10-year overall survival, at least for germinomas, in the order of 80–100%. In Japan, the standard of care was administration of a radiodiagnostic trial of 20 Gy followed by definitive doses of radiation if 20 Gy induced a tumor response (Handa and Yamashita 1981). Conventional radiotherapy for CNS germinomas involved 30 Gy of CSI followed by a boost to the primary disease site to a total dose of 50 Gy. The main role of surgery at that time was for treatment of hydrocephalus by placement of ventriculo-peritoneal shunts, which resulted in peritoneal metastases at times (Brandes et al. 2000). Currently, other than as a diagnostic tool, surgery has no proven role in the treatment of intracranial germinomas. Several studies have shown no benefit to radical surgical resection in overall survival for germinoma patients (Sawamura et al. 1997).

For NGGCTs, surgery plays an important role along with other treatment modalities. In a study by Weiner et al., radical resection in addition to chemotherapy improved prognosis for patients with intracranial NGGCT. They recommended delayed surgical resection for patients who have normalized tumor markers with persistent radiographic abnormalities after three cycles of initial chemotherapy in order to avoid unnecessary radiation or further chemotherapy (see also Chap. 14) (Balmaceda et al. 1996; Weiner et al. 2002). For mature teratomas, it is generally accepted that gross total surgical resection is sufficient for cure. For immature teratomas, adjuvant chemoradiotherapy should be used if tumor markers are present because it is assumed that malignant germ-cell elements are present. Even following gross total resection of nonsecreting immature teratomas, there is still a risk of relapse without additional adjuvant therapy (Sawamura et al. 1998b).

Second-look surgery in particular has gained favor based on recent published literature (Friedman et al. 2001; Weiner et al. 2002). A retrospective review of 126 patients enrolled on the First and Second International Central Nervous System Germ-Cell Tumor Studies for patients with newly diagnosed CNS GCTs sought to establish the role of delayed surgical resection in patients who exhibit less than complete radiographic response despite declining tumor markers after initial chemotherapy. Indeed, after at least three cycles of chemotherapy, 10 patients underwent delayed surgical resection due

to residual radiographic abnormalities in the setting of declining or completely normalized serum and CSF levels of β-HCG and AFP. Second-look surgery revealed 3 mature teratomas, 2 immature teratomas, and 5 cases of necrosis or scar tissue alone. At an average follow-up time of 36.9 months (range 3–96 months), only 3 of the 10 patients had experienced tumor recurrence. Three of the four patients with NGGCTs whose tumor markers had not completely normalized ultimately developed tumor dissemination/progression and required radiation therapy even though pathology at second-look surgery showed only teratoma or necrosis/scar tissue. In contrast, 3 of 4 patients with NGGCTs whose tumor marker levels had completely normalized did not progress and did not require radiation therapy. The authors concluded that delayed surgical resection was indicated in patients with GCTs who have residual radiographic abnormalities and normalized tumor markers following chemotherapy (Weiner et al. 2002).

6.6.2 Chemotherapy

Chemotherapy was incorporated into the treatment of intracranial GCTs after agents known to have activity against testicular GCTs were shown to cross the blood–brain barrier (Ginsberg et al. 1981; Brandes et al. 2000). As single agents, actinomycin-D, vinblastine, bleomycin, doxorubicin, cisplatin, carboplatin, etoposide, ifosfamide, and cyclophosphamide are active against GCTs and combinations of these agents are the basis for treatment regimens. The most common combinations are PEB (cisplatin, etoposide and bleomycin), PVB (cisplatin, vinblastine and bleomycin), and JEB (carboplatin with etoposide and bleomycin) (Hawkins et al. 1986; Pinkerton et al. 1990; Cushing et al. 2002; Einhorn and Donohue 2002). In addition, ifosfamide has been found to be the third most active agent against GCTs, following cisplatin and etoposide, and was investigated as salvage therapy in patients with refractory disease (Nichols 1996). The most recent Children's Oncology Group NGGCT study, ACNS0122, has utilized a regimen of carboplatin and etoposdie alternating with ifosfamide and etoposide.

However, efforts to omit radiation and treat intracranial GCTs with chemotherapy alone have been less promising. Yoshida et al. saw a response rate of 80–85% in patients treated with a combination regimen of cisplatin and etoposide, but survival rates at 2 years were disappointing at 88% in patients with germinomas and 48% in patients with NGGCTs. Baranzelli et al. reported that of 13 AFP- and β-HCG-secreting GCTs treated by chemotherapy and surgery alone, 12 recurred. Approximately 50% of the patients with tumor recurrence experienced remission following salvage radiation therapy. Because of the need for salvage radiation therapy, the authors concluded that focal radiation therapy should be part of the treatment of these tumors.

Finally, Balmaceda et al. enrolled 45 patients with germinomas and 26 with NGGCTs in a clinical study and treated them with four cycles of carboplatin, etoposide, and bleomycin. Those with a complete response defined by imaging studies received two additional cycles and those with less than a complete response received two additional cycles intensified by cyclophosphamide. Overall, 78% of patients achieved a complete response with chemotherapy only. However, of the 54 patients surviving at 2 years, 32 (59%) received irradiation. The 2-year survival was 84% for patients with germinoma and 62% for those with NGGCT. Thus, it appears that chemotherapy alone does not provide comparable cure rates when compared to combined modality treatment (Yoshida et al. 1993; Balmaceda et al. 1996; Baranzelli et al. 1998). Of particular pertinence to NGGCTs, results from the First International CNS GCT Study Group indicated that approximately one third of NGGCT patients who initially had a complete response to chemotherapy had recurrent disease. And most importantly, unlike recurrent germinoma patients, these NGGCT patients were not amenable to salvage with radiation therapy (Balmaceda et al. 1996).

Due to their differing prognoses, more recent studies have made an effort to exclusively enroll and evaluate specific GCT subtypes in order to assess the efficacy of chemotherapy-only regimens. Kellie et al., looking exclusively at germinomas, confirmed the aforementioned generally disappointing results with chemotherapy (Kellie et al. 2004a). Here 19 patients

were enrolled and treated with two courses of cisplatin, etoposide, cyclophosphamide, and bleomycin. If a complete response was achieved, patients then completed two courses of carboplatin, etoposide, and bleomycin. If complete response was not achieved, patients still received the above second regimen, and, following a complete response, an additional cycle of both regimens. However, if, even after this intensive treatment, residual disease was still present, patients underwent second-look surgery and/or irradiation. Five-year event-free survival (EFS) was 47% and 5-year overall survival was 68%. Thus, because of the higher cure rates achieved with radiation therapy, there is no currently established role for chemotherapy-only regimens in the treatment of germinomas.

For NGGCTs, radiation alone produces 5-year survival rates of only 30–40%. Excellent response rates to chemotherapy have shifted the standard treatment of NGGCT to combined modality therapy consisting of chemotherapy and radiation. However, a recent study by Kellie et al. suggested promising results for chemotherapy-only regimens in the treatment of NGGCT. In this study, 20 NGGCT patients were enrolled and received two courses of cisplatin, etoposide, cyclophosphamide, and bleomycin (Regimen A). Patients who had a complete response subsequently received two cycles of carboplatin, etoposide, and bleomycin (Regimen B). Those with less than a complete response to the initial regimen still received two cycles of Regimen B. If a complete response was then achieved, they received two additional cycles – one of Regimen A and one of Regimen B. If a complete response was absent, patients who did not respond to either Regimen A nor B were taken off protocol for surgery and/or irradiation. These results improved upon historical controls, with a 5-year overall survival of 75% and a reduction in deaths from chemotherapy-related toxicities (Kellie et al. 2004b).

6.6.3 Radiation Therapy

Published reports corroborate poorer prognoses for patients with NGGCT compared to those with germinoma. For NGGCTs, radiation alone produces 5-year survival rates of only 30–40% (Fuller et al. 1994). These dismal results for radiation-only therapies, coupled with the success of chemotherapy in improving overall survival, have shifted the standard of care for NGGCTs toward multimodality approaches. However, open questions still remain, regarding radiation dose and volume.

There is little literature addressing the appropriate radiation field for localized NGGCT, with only small patient numbers. In a study by the French Society of Pediatric Oncology, chemotherapy and focal radiation resulted in 5 relapses among 24 patients with localized NGGCTs (Bouffet et al. 1999). A similar regimen in a separate study resulted in 3 of 18 patients experiencing disease recurrence, 2 with isolated spinal relapses (Robertson et al. 1997).

Additional studies support the opinion that "intermediate"-risk NGGCT patients (see Sect. 6.5.3 earlier for delineation of "intermediate"- and "high"-risk groups), particularly those with complete responses, do not require CSI. The Japanese Cooperative Group reported an excellent 5-year survival rate of 89% for "intermediate"-risk patients who were treated with five cycles of chemotherapy, 30 Gy to whole ventricular fields, and 54 Gy total dose to the primary tumor volume (Matsutani 2008). The International Society of Pediatric Oncology treated patients with localized NGGCTs with four cycles of cisplatin, etoposide, and ifosfamide, followed by focal radiation to a total dose of 54 Gy. Progression-free survival was 67%, although nearly half of the 34 patients with residual disease faced a recurrence even after chemotherapy (Calaminus and Patte 2005).

Because of their relative radioresistance, recommendations for the multimodality approach to NGGCT have emerged from recent studies. Within that context, for patients with NGGCT and complete responses to chemotherapy, Buckner recommends 54 Gy limited field irradiation and 30 Gy CSI, if the spinal axis is involved; in patients with partial response, 59.4 Gy limited field was recommended with 36 Gy CSI, if spinal involvement is evident (Buckner et al. 1999).

Our recommendation for NGGCTs again depends on the stage at diagnosis. For disseminated disease (M1-M3), we recommend CSI to a dose of 24–36 Gy depending on variables that include patient age,

tumor response, and disease bulk, with focal boosts to macroscopic disease to a dose of 54 Gy. For M0 lesions, because adjuvant or neoadjuvant chemotherapy is now often included in the treatment regimen, we frequently limit radiation volumes. For those with "intermediate" risk disease and a complete response to induction chemotherapy, we recommend 30 Gy to a whole ventricular field and 54 Gy total dose to a focal radiation field. For those with "intermediate" risk with less than a complete response and for "high"-risk patients we recommend 36 Gy to the craniospinal axis and 54 Gy to the primary tumor volume.

Among intracranial GCTs, germinoma represents the most common and prognostically favorable subgroup. The roles of surgery, chemotherapy, and radiation are constantly evolving. Unlike surgery, radiation remains a critical component of the treatment of intracranial germinomas. In fact, the gold standard against which all new approaches must be measured remains radiotherapy alone. For M1-M3 disease, volumes involving the entirety of the craniospinal axis with focal boosts to macroscopic disease remain standard of care. Controversy persists regarding the appropriate fields and volumes for localized, nondisseminated germinomas (M0). A key point of controversy involving radiation for localized germinomas has been the need for CSI. Current evidence substantiates omitting CSI from the treatment of localized germinoma. Spinal failure rates of <10% in the absence of CSI, reported in most contemporary series, do not justify routine incorporation of CSI into treatment strategies for localized germinoma. Indeed, a recent review of the data regarding volumes and doses for M0 germinoma concluded that, because the rate of spinal relapse is similar, regardless of whether CSI or whole brain irradiation is used, prophylactic whole brain and CSI are contraindicated (Rogers et al. 2005). Some have gone still further in questioning the value of whole ventricular radiation, although whole ventricular fields are advocated by many investigators.

Although most investigators now omit whole brain radiation, several studies have reported higher recurrence rates when only the tumor volume is treated (Uematsu et al. 1992; Shibamoto et al. 1994b; Wolden et al. 1995; Brandes et al. 2000; Rogers et al. 2005). Specifically, tumor recurrences following radiation fields confined to the primary tumor volume usually occur within the adjacent brain parenchyma and ventricles. Therefore, investigators have recommended initial inclusion of the entire ventricular field followed by a boost to the primary tumor to a total dose of 45 Gy for tumors less than 4 cm in size, and 20 Gy for spinal prophylaxis in case of positive cytology (Uematsu et al. 1992; Shibamoto et al. 1994a). Shibamoto et al. suggested modulating the radiotherapy dose according to tumor diameter with 40 Gy for tumors up to 2.5 cm, 45 Gy for tumors between 2.5 and 4 cm, and 50 Gy for tumors over 4 cm (Shibamoto et al. 1994b). Dissemination to hypothalamus, third ventricle, or spinal cord identifies a high-risk group that warrants consideration of CSI with systemic chemotherapy (Jennings et al. 1985b).

We recommend whole ventricular irradiation, followed by a boost to the primary tumor for localized germinoma, when using radiation alone. Some question the rationale of whole ventricular irradiation, given the continuity of CSF space throughout the entire CNS. We argue that the natural history of germinomas is characterized by multifocality and intracranial relapses at foci separate from the primary tumor with lesser propensity for diffuse CNS involvement (Eom et al. 2008). These features distinguish germinomas from other CNS malignancies, such as medulloblastoma, that require CSI for cure. Whether more generous local radiation fields sterilize occult multifocal disease or target direct ventricular invasion, there appears to be a role for whole ventricular irradiation in the treatment of localized germinoma. In addition, the literature supports a dose of ≥45 Gy to the primary tumor for germinomas treated with radiation alone.

6.6.4 Combined Modality Treatment

In an effort to increase cure rates and limit toxicities associated with radiation, investigators have formulated multimodal regimens for the treatment of these lesions (Allen et al. 1987). Calaminus et al. reported promising results for patients with secreting intracranial GCTs given four courses PEI, cisplatin (20 mg/m^2 day 1–5), VP16 (100 mg/m^2 day 1–3), and ifosfamide

(1.5 g/m^2 day 1–5), resection, if feasible, of the residual tumor, followed by radiation consisting of 30 Gy CSI and an additional 24 Gy boost to the primary site. EFS was 81% with 11 months follow-up, representing a significant improvement from previous studies (Calaminus et al. 1997). Robertson et al. reported improved outcome for intracranial NGGCTs after a treatment plan of initial radical surgical resection followed by three to four cycles of adjuvant chemotherapy with cisplatin (100 mg/m^2/cycle) and VP-16 (500 mg/m^2/cycle), followed by radiotherapy, and finally four additional cycles of postradiation chemotherapy. Four-year actuarial EFS and overall survival rates were 67 and 74%, respectively (Robertson et al. 1997). It remains to be seen whether further intensification using myeloablative chemotherapy with autologous stem-cell rescue has a role in patients with poor-prognosis GCTs or relapsed GCTs.

A retrospective analysis of 41 patients concluded that treatment for NGGCTs should be tailored to histological subtype. For patients in the intermediate-risk group, which included those with germinoma with syncytiotrophoblastic giant cells, immature teratoma, teratoma with malignant transformation, and mixed tumors composed of germinoma or teratoma, there was a significant difference in overall survival for patients who had combined chemotherapy, radiation, and surgery (84%) compared to those who had only radiation and surgery (44%) (Ogawa et al. 2003). In this instance, chemotherapy consisted of various carboplatin or cisplatin combinations. However, in the poor-prognosis group (choriocarcinoma, yolk sac tumor, embryonal carcinoma, and mixed tumors), those who had incomplete resection, chemotherapy, and radiation had an abysmal 5-year survival rate of 8%. For those with complete macroscopic resection, survival was more favorable, arguing for a possible role for surgery in NGGCT patients with these particular subtypes.

Sawamura et al. have also recommended further risk stratification of patients into three categories. They have categorized pure germinoma and mature teratoma as the good-prognosis group, with the poor-prognosis group including embryonal carcinoma, yolk sac tumor, choriocarcinoma, and mixed GCT containing any embryonal carcinoma, yolk sac, or choriocarcinoma elements. The intermediate-prognosis group includes germinoma with elevated (β-HCG, immature teratoma, extensive/multifocal germinoma, and mixed GCT containing only germinoma with teratoma elements (Sawamura et al. 1998a). Further therapeutic studies incorporating this type of risk stratification are warranted to determine if prognosis can be improved in the poor-prognosis group, while minimizing therapy-induced physical or cognitive sequelae.

Historically, intracranial germinomas have been treated with radiation alone, producing excellent cure rates. The significant long-term toxicity of radiation, particularly in children, has prompted investigations into alternative treatments that minimize the dose and volume of irradiation. However, these alternative approaches must preserve the high cure rates established with radiation alone. Combined modality approaches in which chemotherapy precedes radiation have gained credence, and are now considered a standard alternative to radiation alone.

Several series have reported excellent clinical outcome with preirradiation chemotherapy followed by focal irradiation. Buckner et al. and Sawamura et al. reported 100% survival with median follow-up times of 51 months and 24 months, respectively (Sawamura et al. 1998c; Buckner et al. 1999). Buckner et al. treated 9 patients with germinomas and 8 with mixed GCTs. Treatment consisted of etoposide (100 mg/m^2/day) plus cisplatin (20 mg/m^2/day) daily for 5 days every 3 weeks for four cycles, followed by radiation therapy. They recommend that germinoma patients with complete responses after standard chemotherapy receive 30 Gy to a limited field with the addition of 20 Gy CSI for disseminated disease. For patients with partial responses, doses of 54 Gy to a limited field were recommended with 30 Gy CSI for disseminated disease.

Another recent study reported excellent results for patients treated with chemoradiation. Patients with pure germinomas were treated with EP (etoposide-100 mg/m^2 and cisplatin-20 mg/m^2) given for 5 days every 4 weeks for four cycles and patients with other pathologic types were treated with ICE (ifosfamide-900 mg/m^2, cisplatin-20 mg/m^2, and etoposide-60 mg/ m^2) for 5 consecutive days every 4 weeks

for up to 6 cycles depending on chemoresponsiveness, extent of surgical resection, and tumor-marker levels. At 5 years, the overall survival rate was 100% and relapse-free survival rates were 90% for germinoma patients and 44% for patients with β-HCG-secreting germinomas, which represent a mix-ed GCT with β-HCG-secreting syncytiotrophoblastic giant cells. This is strong evidence that treatment should be directed at the most malignant element. The 5-year overall survival rates were 93% for non-β-HCG-secreting germinomas and 75% for β-HCG-secreting germinomas (Aoyama et al. 2002). The authors recommend that following EP chemotherapy, dose and volume be reduced to 24 Gy in 12 fractions for non-β-HCG-secreting germinomas, but higher radiation doses should be maintained for β-HCG-secreting germinomas (Aoyama et al. 2002). Most recently, the volume of radiation in the setting of chemoradiation for germinomas has been addressed by Eom et al. They reviewed 81 patients treated for histologically confirmed intracranial germinomas with either radiation alone or chemoradiation. Of 42 patients who received chemotherapy followed by focal radiation, 4 relapsed, 1 in the primary tumor bed, 2 in the ventricles outside the radiation fields, and 1 in the spinal epidural space. This contrasts with no relapses among 39 patients who were treated with radiation alone consisting of craniospinal fields followed by a focal boost. Thus, recurrence-free survival at 5 years was 100% in the radiation alone arm and 88.1% in the chemoradiation arm, a difference that was statistically significant. The authors concluded that chemotherapy cannot prevent subependymal spread that is very effectively controlled by radiation, and they argued that whole ventricular radiation fields are appropriate following induction chemotherapy(Eom et al. 2008).

6.6.5 Treatment of Recurrent Disease

As with most malignancies, relapse poses a formidable problem. For patients who relapse with intracranial GCTs, salvage therapy using the same chemotherapy regimen followed by radiotherapy has been effective (Sawamura et al. 1998a). Kobayashi et al. used combinations of cisplatin and etoposide in four cases of recurrent intracranial GCT (3 malignant teratomas and 1 germinoma), and saw a response rate of 100% (Kobayashi et al. 1989). Aoyama et al. successfully treated recurrent germinomas with further chemotherapy and reirradiation (Aoyama et al. 2002). However, improving prognosis for NGGCTs remains a concern. Encouraging results from a study using high-dose chemotherapy (200 mg/m^2 cisplatin, 1250 mg/m^2 etoposide, and 150 mg/m^2 ACNU) with autologous stem-cell rescue in 6 patients with high-risk, intracranial NGGCT showed 100% survival at 1–7 year follow-up (Tada et al. 1999). Although trials using high-dose chemotherapy with stem-cell rescue show promise in relapsed extracranial GCTs, it remains to be seen whether myeloablative consolidation therapy has a role in the treatment of intracranial GCTs.

6.6.6 Future Trials

The Children's Oncology Group has been actively investigating treatment approaches for intracranial GCTs. The first trial has focused exclusively on NGGCTs, attempting to improve overall and progression-free survival by using a neoadjuvant 3-drug combination consisting of carboplatin, VP-16, and ifosfamide, followed by CSI with involved-field boost. For those patients that have persistently positive markers, residual tumor, or unresectable disease, even after induction chemotherapy, myeloablative chemotherapy followed by stem-cell rescue is to be attempted before CSI.

For germinomas, a Phase III trial has stratified patients according to extent of disease (M0 for local, M+ for multifocal, and modified M+ for assumed occult multifocal), and then randomized them into 1 of 2 treatment arms: Regimen A consists exclusively of radiotherapy; M0 and modified M+ patients receive ventricular radiation with a focal boost, while those with disseminated disease receive CSI. In Regimen B, patients with focal disease that experience a favorable response to induction chemotherapy receive reduced dose and volume-involved field radiotherapy. Those with disseminated disease who respond well to induction chemotherapy receive a reduction in CSI and boost doses. Those with modified M+ disease who respond well receive reductions

in ventricular and boost doses. Results of these two studies are pending. Such response-directed fields and doses of radiation have gained favor.

Future trials for intracranial NGGCTs will likely further stratify patients into "intermediate" and "high" risk groups in an effort to identify those patients who do not require as aggressive a regimen as is currently administered. Such a group of "intermediate" risk tumors will include those with immature teratoma, mixed GCT with predominantly germinoma or teratoma components, and histologically confirmed NGGCTs with β-HCG <1,000 IU/L or AFP < 1,000 ng/mL. Although the current NGGCT Children's Oncology Group protocol dictates CSI for all such patients, emerging evidence indicates that less toxic approaches will not compromise clinical outcome in this group of patients. Thus, in future trials, M0 "intermediate" risk NGGCT patients will likely receive chemotherapy followed by response-based radiation consisting of a whole ventricular field, and a boost to the primary tumor region.

6.7 Outcome

The outcome for patients with pure intracranial germinoma is significantly better than the outcome for those with NGGCT. Cure rates above 90% with radiation alone establish radiation as the benchmark against which combined modality therapy must be compared. Comparable outcomes are achieved in patients with intracranial teratoma. Prognosis for NGGCTs other than teratoma is worse than that for germinomas, and historically the 5-year survival rates for these tumors have been between 20 and 49% (Jennings et al. 1985b; Schild et al. 1996; Matsutani et al. 1997; Drummond and Rosenfeld 1999; Jaing et al. 2002). However, it is clear that combined modality therapy has improved dramatically on the poor historic survival rates of patients with NGGCTs. The roles of surgical resection and high-dose chemotherapy with stem-cell rescue for patients with NGGCTs are currently under investigation.

Early studies identified "intermediate-" and "high-" risk groups among NGGCT patients. More than a decade ago, Matsutani et al. found 27% survival rates at 3 years for those with pure malignant GCTs (choriocarcinoma, endodermal sinus tumor, and embryonal carcinoma), compared with 70% or greater survival rates for patients with mixed germinoma and teratoma, and mixed teratoma or germinoma with some pure malignant elements (Matsutani et al. 1997). In contrast, mixed tumors with predominantly pure malignant elements had less than 10% survival at 3 years.

In addition to histology, a key prognostic factor for NGGCTs is tumor-marker elevation. In particular, serum and/or CSF β-HCG or AFP levels greater than 1000 IU/L or 1000 ng/mL, respectively, portent significantly worse outcome (Matsutani et al. 1997; Kellie et al. 2004b; Kretschmar et al. 2007). For example, the Second International CNS Germ-Cell Study Group reported that from 20 patients with NGGCTs treated with chemotherapy alone, 4 of 9 patients with serum and/or CSF β-HCG or AFP levels greater than 1000 IU/L or ng/mL, respectively, died of disease progression, whereas only 1 death occurred among 11 patients without such marker elevations (Kellie et al. 2004b).

Given higher cure rates for patients with intracranial GCTs, long-term toxicities are clearly evident. Sawamura et al. reported a variety of late, adverse effects of therapy including stroke, secondary malignancy, and cognitive, endocrinologic, auditory, and visual dysfunctions. Of 85 patients, 58 required hormone-replacement therapy and 26 showed poor performance status (Sawamura et al. 1998a). Young patients are at an increased risk of physical as well as neuropsychologic deficits. As expected, patients who received less than 55 Gy showed higher Karnofsky Performance scores (Ono et al. 1994).

Sands et al. reported on quality of life and neuropsychologic functioning in patients enrolled in the First International CNS Germ Cell Tumor Study. Patients who received CNS radiation therapy had worse physical health, but similar psychosocial health. Patients with germinomas significantly outperformed those with NGGCTs on all neuropsychologic measures, and younger patients were at increased risk for psychosocial and physical problems as well as neuropsychologic deficits (Sands et al. 2001). In the study by Aoyama et al. using chemotherapy followed by low-dose, involved-field radiotherapy, the authors noted

no remarkable deterioration in quality of life or neurocognitive function (Aoyama et al. 2002).

Combination chemoradiotherapy regimens with risk stratification and dose adjustments will likely decrease the long-term side effects of therapy, while improving the prognosis for those with the high-risk intracranial GCTs. A study of 9 children with germinomas, all of whom received radiotherapy and 5 of whom received neoadjuvant chemotherapy, confirmed the relative safety of limited-field and reduced-dose radiotherapy when supplemented with chemotherapy (Strojan et al. 2006). Another retrospective study examined data from 19 patients, 14 of whom received various chemotherapies in addition to radiation, and the authors found adverse effects to be relatively limited (Osuka et al. 2007).

While chemoradiation is the reigning paradigm for the treatment of both germinoma and NGGCT, new approaches hold promise as well. Osada et al. provide a case report of dendritic cell-based immunotherapy in a patient with relapsed, intracranial GCT who had significant tumor shrinkage as well as decrease in tumor markers after four infusions of peripheral blood dendritic cells followed by monocyte-derived dendritic cells (Osada et al. 2001).

6.8 Conclusions

In this chapter, we have reviewed the epidemiology, pathology, clinical features, diagnosis, and treatment of intracranial GCTs. The use of tumor markers, improved imaging technologies, and safer biopsy techniques has made the diagnosis of intracranial GCTs relatively straightforward. Mixed GCTs remain a diagnostic challenge. The outcomes of patients with GCTs have paralleled the success that has been achieved with other types of pediatric cancers, with the advances in combinatorial regimens and intensification of treatments. As with other pediatric malignancies, the challenge is to distinguish the patients who require more intensive therapy from those needing standard treatment. Risk-stratified treatment protocols individualized to a patient's tumor profile are clearly the next step. Technological advances in the field of neurosurgery and radiation oncology continue to impact the treatment successes, while decreasing the long-term sequelae of therapies. It is hoped that further understanding of the biology of intracranial GCTs will result in novel, targeted, and less-toxic therapeutics.

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Craniopharyngioma

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Contents

7.1 Introduction

Craniopharyngiomas are histologically benign neuroepithelial tumors that arise from rests of squamous-cell epithelium that remain along the path of the primitive craniopharyngeal duct and adenohypophysis. They frequently involve vital structures in the sellar region including the optic apparatus and the pituitary, and often lead to visual, endocrine, and mental disturbances. Despite their benign histology, the involvement of various neural structures in the suprasellar region makes the treatment and management of craniopharyngiomas difficult. There remains an ongoing controversy regarding optimal treatment of craniopharyngiomas. The debate revolves around the risks and benefits of attempted gross total resection as compared to subtotal resection or biopsy followed by other therapy such as external beam radiotherapy, radiosurgery, intracavitary radiation or sclerosis, and/or chemotherapy (Karavitaki et al. 2006).

7.2 Epidemiology

The incidence of craniopharyngioma is 1.3 per 1,000,000 person-years and does not vary with gender or race. There is a bimodal distribution with peaks occurring during childhood (5–14 years) and later in adulthood (65–74 years in the Central Brain Tumor Registry of the United States (CBTRUS), and 50–74 years in the Los Angeles County Cancer Surveillance Program) (Bunin et al. 1998). Although craniopharyngiomas comprise 5–10% of pediatric brain tumors

and 1–4% of adult brain tumors (Kernohan 1971; Samii and Tatagiba 1997; Bunin et al. 1998; Moore and Couldwell 2000), the majority of craniopharyngiomas occur in adults because the overall incidence of brain tumors in adults is much greater than in children. Craniopharyngioma is the most common neuroepithelial intracranial tumor in children and comprises 56% of pediatric sellar and suprasellar tumors (Miller 1994).

7.3 Pathology

7.3.1 Etiology

In the middle of the fourth week of gestation, Rathke's pouch projects upward from the roof of the stomodeum (oral cavity), and grows toward the infundibulum, which is a downward growth from the diencephalon (Fig. 7.1). During the sixth week of gestation, the connection between Rathke's pouch and the oral cavity (the pharyngohypophyseal stalk) disappears. Rathke's pouch then develops into the pars distalis, pars intermedia, and pars tuberalis which comprise the adenohypophysis (Moore and Persaud 1993; Miller 1994; Samii and Tatagiba 1997). Craniopharyngiomas are generally believed to develop from squamous-cell rests found along the path of the primitive craniopharyngeal duct and adenohypophysis (Donovan and Nesbit 1996; Moore and Couldwell 2000). A metaplastic origin from adenohypophyseal cells has been proposed for the papillary subtype of craniopharyngioma, but the exact origin of these tumors remains controversial (Miller 1994).

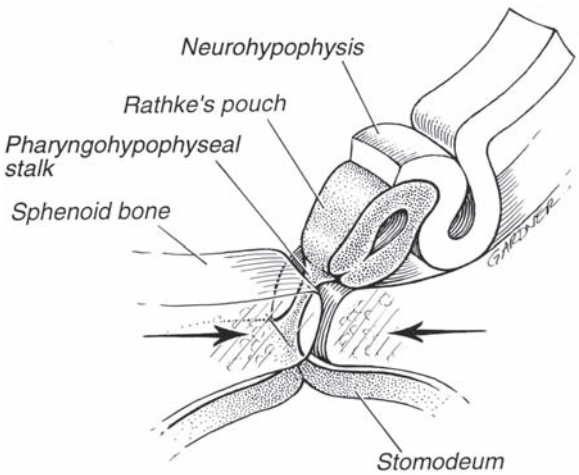

Figure 7.1
Rathke's pouch projects from the roof of the stomodeum and grows towards the infundibulum during the fourth week of gestation. During the sixth week of gestation, the connection between Rathke's pouch and the pharyngohypophyseal stalk disappears. Rathke's pouch then develops into the adenohypophysis. Craniopharyngiomas are generally believed to develop from squamous cell rests along the path of the primitive craniopharyngeal duct and adenohypophysis

7.3.2 Classification

Craniopharyngiomas are divided anatomically into four groups based on the relationship of the tumor to the optic chiasm: prechiasmatic, retrochiasmatic, subchiasmatic, and laterally expansile (Hoffman et al. 1999). Most craniopharyngiomas are both intra- and extrasellar (75%), but some are purely suprasellar (20%), and others purely intrasellar (5%). Thirty percent extend in an anterior direction, 25% extend laterally into the middle fossa, and 20% are retroclival in location. Intraventricular craniopharyngiomas, which arise within the third ventricle and extend downward through the sphenoid bone into the nasopharynx are very uncommon (Harwood-Nash 1994).

7.3.3 Histopathology

Craniopharyngiomas can also be classified by pathologic type; adamantinomatous, papillary, and mixed. The adamantinomatous type is the most common. This type is cystic and filled with dark brown fluid (Sidawy and Jannotta 1997). The epithelium resembles tumors of tooth-forming tissues or ameloblastomas, and less commonly tumors of long bones, known as adamantinomas, thereby giving these tumors their name. Microscopically, the epithelium consists of a basal layer of small basophilic cells, followed by an intermediate layer of variable thickness

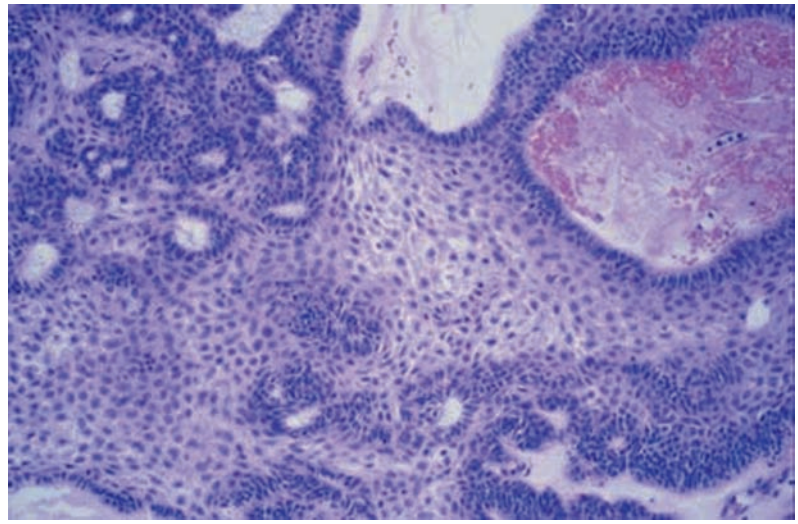

Figure 7.2
Adamantinomatous craniopharyngioma showing palisading basal squamous epithelium surrounding loosely arranged epithelial cells (stellate reticulum) and nodules of eosinophilic keratinized cells

composed of a loose collection of stellate cells, whose processes traverse the intercellular spaces (Fig. 7.2). The top layer consists of keratinized squamous cells, which desquamate as stacks of flat keratin plates within the cyst cavity. Therefore, the cyst fluid is rich in membrane lipids such as cholesterol and keratin, and can cause chronic inflammation within the cyst walls. The desquamated cells often calcify, and can rarely progress to metaplastic bone formation (Miller 1994).

The second type is squamous papillary craniopharyngiomas, which are composed of stratified squamous epithelium with papillary projections of epithelial cords into the surrounding tissues. These tumors rarely calcify or desquamate, with the cell layers being solid, compact, and with no stellate regions. Squamous papillary craniopharyngiomas occur mostly in adults. Mixed craniopharyngiomas, the third type, have features of both adamantinomatous and papillary types.

Although the adamantinomatous type is common in all age groups, the squamous-papillary type is rare in children. In pediatric studies, 92–96% were adamantinomatous, 0% were squamous papillary, 0–4% were mixed, and 4% were not classified (Miller 1994; Weiner et al. 1994). In adults, 63–66% were adamantinomatous, 27–28% were squamous papillary, 6–7% were mixed, and 3% were not classified.

7.3.4 Tumor Biology

Although craniopharyngiomas are not malignant neoplasms, their morphogenesis suggests that abnormal developmental signaling plays a role in their molecular pathogenesis. The proliferative activity of craniopharyngiomas based on their MIB-1 immunostaining for the Ki-67 nuclear antigen was measured, but no correlation was identified with morphological features or clinical outcomes (Raghavan et al. 2000). It has been reported that the estrogen-receptor gene is expressed in the proliferative epithelial component of adamantinomatous and papillary craniopharyngiomas, suggesting hormonal involvement in the genesis and/or progression of craniopharyngiomas (Thapar et al. 1994). However, there was no correlation between the presence of estrogen receptor mRNA hybridization signal and clinical outcome. Barbosa et al. studied acetylcholinesterase and butyrylcholinesterase histochemical activities in several brain tumors and found a high level of acetylcholinesterase activity and a low level of butyrylcholinesterase activity in all three craniopharyngiomas studied (Barbosa et al. 2001). Low levels of butyrylcholinesterase were correlated with slow growth in the tumors studied, but the correlation between the butyrylcholinesterase level and clinical outcome was not studied. Strong cytoplasmic

immunoreactivity for vascular endothelial growth factor (VEGF) in the epithelial cells of both adamantinomatous and papillary craniopharyngiomas was identified and microvessel density, a measure of angiogenesis, correlated with an increased risk of recurrence (Vidal et al. 2002). However, not every recurrent tumor had a high microvessel density, indicating that other factors are involved.

Genetic alterations in craniopharyngiomas are not well described. Sarubi et al. studied three genes associated with odontogenic tumors, *Gsα*, *Gi2α*, and *patched* (*PTCH*), in a group of 22 adamantinomatous craniopharyngiomas, but did not identify any mutations. Matsuo et al. demonstrated the expression of prostaglandin H synthetase-2 (PHS-2) in a variety of brain tumors, including 2 out of 4 craniopharyngiomas, but the significance of this isolated finding remains unclear (Matsuo et al. 2001). Nozaki et al. found no evidence of *p53* mutations in four craniopharyngiomas (Nozaki et al. 1998).

Recently, Buslei et al. examined the role of the Wnt signaling pathway in the pathogenesis of craniopharyngioma. Nuclear localization of β-catenin, a transcriptional regulator involved in tumorigenesis and inhibited by the Wnt signaling cascade (Takamaru et al. 2008), is seen in adamantinomatous craniopharyngioma, but not in the more benign Rathke's cleft cyst (Hoffman et al. 2006). This group also found mutations within Exon 3 of the *CTNNB1* gene, which codes for β-catenin and translates into aberrant target gene expression within the adamantinomatous craniopharyngioma (Hölsken et al. 2008). These initial studies may lead to an improved understanding of the molecular abnormalities that contribute to tumor growth.

7.4 Clinical Features

7.4.1 Neurologic Signs and Symptoms

The sellar and suprasellar location of craniopharyngiomas can result in compression or destruction of the optic chiasm, nerves and/or tracts, hypothalamus, pituitary stalk, or adjacent vascular structures. The involvement of these structures directly results in the usual presenting clinical signs, which include progressive visual loss, headaches, and/or endocrine abnormalities (Miller 1994). The exact location of the tumor can affect the clinical picture. Retrochiasmatic tumors extend posteriorly and push the chiasm anteriorly against the tuberculum sella. These tumors tend to fill the third ventricle and cause hydrocephalus; thus roughly 60% of patients present with headache, 50% with nausea, 35% with vomiting, and 10–20% with lethargy (Sanford 1994; Hoffman et al. 1999; Merchant et al. 2002; de Vries et al. 2003; Stripp et al. 2004). Elevated intracranial pressure results from either hydrocephalus or mass effect. Children are more likely to present with headache and vomiting than with visual disturbances, and 20% of children have papilledema at presentation (Moore and Couldwell 2000). Approximately 10–20% of children present with acute neurologic deterioration, which requires urgent cyst decompression or tumor removal.

Lateral extension of the tumor can cause displacement of internal carotid arteries and posterior communicating arteries. Posterior extension of the tumor can displace the tip of the basilar artery, posterior cerebral arteries, oculomotor nerves, and rostral brainstem (Miller 1994).

Although a midline suprasellar mass typically causes a superior temporal quandrantanopia by compression of the overlying optic chiasm, eccentric growth of a craniopharyngioma can lead to patterns of visual loss that vary in type and severity. These include decreased acuity, diplopia, blurred vision, subjective visual field deficits, and even reported cases of unilateral or bilateral blindness (Hoffman et al. 1999). Eighty percent of adults experience visual disturbance, while only 20–63% of children have this sign (Fisher et al. 1998; Moore and Couldwell 2000; Merchant et al. 2002; de Vries et al. 2003; Stripp et al. 2004); this discrepancy may be due to the lack of awareness among children of a progressive narrowing of the peripheral fields. Toddlers, in particular, can become virtually blind before the extent of visual loss becomes apparent. Mental status changes are unusual in children, but occur in 25% of adults. Tumor growth involving the frontal lobe can lead to dementia, apathy, and abulia. Temporal lobe involvement can lead to seizures and amnesia (Moore and Couldwell 2000).

7.4.2 Endocrine Signs and Symptoms

Regardless of their exact origin, craniopharyngiomas can compress or destroy the hypothalamus, anterior pituitary, or the pituitary stalk, leading to varying patterns of endocrinopathy. For example, pure intrasellar craniopharyngiomas, while rare, lead to loss of hormone secretion from direct compression of the hypothalamus or destruction of the pituitary stalk; while larger tumors can cause destruction of the hypothalamus itself. Various signs of hypopituitarism, such as short stature and delayed puberty, are present in approximately 14–53% of children, and diabetes insipidus can be seen in 16% upon diagnosis (Thomsett et al. 1980; Moore and Couldwell 2000; Merchant et al. 2002; de Vries et al. 2003; Stripp et al. 2004). However, review of the German Kraniopharyngiom database reveals that virtually all children exhibit a reduction in growth prior to diagnosis (Muller et al. 2004). In adults, growth hormone (GH) deficiency can lead to fatigue, muscle wasting, and excess adiposity, while gonadotropin deficiency leads to loss of libido or secondary amenorrhea. Subtle endocrinopathies often escape clinical detection for long periods of time, and are only apparent in hindsight.

Virtually all of the pituitary hormones can be affected, including GH (75%), luteinizing hormone (LH) or follicle stimulating hormone (FSH) (40–44%), adrenocorticotropic hormone (ACTH) (25–56%), and thyroid stimulating hormone (TSH) (25–64%). Hyperprolactinemia occurs in 1–20% of cases from impingement on the pituitary stalk (also known as the "stalk effect"), due to reduced amounts of prolactin inhibitory factor (mainly dopamine) reaching the lactotrophs of the anterior pituitary. Diabetes insipidus occurs in approximately 16% of patients prior to surgery (Sanford and Muhlbauer 1991; Honneger et al. 1999; Moore and Couldwell 2000; de Vries et al. 2003), although it is extremely common in the postoperative setting (see Sect. 7.9.1).

GH deficiency, hypothyroidism, and gonadotropin deficiency are the three most common endocrine abnormalities at presentation in children (Sanford and Muhlbauer 1991; Merchant et al. 2002; de Vries et al. 2003; Stripp et al. 2004). These, in turn, can lead to a constellation of other clinical features. GH deficiency results in growth retardation and delayed bone age. Hypothyroidism leads to poor growth, weight gain, cold intolerance, and fatigability (Rose et al. 1999b; Zhou and Shi 2004). Gonadotropin deficiency may only be evident in adolescents, but interferes with the pubertal growth spurt. Thus, growth failure can be a result of GH deficiency, central hypothyroidism, gonadotropin deficiency, or a combination of all three. ACTH deficiency is less common at presentation (Honneger et al. 1999), but is potentially life-threatening (see Sect. 7.9.4). Lastly, many of these children have increased body mass index (BMI) at presentation, due to continued weight gain in the absence of normal growth (Muller et al. 2004). However, the obesity is likely to worsen, due to post-therapy damage of the ventromedial hypothalamus, with resultant dysregulation of energy balance, termed "hypothalamic obesity" (see Sect. 7.9.4) (Hoffman et al. 1999; Lustig 2002, 2008; Lustig et al. 2003).

7.5 Natural History

Craniopharyngiomas are histologically and cytologically benign, but locally aggressive and tend to recur. Untreated craniopharyngiomas that demonstrate progressive growth cause mass effect or hydrocephalus. The rate of recurrence with any form of treatment is 8–26% at 5 years and 9–100% at 10 years (Fahlbusch et al. 1999; Stripp et al. 2004). If recurrence cannot be controlled, local invasion and growth can result in death. Malignant change, however, is extremely rare. There is one report of an adamantinomatous craniopharyngioma in a patient who underwent surgical resections and three courses of radiotherapy, which underwent subsequent transition into a moderately differentiated squamous-cell carcinoma (Kristopaitis et al. 2000). Other cases of malignant transformation reported in literature were presumably from transplantation of tumor fragments during surgery or from meningeal seeding (Barloon et al. 1988; Ragoowansi and Piepgras 1991; Malik et al. 1992; Israel and Pomeranz 1995; Gupta et al. 1999; Lee et al. 1999; Ito et al. 2001).

7.6 Diagnosis and Imaging

7.6.1 Computed Tomography and Magnetic Resonance Imaging

Plain radiographs are rarely used for diagnosis, but if performed, can demonstrate sellar changes and associated calcifications (Harwood-Nash 1994). Sixty-six percent of adults and 90% of children will have abnormalities such as sellar enlargement, erosion of the clinoid processes or dorsum sella, or calcifications on plain radiographs. Tumor-associated calcification is observed in 40% of adults and 80% of children (Moore and Couldwell 2000). Sellar enlargement is seen in 65% of patients, while sellar erosion is seen in 44% (Donovan and Nesbit 1996).

Calcifications, particularly in the suprasellar region, are best demonstrated by CT. The presence of abundant suprasellar calcification is an important piece of information for the surgeon as this feature is associated with tumors that adhere to surrounding brain tissue, thereby greatly increasing the difficulty of resection. The calcification can be obvious with large confluent areas or small punctuate or curvilinear areas (Fig. 7.3). Sellar enlargement and erosion are also seen well on CT. The tumor often appears as a lobulated, heterogeneous, and cystic suprasellar mass. The cyst fluid is either isodense or hypodense. The solid portion and cyst capsule enhance with contrast (Harwood-Nash 1994; Moore and Couldwell 2000).

Calcification is more difficult to detect on magnetic resonance imaging (MRI), but MRI provides far more detail regarding the relationship of the tumor to adjacent anatomical and vascular structures. High-resolution sequences of the sellar region, with and without contrast enhancement, should be obtained in all cases. The signal characteristics of craniopharyngiomas on MRI scans are typically heterogeneous and depend upon the amount of cystic and solid components, as well as the amount of cholesterol, keratin, hemorrhage, and calcification (Figs. 7.4 and 7.5). On T1-weighted images, the cystic component is hypointense, while the cyst rim enhances following contrast administration. The solid component is isointense, but enhances with contrast (Moore and Couldwell 2000). The tumor is almost always hyperintense on T2-weighted images (Donovan and Nesbit 1996). An important feature on MRI is the position of the anterior communicating artery, which is almost always closely related to the optic chiasm. The anterior communicating artery can still be seen with large tumors, while the chiasm may be so thin that it cannot be distinguished from the solid tumor or capsule. The position of the anterior communicating artery and the chiasm relative to the tumor strongly influences the choice of surgical approach.

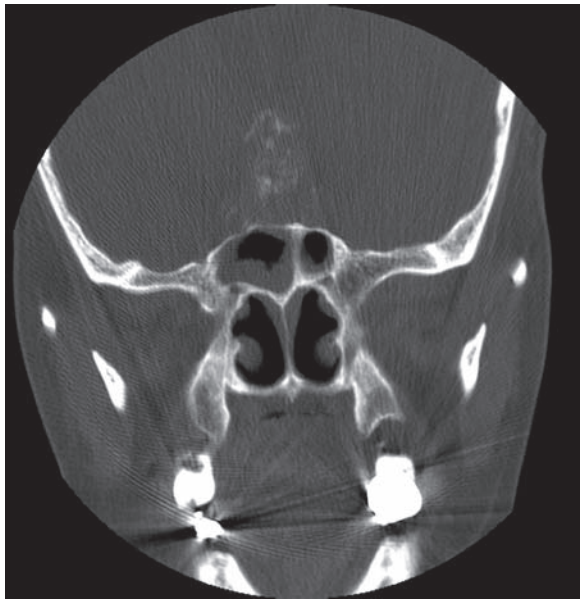

Figure 7.3
CT scan (coronal view) showing punctate calcifications within a tumor

The differential diagnosis of cystic suprasellar masses include Rathke's cleft cysts (which usually do not have a solid component, are not lobulated, are nonenhancing, and are more homogeneous), pituitary adenomas (which enlarge the sella, are more homogeneous, and are usually less cystic), meningiomas (which are rarely cystic and are isointense on T1- and T2-weighted images), optic pathway gliomas (which are usually not calcified), and giant aneurysms

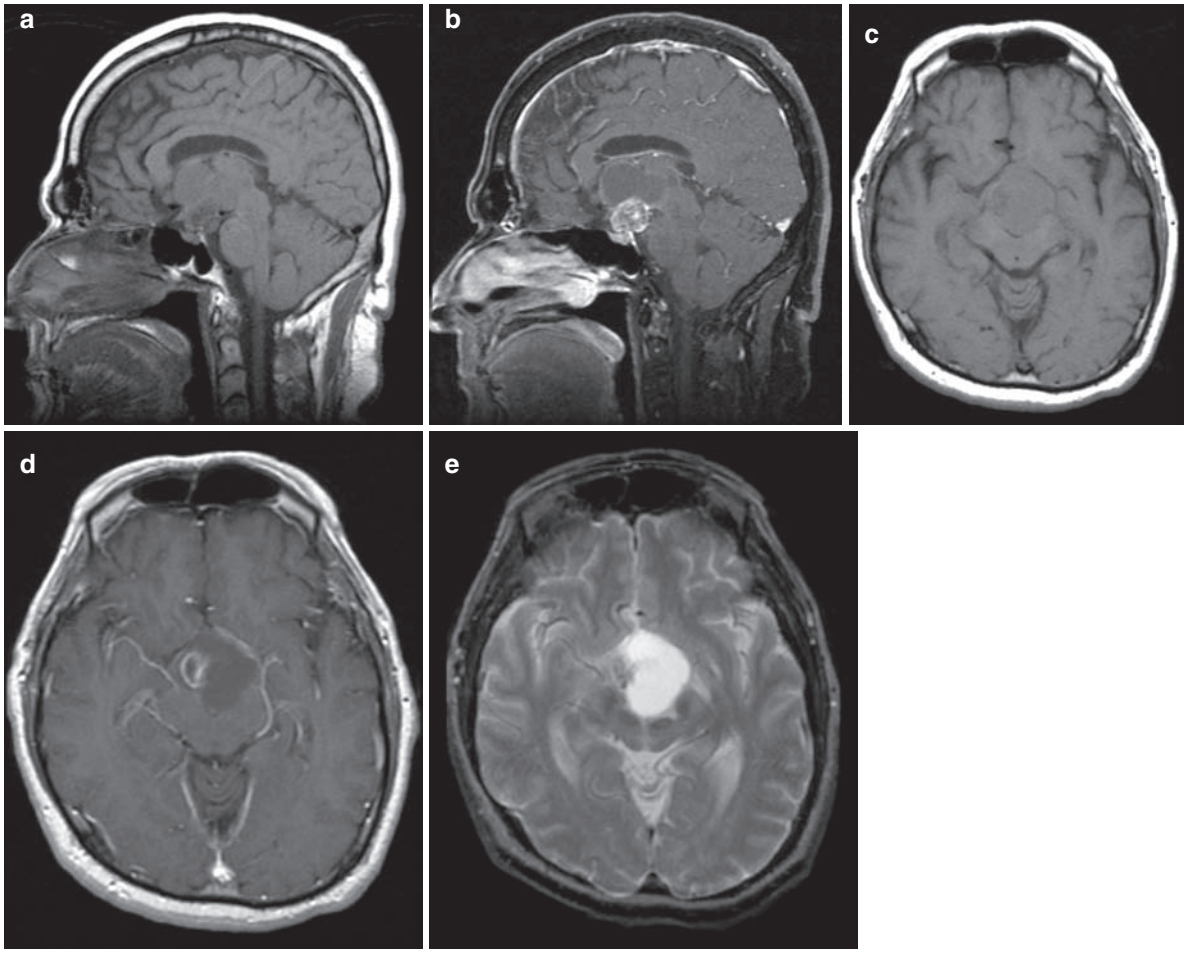

Figure 7.4

Multiple MRI sequences of a typical cystic craniopharyngioma: (**a**) Sagittal T1-weighted image without contrast. A multilobulated mass is seen in the suprasellar region. (**b**) Sagittal T1-weighted image following gadolinium. The suprasellar solid component enhances while the cystic area above it does not. (**c**) Axial T1-weighted image without contrast. (**d**) Axial T1-weighted image with gadolinium, (**e**) axial T2-weighted image

(which usually contain a laminated thrombus) (Donovan and Nesbit 1996; Fischbein et al. 2000)

7.6.2 Clinical Evaluation

The evaluation and management of patients with craniopharyngiomas requires a multidisciplinary team approach, with the active participation of subspecialties such as neurosurgery, radiation and medical oncology, neuroophthalmology, endocrinology, and psychology.

If the patient does not require immediate neurosurgical intervention, then they should have complete assessment of visual acuity and a visual field examination prior to treatment. Furthermore, hormonal deficiencies should be evaluated both clinically and

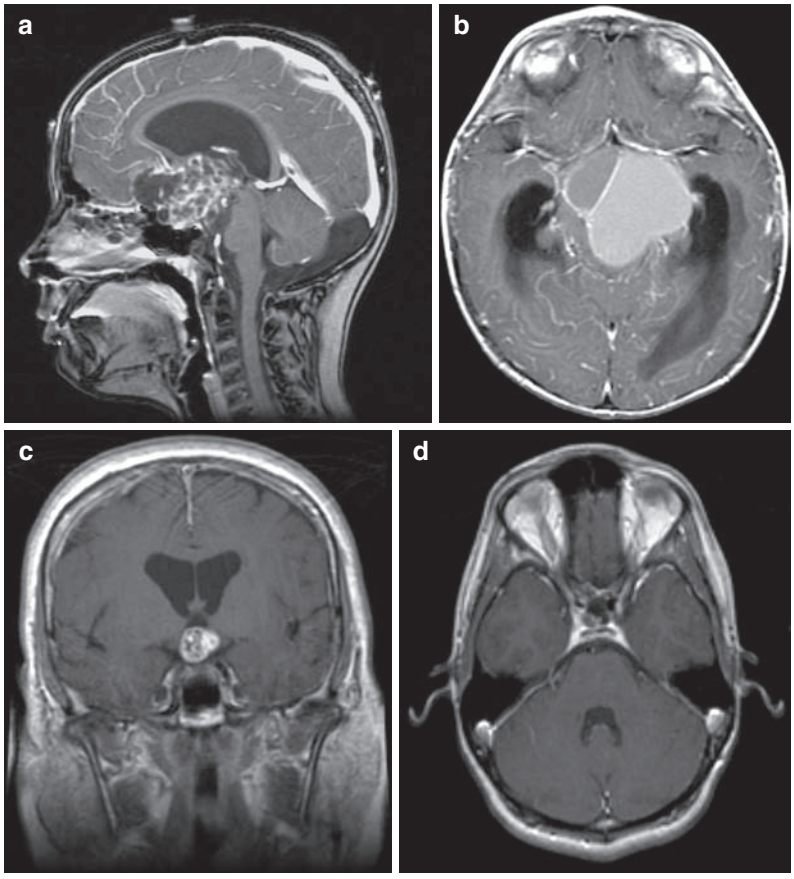

Figure 7.5
Other examples of craniopharyngiomas: (**a**) Sagittal T1-weighted image with contrast showing a large mixed solid and cystic craniopharyngioma. (**b**) Axial T1-weighted image with contrast showing a large cystic craniopharyngioma with two major compartments. (**c**) Coronal T1-weighted image with contrast showing a small, solid suprasellar craniopharyngioma. (**d**) Axial T1-weighted image with contrast showing a small, recurrent craniopharyngioma within the sella

via laboratory measurements. A complete endocrinologic assessment is necessary prior to surgery, and is invaluable when varying degrees of endocrine dysfunction may develop (Table 7.1). Where possible, based on the projected time to surgery, hormonal deficiencies should be treated (Wilson et al. 1998). All patients should get stress-dose steroids prior to surgery on the assumption that normal ACTH regulation is blunted (Samii and Tatagiba 1997); however, the use of dexamethasone to reduce brain swelling provides more than adequate glucocorticoid coverage. Hypothyroidism can take several days to correct and should be begun preoperatively; however, thyroxine supplementation can induce hepatic P450 enzymes responsible for metabolizing glucocorticoid, thereby unmasking glucocorticoid insufficiency and leading to hypotension and shock. Thus, glucocorticoid must be replaced prior to thyroxine supplementation (Moore and Couldwell 2000). Finally, any fluid and electrolyte abnormalities, including diabetes insipidus, should be identified and treated prior to surgery.

7.7 Treatment

The overall treatment philosophy for craniopharyngioma is controversial and remains the subject of ongoing debate. The individual modalities of treatment include surgical resection, cyst aspiration, radiation therapy, stereotactic radiosurgery, intracavitary irradiation or sclerosis, and new approaches such as chemotherapy and use of interferon-α (IFN-α). Mainly due to strongly held opinions and a lack of

Table 7.1. Endocrinologic evaluation

Endocrine function	Tests
Adrenal axis	8 A.M. cortisol level 24-h urine free cortisol level ACTH stimulation test Metyrapone test (difficult to get metyrapone currently)
Thyroid axis	Free T4 level Thyroid stimulating hormone level Thyrotropin-releasing hormone stimulation test in questionable cases
Gonadal axis	Follicle stimulating hormone level Luteinizing hormone level Sex steroids: estradiol in women, testosterone in men
Growth hormone (GH)	IGF-I level IGFBP-3 level GH stimulation test (GH is pulsatile, and low during the day, so a single random level is useless)
Prolactin	Prolactin level
Antidiuretic hormone (ADH)	Serum sodium or osmolality Urine specific gravity or osmolality Fluid intake vs. urine output Water deprivation test in difficult cases
Hypothalamic obesity	Oral glucose tolerance test with simultaneous insulin levels

randomized clinical-trial data, one group views gross total resection as offering the best chance for long-term survival (Caldarelli et al. 2005), while another group feels that gross total resection leads to unacceptable long-term morbidity and does not decrease recurrence rates (Spoudeas et al. 2006). The various treatment modalities and their associated advantages and disadvantages are described in the following sections.

7.7.1 Surgery

7.7.1.1 Surgical Indications

There are three goals in the surgical treatment of craniopharyngiomas: diagnosis, decompression, and prevention of recurrence (Van Effenterre and Boch 2002). Hydrocephalus and endocrine abnormalities are associated with high perioperative morbidity, and must be treated first. Hydrocephalus can be treated acutely with either an external ventricular drain or a ventriculoperitoneal shunt prior to definitive surgery. Patients with craniopharyngiomas who present with acute visual deterioration or symptoms of elevated intracranial pressure from tumor-associated mass effect also require urgent surgical decompression. Since endocrine abnormalities such as hypothyroidism or diabetes insipidus may take several days to correct, a patient who is neurologically stable should have surgery performed electively after all endocrine abnormalities are controlled. Patients with large tumors will benefit from dexamethasone to reduce cerebral edema.

7.7.1.2 Surgical Approaches

Craniopharyngiomas can be addressed surgically in a number of ways that can be broadly classified into open microsurgery, endoscopic-assisted open surgery, and pure endoscopic surgery through an endonasal approach. The surgical approach is

determined by the anatomic location and the consistency of the tumor (cystic vs. solid). The most common open approaches are bifrontal or extended frontal, unilateral subfrontal, pterional, transsphenoidal, transcallosal/transventricular, and subtemporal. Endoscopy-based approaches include the endoscopically assisted subfrontal approach through a supraorbital craniotomy, a transventricular endoscopic approach for biopsy, cyst fenestration or tumor removal, and the endonasal transsphenoidal and transplanum approaches for tumor removal. Each of these approaches has its advantages and disadvantages, although some are better suited for tumors in specific locations.

The bifrontal and subfrontal approach are used for primarily suprasellar tumors such as prechiasmatic and large retrochiasmatic lesions that extend anteriorly and fill the third ventricle (Samii and Tatagiba 1997; Moore and Couldwell 2000). A bifrontal craniotomy is followed by an extradural bilateral supraorbital osteotomy from the frontozygomatic processes laterally, through the roof of both orbits and the frontonasal suture in the midline. The extent of frontal lobe retraction following removal of the supraorbital ridge is minimized and the visualization of the tumor is improved using this technique (Chi et al. 2006).

The unilateral subfrontal approach also allows good visualization of the optic nerves, the internal carotid arteries, and access to the third ventricle via the lamina terminalis (Moore and Couldwell 2000). Although it gives good exposure of both optic nerves, it does not provide access to the contralateral nerve and tract, and lateral exposure of the suprasellar region behind the supraclinoid carotid is limited (Einhaus and Sanford 1999). For retrochiasmatic tumors, the majority of the tumor must be removed via the lamina terminalis.

Alternately, principally prechiasmatic suprasellar lesions can be removed via a supraorbital craniotomy with the aid of an endoscope. In this approach, a small incision is made into the eyebrow, and a limited craniotomy is made up to the orbital rim, flush with the frontal floor, in order to introduce the endoscope via a subfrontal approach. This approach has the appeal of minimizing brain retraction, and the ability to achieve superior visualization of the optic apparatus and the perforating vessels. In addition, intraventricular tumor can be removed via the lamina terminalis. This approach, however, requires a great deal of experience with endoscopy, and significant attention must be paid to cosmesis as the incision is made in the face, and cosmetic mistakes will be more apparent than with the open approaches that are made behind the hairline.

The pterional approach allows a more lateral view than the subfrontal approach, and is used for large retrochiasmatic tumors with both anterior and posterior extensions (Samii and Tatagiba 1997; Moore and Couldwell 2000). This approach can be combined with the unilateral subfrontal approach (Einhaus and Sanford 1999).

The transsphenoidal approach is used for cystic infradiaphragmatic lesions, as well as symmetrical and well-defined suprasellar and retrosellar lesions with an enlarged sella, and tumors without calcification that are not adherent to parasellar structures (Norris et al. 1998; de Divitiis et al. 2000). The use of an angled endoscope can allow for better visualization of the suprasellar portions, and facilitate resection of otherwise inaccessible tumor across the planum sphenoidale (Kitano and Taneda 2008). In most cases where the transsphenoidal microsurgical approach is used for large tumors, the extended transsphenoidal approach can be used, which involves removal of the bone of the planum and tuberculum (Liu et al. 2003). The transsphenoidal approach may result in lower surgical morbidity and postoperative visual loss as compared to the various intracranial routes (Rilliet et al. 1999). In two recent studies involving 45 patients, no patient had deterioration in vision after transsphenoidal surgery (Fahlbusch et al. 1999; Rilliet et al. 1999). The disadvantages include the limited lateral exposure and the possibility of a cerebrospinal fluid leak. If suprasellar calcifications are found, complete tumor removal is unlikely via the transsphenoidal approach, and a subfrontal approach is necessary (Samii and Tatagiba 1997).

Recently, there has been much interest in a purely endoscopic, transnasal, transsphenoidal approach to tumors of the sella and suprasellar region.

Advantages include wider field of view and greater depth of placement of the endoscope into intradural and intraventricular spaces. Disadvantages include loss of stereoscopic vision and depth perception, and problems with water-tight closure and subsequent cerebrospinal fluid leaks. The technique for removal of craniopharyngiomas is evolving at present and long-term follow-up is necessary to compare this technique to other surgical approaches (de Divitiis et al. 2000; Nakamizo et al. 2001).

Options for purely intraventricular tumors include the open transcortical/transventricular and interhemispheric transcallosal approaches (Samii and Tatagiba 1997; Moore and Couldwell 2000); endoscopic approaches including transcortical ventriculoscopic; and approaches across the lamina terminalis (Kitano and Taneda 2008). For these approaches, a major portion of the tumor lies within the third ventricle, which is expanded, and the foramen of Monroe is typically enlarged. A staged surgical approach can also be used to combine the intraventricular approach with the subfrontal or pterional approach at a later date to resect portions of the tumor within the sella. Additionally, ventriculoscopy can be utilized to assist a second approach by pushing otherwise inaccessible portions of the tumor in the third ventricle into the field of a second transsphenoidal approach addressing other portions of the tumor.

For tumors that are mainly cystic, stereotactic cyst aspiration followed by tumor resection or radiotherapy with instillation of radioisotopes into the cyst cavity may be successful (Samii and Tatagiba 1997; Hayward 1999; Nakamizo et al. 2001). Cyst aspiration can also relieve hydrocephalus (Hayward 1999). Regardless of surgical approach, any open procedure should be followed by a postoperative MRI scan to document the degree of resection. This study should be done within 48 hours of surgery before postoperative enhancement appears and confuses the interpretation of the study (Harwood-Nash 1994).

7.7.2 Radiotherapy

Radiation therapy is often used in the management of craniopharyngiomas, either as an adjuvant to subtotal resection or in cases in which the tumor has recurred following surgical management.

7.7.2.1 Conventional Radiotherapy

Fractionated radiation therapy represents the delivery of a high dose of radiation to the target by dividing the treatment into multiple doses, with a single dose, or fraction, typically given each day, allowing for normal tissue repair between fractions. Total doses have typically ranged from 50 to 65 Gy, divided into 1.8–2 Gy daily fractions (Einhaus and Sanford 1999). Typically, the maximum dose delivered to the optic apparatus is 50–54 Gy. Radiation therapy is often used as an adjuvant to subtotal resection. In most reported external beam series, local control is quite good. Radiation therapy can also be used in cases where tumor recurs following surgical management. In some series, results for treatment of recurrent disease are inferior to primary therapy. However, other series report results comparable to primary therapy.

Doses less than 54 Gy have been associated with a 50% recurrence rate in children and a 33% recurrence rate in adults, while doses greater than 54 Gy have a 15 % recurrence rate in children and a 17% recurrence rate in adults (Regine et al. 1993). Other factors predictive of local control include age, era of radiation treatment, use of modern imaging, extent of resection, large tumor size (>5 cm), and radiation technique.

Radiation techniques have advanced significantly in recent years, with modern techniques incorporating three-dimensional imaging, including MRI and CT scans. The use of such imaging for target and normal structure delineation, combined with advances in treatment techniques, improves delivery of dose to tumor, while minimizing dose to critical structures, widening the therapeutic ratio. These modern techniques include:

1. Intensity-modulated radiation therapy (IMRT)
2. Proton beam therapy
3. Stereotactic radiosurgery

4. Fractionated stereotactic radiotherapy
5. Intracavitary brachytherapy

IMRT represents an evolution of three-dimensional conformal radiotherapy, in which treatment beams are subdivided into multiple "beamlets" of varying intensity. This enables development of complex treatment plans with rapid fall-off of dose away from tumor, potentially allowing better sparing of adjacent normal tissues. Care needs to be taken during planning to ensure that the maximum dose within the targeted volume (which is nonuniform) does not exceed the threshold for delayed radiation toxicity.

Proton beam therapy exhibits dose deposition and fall-off over a very narrow range (Bragg peak effect), allowing for superior dose distribution in certain situations. This has led to a great deal of interest in the use of protons in the treatment of pediatric neoplasms. Initial results of the use of proton beam therapy in the treatment of craniopharyngiomas are encouraging (Austin-Seymour et al. 1990), and use of this modality will no doubt increase as more proton facilities open. Any benefit over conformal external beam radiotherapy remains unknown.

7.7.2.2 Stereotactic Radiosurgery

Radiosurgery usually involves 1–5 treatment sessions. Using image guidance, a neurosurgeon and radiation oncologist directs a large number of intersecting beams to deliver a high dose of radiation to a small area, while minimizing the radiation dose to adjacent critical structures. Radiosurgery can be delivered using frame-based and nonframe-based delivery systems. A number of devices can deliver radiosurgical treatments, including linear accelerator (LINAC) based systems, robotic systems (Cyberknife, Accuray, Sunnyvale, CA), and multiple cobalt-60 sources (Gamma Knife, Elekta AB, Stockholm). Radiosurgery allows the radiation dose to be closely tailored to the tumor volume with minimal exposure of the hypothalamic-pituitary axis and the optic apparatus (Mokry 1999). This has rapidly led to radiosurgery becoming the favored modality in appropriate cases. Results of radiosurgical series are summarized in Table 7.2.

Radiosurgery is limited in its ability to treat large tumor volumes (greater than 3 cm), and in treatment of tumors for which there are no distinguishing boundaries between tumor and adjacent critical structures. Other treatment options, however, can be

Table 7.2. Outcomes for craniopharyngiomas treated with Gamma Knife radiosurgery

References	Number of patients	Percentage of tumor progression	Follow-up
Kobayashi et al. (1994)	33	11	3.5 years (mean)
Mokry (1999)	23	36	28 months (mean)
Yu et al. (2000)	38	10 solid tumors 14 mixed tumors	6–24 months
Chung et al. (2000)	31	13	36 months (mean)
Chiou (2001)	10	0 solid tumors 62.5 mixed tumors	5.65 years (mean)
Ulfarsson (2002)	21	85 (<6 Gy) 33 (≥6 Gy)	7.5 years (mean)
Barua (2003)	7	0	4.2 years (mean)
Amendola (2003)	14	14	3.3 years (mean)
Albright (2005)	5	20	2.4 years (mean)

Table 7.3. Outcomes of primary surgery, gross total resection, for craniopharyngiomas

References	Number of patients	Recurrence-free survival (%)	Percent survival
Lin (2008)	14	54 at 6 years	100 at 6 years
Shi (2008)	276	86 at 6 years	98 at 6 years
Puget (2007)	33	64 at 6 years	94 at 6 years
Bojanowski (2006)	12	91 at 2–14 years	91 at 2–14 years
Stripp et al. (2004)	44	47 at 10 years	86 at 10 years
Duff et al. (2000)	121	77 at 5 years	88 at 10 years
			74 at 15 years
Kalapurakal et al. (2000)	14	92 at 5 years	100 at 5 years
		60 at 10 years	86 at 10 years
Fahlbusch et al. (1999)	73	87 at 5 years	93 at 10 years
		81 at 10 years	
Villani et al. (1997)	17	82 at 7 years	94 at 7 years
Hetelekidis et al. (1993)	5	0 at 10 years	100 at 10 years

used to render a tumor a more amenable target for radiosurgery. For example, if a tumor is largely cystic, aspiration of the cystic portion can decrease the total target volume and allow better delineation of tissue planes (Chung et al. 2000).

7.7.2.3 Fractionated Stereotactic Radiotherapy

Fractionated stereotactic radiotherapy is typically done in more than 5, and usually 25–28, treatment sessions. This technique has the advantages of both fractionated external beam radiation therapy (normal tissue repair between fractions) and radiosurgery (minimal dose to structures away from the targeted region), and can be used to treat tumors that are greater than 3 cm, as well as those that abut the optic apparatus.

The largest reported series from University of Heidelberg (Combs et al. 2007) reported 100% local control at both 5 and 10 years following treatment. Overall survival rates were 97 and 89%, respectively. The median target dose was 52.2 Gy, given with conventional fractionation of 1.8 Gy per fraction. A complete response was observed in 4 patients, partial response in 25 patients, and stable disease in 11 patients. There were no visual impairments or second malignancies reported at a median follow-up time of 98 months. These results were corroborated by a similar series using stereotactic techniques with conventional fractionation from the Royal Marsden Hospital (Minniti et al. 2007). A third series from Stanford University consisted of 16 patients treated with Cyberknife® radiosurgery to a median dose of 21.6 Gy (range of 18–38 Gy) given over 3–10 fractions. Tumor was controlled in 10 of 11 assessable patients, with cyst enlargement from residual tumor in one patient. No worsening of visual or neuroendocrine function was seen in these patients.

7.7.2.4 Intracavitary Therapy

Intracavitary therapy of cystic craniopharyngiomas, first reported by Leksell and Liden in 1952, has been used both as a primary mode of therapy as well as an adjunctive therapy for recurrent cases (Leksell and Lidén 1952). Intracavitary therapy refers to the instillation of a radioisotope such as ^{90}yttrium, ^{32}phosphorus,

or ^{186}rhenium through an indwelling catheter into the tumor cyst cavity so that a high dose of radiation can be delivered to the surrounding secretory epithelial layer. From a review by Blackburn et al., 121 of 149 cysts treated in 127 patients reduced in size or were obliterated in the follow-up period of 0.2–13 years. However, the distinction between recurrence of a cyst versus recollection of the initial lesion varied among the different studies (Blackburn et al. 1999). In a study of 30 patients treated with ^{32}phosphorus, where cyst regression was defined as more than 50% reduction in volume, 88% of patients were found to have cyst regression, with response occurring within 3 months of surgery and continued decrease in cyst size up to 2 years after surgery (Pollock et al. 1995). Overall survival rate was 55% at 5 years and 45% at 10 years, with a mean survival of 9 years (Voges et al. 1997). The impact of intracavitary irradiation on vision varied widely among studies ranging from 100% deterioration to 100% improvement, with improvement in 53% of patients, over all the studies considered (Voges et al. 1997; Blackburn et al. 1999). The effect on endocrine function was equally varied. More recent studies have also shown wide variability in visual and endocrine complications (Hasegawa et al. 2004; Julow et al. 2007). Because of these confusing results and difficulties in handling radioactive compounds, this technique has not been widely adopted despite relatively good outcomes with regards to control of cystic lesions.

7.7.3 Chemotherapy

The use of chemotherapeutic agents in the treatment of craniopharyngioma for the most part must be considered experimental. One agent under investigation is IFN-α, which is effective for the treatment of squamous-cell carcinoma. The rationale for its use with craniopharyngiomas is that the two neoplasms share a similar epithelial origin. A Phase II trial of IFN-α for progressive, recurrent, or unresectable craniopharyngiomas in children under 21 years of age has been reported by Jakacki et al. (2000). Treatment consisted of an induction phase of 8,000,000 U/m^2 daily for 16 weeks. Patients without progressive disease at 16 weeks then continued at the same dose three times a week for 32 weeks. Time to progression after discontinuation of IFN-α was 6–23 months. IFN-α toxicity occurred in 60% of cases during the first 8 weeks of treatment, but resolved with discontinuation or dose reduction. Toxicities include hypoadrenal crisis with fever, neutropenia, transaminitis, fatigue, rash, insomnia, and seizures (Jakacki et al. 2000). Recently, administration of intracystic IFN-α was reported to reduce tumor size and induce apoptosis (Ierardi et al. 2007). Similarly, a short experience with intracavitary bleomycin was recently reported, and may provide a means for delaying the need for further intervention by several years (Hukin et al. 2007).

7.8 Outcome

On the basis of postoperative imaging, gross total resection varies widely in various series ranging from 29 to 77% of cases (Sanford 1994; Villani et al. 1997; Einhaus and Sanford 1999; Fahlbusch et al. 1999; Duff et al. 2000; Van Effenterre and Boch 2002; Stripp et al. 2004; Caldarelli et al. 2005; Shi et al. 2008). Reflecting the heterogeneity of patient groups, recurrence has been reported to occur in 8–100% of patients after initial gross total resection. The mean duration of follow-up in these studies ranges from 5 to 10 years (Table 7.3) (Hetelekidis et al. 1993; Villani et al. 1997; Fahlbusch et al. 1999; Duff et al. 2000; Kalapurakal et al. 2000; Poretti et al. 2004; Stripp et al. 2004; Shi et al. 2008). Recurrence following gross total resection can be assumed to occur because of unrecognized deposits of tumor capsule. Even high-quality imaging will miss small amounts of epithelium that have the potential to develop into recurrent tumors. The use of adjunctive radiation therapy following gross total resection is controversial. Since radiation is not likely to increase the risk of endocrinopathy further, and because risk of recurrence is diminished, some advocate adjunctive radiation. Others feel that radiation therapy should be reserved for rescue following tumor recurrence. Thus, the role of adjunctive radiation as therapy immediately after gross total resection has not been satisfactorily explored.

In many cases, only a portion of the tumor can be removed. The main reasons for incomplete tumor removal are adhesions to vessels and vital structures

such as the optic nerve and chiasm, and major calcifications (Samii and Tatagiba 1997; Fahlbusch et al. 1999). In patients undergoing subtotal resection without radiation therapy, the recurrence rate is 43–75% with mean follow-up periods of 5–7 years (Villani et al. 1997; Fahlbusch et al. 1999; Khoo et al. 2001). For partial resection followed by radiotherapy, the recurrence rate was 43–54% during a mean follow-up period of 65–84 months, which is comparable with the rate for gross total resection (Villani et al. 1997; Fahlbusch et al. 1999; Stripp et al. 2004). The management of recurrent tumors is often fraught with difficulties. If a focal recurrence is present on imaging studies, repeat surgical exploration may be warranted. Not surprisingly, recurrent tumors are more difficult to resect, and have a resection rate of 13–50% via the transcranial approach (Villani et al. 1997; Fahlbusch et al. 1999; Duff et al. 2000) and 53% through the transsphenoidal route (Fahlbusch et al. 1999). The latter group represents a closed area that limits the extension of the tumor and is more amenable for repeat surgery. Overall, 81% percent of patients who underwent surgery (intracranial or transsphenoidal) were disease-free on follow-up at 65 months (Fahlbusch et al. 1999).

Survival of patients with craniopharyngioma treated with radiation therapy for initial or recurrent disease is comparable to those treated with different modalities (Table 7.4). Overall survival for two series of patients treated in a variety of ways at 5, 10, and 15 years was 100, 68–86, and 59–86%, respectively (Bulow et al. 1998; Kalapurakal et al. 2000). At UCSF, the overall survival rates for patients treated for initial disease with surgery followed by radiation therapy at 5, 10, and 15 years were 88, 80, and 77%, while disease-specific survival probabilities at 5, 10, and 15 years were 97, 92, and 92% (unpublished data). Overall survival for patients with recurrent tumors treated with radiation therapy at 5 and 10 years were similar at 87 and 82%, and disease-specific survival rates at 5 and 10 years were 97 and 91%. These results provide some basis for the argument that radical resection should not be the primary goal for all tumors (Karavitaki et al. 2006; Spoudeas et al. 2006).

Radiation therapy has been shown to be an effective adjuvant treatment to subtotal surgical resection for initial disease as well as for recurrent disease compared with treatment with surgery alone. In a study of patients treated with surgery only, recurrence occurred in a median time of 19 months (Duff

Table 7.4. Outcomes for subtotal resection combined with radiotherapy for patients treated for primary and recurrent disease

References	Primary disease vs. recurrence	Number of patients	Recurrence-free survival (%)	Percent survival
Stripp et al. (2004)	Primary	18	84 at 10 years	83 at 10 years
	Recurrence	36	91 at 5 years	87 at 5 years
			82 at 10 years	82 at 10 years
Habrand et al. (1999)	Primary and	37	78 at 5 years	91 at 5 years
	recurrence		57 at 10 years	65 at 10 years
Gurkaynak (1994)	Primary	23	74 at 5 years	N/A
			62 at 10 years	
Hetelekidis et al. (1993)	Primary	37	86 at 10 years	86 at 10 years

N/A not available, not reported

et al. 2000). In those treated with surgery combined with radiation at UCSF, recurrences occurred from 3 to 125 months, with a median of 41 months. The recurrence rate did not differ between those treated with radiation therapy for initial and recurrent disease. Progression-free survival rates at 5, 10, and 15 years were 89, 83, and 79% for patients treated with radiation for their initial disease. Progression-free survival at 5, 10, and 15 years was 91–100, 82–83, and 83% for patients with recurrent tumors treated with surgery and radiation therapy, and 67, 0, and 0% for patients with recurrent tumors treated with surgery alone (Kalapurakal et al. 2000). For recurrent tumors, surgery combined with radiotherapy can achieve a much better result than surgery alone. However, Bulow et al. found that when patients who died within 6 months of therapy were excluded, the advantage of radiation therapy was no longer statistically significant. There was also no difference in rate of recurrence with respect to age or extent of surgery (Bulow et al. 1998).

The outcome did not differ between adults and pediatric patients, between papillary and adamantinomatous tumors, or between transsphenoidal and transcranial approaches. Recurrence rates also did not correlate with preoperative radiologic findings (Duff et al. 2000).

7.9 Complications Associated with Treatment

7.9.1 Complications of Surgery

Aside from the mass effect of the tumor, surgical resection itself is associated with significant risks to endocrine function and vision (Table 7.5). The most common postoperative complication is diabetes insipidus, caused by death of the vasopressingeric neurons of the supraoptic and paraventricular nuclei, or by pituitary stalk transsection close to the hypothalamic perikarya, such that axonal regeneration within the posterior pituitary cannot occur. Diabetes insipidus occurs in 59–93% of patients following surgery (Yasargil et al. 1990; Hoffman et al. 1992; Tomita and McLone 1993; Sanford 1994; Fahlbusch et al. 1999; Hoffman et al. 1999; Rilliet et al. 1999).

Anterior pituitary function is also frequently compromised. Although Fahlbusch et al. reported that normal postoperative anterior pituitary function was maintained in over 50% of patients after surgery, and the incidence of hypogonadism increased only from 77 to 80% (Fahlbusch et al. 1999), other series report that panhypopituitarism occurs in 75–100% of patients who underwent surgical resection (De Vile et al. 1996a, b; Kalapurakal et al. 2000).

Visual deterioration occurred in 2–66% of patients who underwent surgical resection (Pierre-Kahn et al. 1994; Fahlbusch et al. 1999; Poretti et al. 2004). Minor surgical trauma to the hypothalamus can also cause sleep disorders, memory problems, apathy, and appetite changes (Samii and Tatagiba 1997).

In addition to neurologic and endocrinologic complications, intellectual, psychological, and social morbidities must also be considered. Neuropsychological and behavioral disturbances were found in 36–60% of children who underwent radical resection (Anderson et al. 1997; Villani et al. 1997; Riva et al. 1998; Kalapurakal et al. 2000). Many of these children are affected by their body images as a result of the obesity, which occurred in 36% of children (see Sect. 7.9.3) (Kalapurakal et al. 2000). There were no changes in long-term or short-term memory (Riva et al. 1998; Kalapurakal et al. 2000). A decrease in school performance and learning disability occurred in 0–50% of children (Zuccaro et al. 1996; Villani et al. 1997; Riva et al. 1998; Poretti et al. 2004). Merchant et al. found a drop in IQ scores by 9.8 points in 15 pediatric patients treated with gross total resection alone (Merchant et al. 2002). While neuropsychological outcome is most often studied in children, adults can have neuropsychological sequelae as well. Donnet et al. found in a study of 22 adults that 9% had severe memory and intellectual defects and 14% had moderate learning defects (Donnet et al. 1999). Van Efferenterre et al. found in a study of 122 patients that the rate of normal neuropsychological function was 91% as assessed by patients and their families (Van Effenterre and Boch 2002). Honneger et al. found that cognitive function in adults remained the same or improved postoperatively (Honegger et al. 1998).

Complications from the transsphenoidal approach are similar to other surgical approaches except for

Table 7.5. Complications for patients treated with surgery

References	Number of patients	Diabetes insipidus (%)	Panhypopituitarism (%)	Visual loss
Zhou and Shi (2004)	40	58	95	N/A
Stripp et al. (2004)	44	88	84	N/A
Merchant et al. (2002)	15	73	N/A	33% decreased visual acuity 40% decreased visual field
Kalapurakal et al. (2000)	14	100	100	N/A
Duff et al. (2000)	31	21	N/A	N/A
Honegger et al. (1998)	92	66 (16% at presentation)	N/A	N/A
Rilliet et al. (1999)	31	74	74	22%
Fahlbusch et al. (1999)	89	N/A	N/A	13%
Villani et al. (1997)	24	81	N/A	19%
Hetelekidis et al. (1993)	13	79 (14% at presentation)	77%	N/A
Yasargil et al. (1990)	141	79 (23% at presentation)	N/A	13%

N/A not available, not reported

a lower incidence of behavioral and visual disturbances. Behavioral disturbance occurred in 9% of children, and only 0–1% of adults and children had visual deterioration (Laws 1994; Norris et al. 1998; Fahlbusch et al. 1999; Rilliet et al. 1999). This low complication rate can be attributed to the types of tumors for which the transsphenoidal approach is best suited; namely, intrasellar and cystic tumors, which do not generally affect hypothalamic integrity.

7.9.2 Complications of Radiotherapy

Radiation therapy results in endocrine dysfunction and visual defects similar to that observed following surgery, but the severity of these complications, particularly with respect to diabetes insipidus, appears to be reduced (Table 7.6). Duff et al. found an overall good outcome rate of 60% in a retrospective study of 121 patients with a mean follow-up of 10 years (Duff et al. 2000). In a review of 72 patients treated for initial disease at UCSF from 1972 to 1999, 32% had visual deficits after subtotal resection followed by radiation, although 81% of these had visual deficits prior to treatment and 72% retained their pretreatment functional status (unpublished data). In the same series, of the 36 patients treated for recurrent disease, only 53% retained the same functional status. No difference was associated with extent of surgical resection, with 78% having permanent deficits. A majority of patients had impaired endocrine function. Sixty-four percent required thyroid hormone replacement, 56% required cortisol, 44% required sex hormones, 17% had diabetes insipidus, and 1% had elevated prolactin levels. The endocrinologic sequelae of radiotherapy compares with other series which report 6–38% incidence of diabetes insipidus after radiation therapy, much lower than that of patients who have undergone total resection (Einhaus and Sanford 1999). In a series by Regine et al., the incidence of endocrinologic sequelae was correlated with both age and

Table 7.6. Complications in patients treated with surgery and radiotherapy

Reference	Number of patients	Diabetes insipidus (%)	Panhypopituitarism	Visual loss (%)
Merchant et al. (2002)	14	33	N/A	33% decreased visual acuity; 60% with decreased visual field
Habrand et al. (1999)	37	66 (22% at presentation)	97% (22% at presentation)	0
Hetelekidis et al. (1993)	34	38 (25% at presentation)	53%	N/A

N/A not available, not reported

maximum dose of radiation, being 80% in children and 26% in adults for doses greater than 61 Gy, and 36% in children and 13% in adults for doses less than 61 Gy (Regine et al. 1993).

The effects of partial or whole brain radiation on the intellectual function of children with various brain tumors has been extensively studied, and has shown much greater effects on younger children (Weiss et al. 1989). In children less than 3 years of age treated with either partial or whole brain radiation for various brain tumors, excluding craniopharyngiomas, 60% were mentally retarded with IQ less than 69. The incidence of mental retardation/dementia and vascular complications of radiation therapy for craniopharyngioma is highly correlated with the maximum dose, being 40% in children and 45% in adults for doses greater than 61 Gy vs. 0% in children and adults at doses less than 61 Gy (Regine et al. 1993). In children who had received radiotherapy, 32–33% had poor school performance or required special schooling due to moderate to severe learning disability after treatment (Zuccaro et al. 1996; Habrand et al. 1999). Merchant et al. found a median drop in IQ scores of 1.25 points in 15 children treated with limited surgery and radiation compared with 9.8 points in the surgery only group (Merchant et al. 2002). Although the results of the damaging effects of radiation on the intellectual function of children less than 3 years of age was not studied in patients with craniopharyngiomas, we do not recommend adjuvant radiation therapy in children under 3 years of age who have undergone a subtotal resection, unless they become symptomatic.

Other complications of radiation therapy include radiation-induced neoplasms (glioblastoma, sarcoma, meningioma), radiation necrosis, vascular occlusion, radiation vasculitis, optic neuritis, dementia, calcification of basal ganglia, hypothalamic-pituitary dysfunction, hypothalamic obesity, and decreased intellect in children (Einhaus and Sanford 1999; Moore and Couldwell 2000; Lustig et al. 2003).

7.9.3 Complications of Radiosurgery

A majority of patients retained good function after treatment with stereotactic radiosurgery. Diabetes insipidus, panhypopituitarism, and visual loss occur in 0–4, 0–2, and 0–4% of patients who have undergone radiosurgery, respectively (Mokry 1999; Chung et al. 2000; Yu et al. 2000). Chung et al. reported good to excellent outcomes (independent living) in all patients with mainly solid or cystic tumors and in 50% of those with mixed solid and cystic tumors (Chung et al. 2000). Visual deterioration occurred in 10–66% of patients (Kobayashi et al. 1994; Einhaus and Sanford 1999). Given its potential effects on vision, stereotactic radiosurgery should be applied only to small tumors less than 2 cm in size and more than 4–5 mm away from the optic apparatus (Lunsford et al. 1994).

Most patients treated with fractionated stereotactic radiosurgery also have good outcomes following treatment. In the Royal Marsden series, vision remained stable following treatment in 88% of patients and improved in 8% of patients. Only one patient, with severely compromised pretreatment vision, showed visual deterioration that was possibly attributable to radiation (Minniti et al. 2007). This is similar to the University of Heidelberg series, where no patient developed a new visual deficit following radiation therapy (Combs et al. 2007). With regard to endocrine function, results of fractionated stereotactic radiosurgery remain similar to those of conventional external beam radiation therapy, with 30–50% of patients developing deficits following surgery and fractionated radiosurgery. Most patients with intact pituitary function following surgery maintain function following radiosurgery (Combs et al. 2007; Minniti et al. 2007). None of the available studies have done formal prospective neuropsychological testing. Thus, it is not possible to conclude that stereotactic treatment is safer in this regard. Likewise, these techniques have not been in use long enough to draw conclusions regarding rates of secondary malignancies.

7.9.4 Hypothalamic Injury

Damage to the hypothalamus, either from the craniopharyngioma itself, or subsequent surgery or radiation, can result in numerous functional morbidities and endocrinopathies (see Sect. 7.4).

The ACTH deficiency is the least common endocrinopathy after hypothalamic damage, perhaps because cortisol is essential for survival, and because the pituitary corticotrophs are the most radioresistant of pituicytes (Rose et al. 2005). Approximately 25% percent of patients with craniopharyngioma manifest ACTH deficiency after treatment (Honneger et al. 1999; Rose et al. 2005). Patients experience fatigue, chronic headache, hypotension, and tachycardia with illness or other severe stress, which can lead to shock and death. Diagnosis is made by suboptimal cortisol response to an ACTH stimulation test, or a suboptimal 11-deoxycortisol response to a metyrapone test (Rose et al. 1999a). Such patients require lifelong hydrocortisone replacement.

Diabetes insipidus is rare on presentation (16%) (Honneger et al. 1999; de Vries et al. 2003), but can reach an incidence of 60–95% after surgical treatment (Honneger et al. 1999; Zhou and Shi 2004). Treatment is lifelong desmopressin acetate (DDAVP) therapy (either oral, intranasal, or subcutaneous). Usually, the patient will be able to drink enough water to maintain eunatremia and adequate hydration, but this can be a problem in infants and toddlers, or in the aged. Diabetes insipidus is particularly worrisome when it is complicated by adipsia (Smith et al. 2004), thus requiring a water prescription and frequent monitoring of serum sodium levels; such patients have a high risk for mortality.

Damage to the ventromedial hypothalamus often results in defective energy balance, termed "hypothalamic obesity" (Bray and Gallagher 1975; Lustig 2002; Daousi et al. 2005). An extremely high frequency of hypothalamic obesity (30–77%) has been documented after craniopharyngioma treatment (Harz et al. 2003). Although slightly increased BMI is common at initial presentation, either surgery or hypothalamic radiation (greater than 51 Gy) can precipitate this syndrome (Lustig et al. 2003). Rates of weight gain range from 12 to 20 kg/year persist without plateau, and obesity often becomes the most debilitating aspect of the postoperative course. Metabolic complications of the obesity are frequent and manifest early (Srinivasan et al. 2004). Children with hypothalamic obesity exhibit weight gain, even in response to forced caloric restriction (Bray and Gallagher 1975). This phenomenon occurs due to ventromedial hypothalamus damage, preventing normal hypothalamic leptin signal transduction, which leads to: (1) defective activation of the sympathetic nervous system (Schofl et al. 2002; Coutant et al. 2003), which retards lipolysis and reduces energy expenditure (Shaikh et al. 2008); and (2) overactivation of the vagus nerve (Lee et al. 1989), which promotes an obligate insulin hypersecretion and energy storage (Lustig et al. 2003; Preeyasombat et al. 2005; Lustig 2007). Diagnosis can be made on an oral glucose tolerance test, where the insulin hypersecretion is evident (Preeyasombat et al. 2005; Lustig 2007). Although several treatments have

been proposed, which include adrenergics to increase energy expenditure (Mason et al. 2002), suppression of insulin secretion using octreotide (Lustig et al. 1999, 2003), and bariatric surgery (Inge et al. 2007), results have been salutary and only stabilize further weight gain. Therefore, it is imperative to diagnose this complication early in the postoperative course, so that preventative and pharmacologic measures can be implemented.

7.10 Conclusions

Despite recent advances in treatment options, craniopharyngiomas remain a challenging disease. The data and experience reported in the literature does not allow one to make a definitive recommendation.. In general, for tumors that remain intrasellar and do not impinge on the hypothalamus, an attempt at gross total resection should be made. However, attempts at gross total resection in the face of hypothalamic involvement should be avoided, given the unacceptable long-term functional sequelae, especially those morbidities associated with mortality, which are primarily endocrinologic in origin. Subtotal resection and treatment with external beam radiation remains an acceptable therapy, whose aim is tumor control rather than removal of all dysplastic tissue. Other therapies such as intracavitary irradiation, radiosurgery, intracavitary chemotherapy with bleomycin, or systemic chemotherapy with agents such as IFN either remain restricted to specific tumor subtypes or are still experimental in nature. Clearly, more data is needed to understand the long-term endocrine, psychological, and social consequences of treatment, especially in the pediatric population.

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Neuronal Tumors

Edward F. Chang • Nalin Gupta

Contents

8.1 Ganglioglioma and Gangliocytoma

Gangliogliomas and gangliocytomas belong to a family of rare, slow-growing, neuronal tumors. Courville first introduced the term "ganglioglioma" in 1930 to describe the mixed neuronal and glial elements typically seen in this tumor (Courville 1930). Although there is a pathologic difference between ganglioglioma and gangliocytoma, the natural history and biology of these two subtypes appear to be the same.

8.1.1 Epidemiology

Gangliogliomas are rare, representing only 0.4% of all central nervous system (CNS) tumors and 1.3% of all brain tumors (Kalyan-Raman and Olivero 1987). A higher percentage of 7.6% was described in one series of pediatric brain tumors (Johannsson et al. 1981). The mean or median age at diagnosis ranged from 8.5 to 25 years in a group of 206 patients. The male: female ratio varies among different series from 1.1:1 to 1.9:1, but supports a slight male predominance (Lang et al. 1993; Prayson et al. 1995; Hirose et al. 1997). The mean age at diagnosis in a series of 99 children was 9.5 years and the male: female ratio was 1:1 (Johnson et al. 1997).

8.1.2 Pathology

Gangliogliomas are slow-growing tumors that can occur throughout the CNS. They occur mostly in the supratentorial region, primarily the temporal lobe, but the frontal lobes and the floor of the third ventricle are also common locations. Less frequently, they have been seen in the cerebellum, brain stem, spinal cord, pituitary, and pineal regions.(Kalyan-Raman and Olivero 1987; Lang et al. 1993; Prayson et al. 1995; Hirose et al. 1997; Jallo et al. 2004; Baussard et al. 2007).

8.1.2.1 Gross Appearance

These tumors can be either solid or cystic. Cystic masses are often associated with a mural nodule (a solid tumor component eccentrically located at the margin of the cyst). The tumor itself is firm and typically well-demarcated from the surrounding brain tissue. Some tumors contain varying degrees of calcification. Mass effect, hemorrhage, and necrosis are rare.

8.1.2.2 Histopathology

Gangliocytomas consist of groups of large, multipolar neurons with dysplastic features. The surrounding stroma contains nonneoplastic glial elements and a network of reticulin fibers (Fig. 8.1b). Gangliocytomas are classified as WHO grade I tumors. Gangliogliomas, in contrast to gangliocytomas, contain neoplastic glial cells, usually astrocytes, but are also classified as WHO grade I tumors (Louis et al. 2007). Grading of gangliogliomas has typically been assigned based on characteristics of the glial component of the neoplasm. However, the standard criteria that are used to grade astrocytomas (e.g., mitotic activity, microvascular proliferation, and necrosis) appear to less reliably predict the clinical behavior of gangliogliomas (Luyken et al. 2003).

A recent review of supratentorial gangliogliomas described the pathologic features of different grades of this tumor. Grade II tumors contain cellular atypia (increased cellularity, conspicuous pleomorphism), microvascular proliferation, or an elevated MIB-1 labeling index (LI) (≥5%) (Louis et al. 2007). Grade III neoplasms are characterized by additional features such as necrosis and MIB-1 proliferation index of 10% or more. Although the numbers of patients in the former grade II and III groups were relatively small, this report demonstrated that the histological grade was associated with the recurrence-free survival rate.

In the current, fourth edition of the WHO classification gangliogliomas are designated WHO grade I and anaplastic gangliogliomas are designated WHO grade III. Necrosis is absent unless the glial component undergoes malignant transformation. Tumors with evidence of malignant transformation are anaplastic gangliogliomas and are considered WHO grade III.

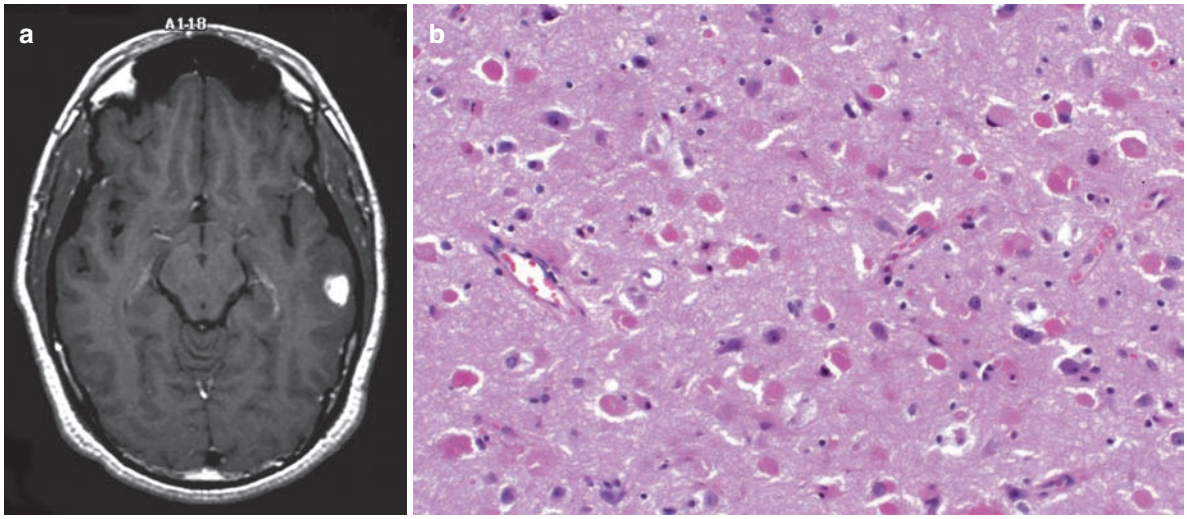

Figure 8.1

Ganglioglioma. (**a**) T1-weighted axial MRI with gadolinium of a ganglioglioma in the left temporal lobe. Nodular enhancement is seen. (**b**) Hematoxylin and eosin staining reveals large, dysplastic neurons and a neoplastic glial component. Necrosis is not seen

8.1.2.3 Immunohistochemistry and Electron Microscopy

Immunohistochemical staining techniques are crucial for identifying the neuronal and astrocytic features within these tumors. Positive staining for synaptophysin, neuropeptides, and biogenic amines are associated with a neuronal phenotype. Similarly, positive staining for glial fibrillary acid protein (GFAP) identifies the astrocytic component. Electron microscopy is also helpful to identify additional neuronal features such as dense core granules and synaptic junctions (Miller et al. 1993; Hirose et al. 1997).

8.1.2.4 Cytogenetics

In a few cases, abnormal karyotypes were observed. Specific cytogenetic abnormalities include a ring chromosome 1, trisomy of chromosomes 5–7, and deletion of chromosome 6 (Neumann et al. 1993). Analysis for microsatellite marker instability in tumor DNA from 6 gangliogliomas found no abnormalities (Zhu et al. 1996). One series of ganglioglioma patients reported a comparatively higher frequency of splice-site-associated single-nucleotide polymorphism in the tuberous sclerosis complex two gene (*TSC2*). This may suggest an underlying genetic susceptibility (Platten et al. 1997) for sporadic ganglioglioma, although the underlying biologic mechanism is unknown. A recently described variant, papillary glioneuronal tumor (WHO grade I), is usually found in adults. chromosomal and structural alterations involving only chromosome 7 with breakpoints at 7p22 have been reported in this variant (Faria et al. 2008).

8.1.3 Clinical Features

Seizure is the most common presenting symptom of gangliogliomas. The seizure history is often long-standing, with a mean duration prior to diagnosis ranging from 6 to 25 years (Lang et al. 1993; Prayson et al. 1995; Luyken et al. 2003). In one series of patients examined, temporal lobe gangliogliomas represented 40% of all tumors causing chronic temporal lobe

epilepsy (Blumcke et al. 1999). The mean duration of symptoms prior to diagnosis for tumors of the brain stem or spinal cord is approximately 1 year (Lang et al. 1993). Patients with brainstem lesions commonly present with involvement of the motor tracts: weakness, spasticity, and gait disturbance. Gangliogliomas of the spinal cord may involve the entire spinal cord and typically produce scoliosis, gait disturbance, and progressive weakness (Park et al. 1993; Hamburger et al. 1997; Jallo et al. 2004). These symptoms can be longstanding. Patients with midline tumors develop symptoms and signs of hydrocephalus, such as headache, papilledema, alterations in the level of consciousness, and nausea or vomiting (Haddad et al. 1992).

8.1.4 Natural History

Gangliogliomas are indolent, slow-growing tumors. Without resection, patients often have prolonged courses of disease, depending on the location of the primary mass. Anaplastic glial changes in ganglioglioma, as well as high MIB-1 labeling indices, may be markers for more aggressive tumor behavior (Kalyan-Raman and Olivero 1987; Prayson et al. 1995; Hirose et al. 1997). Malignant transformation is rare, although one report notes that this occurs in up to 3% of gangliogliomas (Sasaki et al. 1996; Hakim et al. 1997).

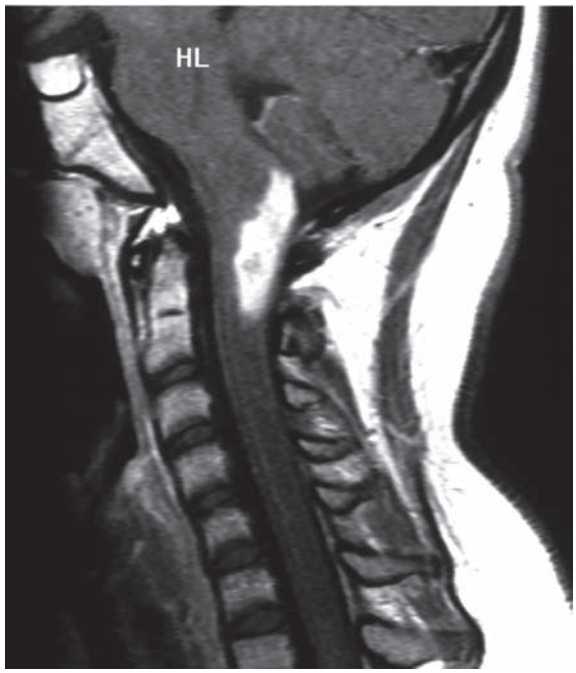

Figure 8.2

An unusual case of a ganglioglioma of the upper cervical spinal cord. The patient is a 14-year-old girl who presented with paresthesias over the left side of the neck. The sagittal T1-weighted postcontrast MRI shows a well demarcated mass arising in the dorsal portion of the spinal cord

8.1.5 Diagnosis and Neuroimaging

No specific laboratory tests are available to allow a diagnosis. A computed tomography (CT) scan, usually performed as a screening test, reveals an iso- to hypodense solid or cystic mass. Cysts may be associated with a mural nodule, although both cyst and nodule are well-circumscribed (Dorne et al. 1986). Calcifications may be present, and contrast enhancement is usually seen, but occasionally can be minimal or absent. Magnetic resonance imaging (MRI) is the best imaging modality, and is required to adequately delineate the mass. Tumors are usually hypointense on T1-weighted images and hyperintense on T2-weighted images. Mass effect and edema are minimal. Contrast enhancement varies in intensity and may be nodular, rim-like, or entirely solid (Figs. 8.1a and 8.2). Syringobulbia or syringomyelia can be seen with spinal-cord gangliogliomas (Park et al. 1993; Hamburger et al. 1997; Jallo et al. 2004). MR spectroscopy is usually of limited value due to the indolent nature of these tumors.

8.1.6 Treatment

Complete surgical resection is the treatment of choice, and when achievable is usually curative (Sutton et al. 1983, 1987; Ventureyra et al. 1986). The neoplasm itself contains no functioning nervous tissue. A postoperative MRI is useful to assess the extent of resection. Subsequent surveillance imaging should be done to evaluate for recurrence, which can occur in a small

percentage of patients. Radiation therapy should be considered for tumor recurrence when further resection is not feasible. Tumors with malignant features (anaplastic features, high MIB-1 LI) may require radiation therapy as an adjuvant therapy, regardless of the extent of resection (Johannsson et al. 1981; Lang et al. 1993; Wolf et al. 1994; Hakim et al. 1997). The impact of radiotherapy on progression-free survival for incompletely resected benign tumors remains uncertain (Haddad et al. 1992; Lang et al. 1993). Because the role of radiation therapy for subtotally resected, low-grade tumors is unclear, the risks and benefits of radiotherapy must be carefully weighed.

8.1.7 Outcome

The prognosis following gross total resection is excellent (Sutton et al. 1983, 1987; Ventureyra et al. 1986; Khajavi et al. 1995). Tumor location is a significant predictor of outcome, most likely because it predicts resectability. In one report, 95% of patients with hemispheric gangliogliomas remained disease-free at 5 years, whereas only 53% of patients with brainstem gangliogliomas remained disease-free at 3 years (Lang et al. 1993). Patients who undergo subtotal excisions, most commonly seen in patients with midline tumors, are at higher risk of tumor progression or recurrence (Haddad et al. 1992). The importance of anaplasia as a prognostic feature is unclear, with different series demonstrating conflicting results (Hall et al. 1986; Ventureyra et al. 1986; Kalyan-Raman and Olivero 1987; Lang et al. 1993). A retrospective analysis in one series of 34 patients did demonstrate a correlation between improved survival and degree of resection as well as tumor grade (Selch et al. 1998). In the largest series reported by Luyken et al., the rate of 7.5-year, progression-free survival was 97% (Luyken et al. 2003). Risk factors for recurrence or malignant progression were residual tumor, frontal tumor location, and a higher-grade lesion. The survival outcomes are also acceptable for gangliogliomas involving the posterior fossa (Baussard et al. 2007) or spinal cord (Jallo et al. 2004).

For patients with tumor-associated epilepsy, seizure control improves significantly after tumor resection (Ventureyra et al. 1986; Haddad et al. 1992). Gross total resection appears to be the most important treatment-related factor (Park et al. 2008), as has been seen with large series of low-grade gliomas (Chang et al. 2008). In recent studies, complete resection resulted in excellent long-term seizure control (greater than 85% of patients were free of seizures at 5 years) to help define "long-term" (Giulioni et al. 2005, 2006; Benifla et al. 2006).

8.2 Dysembryoplastic Neuroepithelial Tumor

Dysembryoplastic neuroepithelial tumor (DNET) is a benign glial-neuronal neoplasm that most commonly occurs in the supratentorial compartment. It was first described by Daumas-Duport and Scheithauer (1988). The initial report described 39 children with a morphologically distinct brain tumor and intractable partial seizures.

8.2.1 Epidemiology

DNET most commonly affects children and young adults in the second and third decade of life. The age at onset of seizures ranges from 2 to 18 years, with a mean of 9 years (Daumas-Duport et al. 1988). The actual population incidence of DNET is difficult to determine. In two series of patients with epilepsy, the frequency of DNET ranged from 0.8 to 5% (Morris et al. 1993; Wolf et al. 1995). In a retrospective review of all neuroepithelial tumors at a single institution, DNETs were found in 0.6% of patients including all ages, in 1.2% of patients under age 20 years, and in 0.2% of patients over age 20 years. Males are more frequently affected than females (Daumas-Duport et al. 1988).

8.2.2 Pathology

8.2.2.1 Gross Appearance

Although the tumor arises from and expands the cortex, the underlying white matter may also be involved (Daumas-Duport 1993). Distended cortical ribbons consisting of gelatinous glioneuronal elements and smaller, firmer glial nodules are seen during surgery.

8.2.2.2 Histopathology

The characteristic pathologic feature is the glioneuronal element which consists of columns of axon bundles lined with small S100-positive and GFAP-negative oligodendroglia-like cells (Fig. 8.3b). Oligodendroglia-like cells have minimal cytoplasm and are rich in mucopolysaccharides. Mature neuronal cells are found interspersed within the tumor, and adjacent cortical dysplasia can be found. Associated cortical dysplasias have been observed in up to 83% of cases of DNET in some series.

Smaller glial nodules are found along the tumor borders of the complex variant of DNETs. In contrast to gangliogliomas, atypical neurons resembling ganglion cells and perivascular lymphocytes are not found with DNETs (Daumas-Duport et al. 1988; Armstrong 1993; Daumas-Duport 1993; Hirose et al.

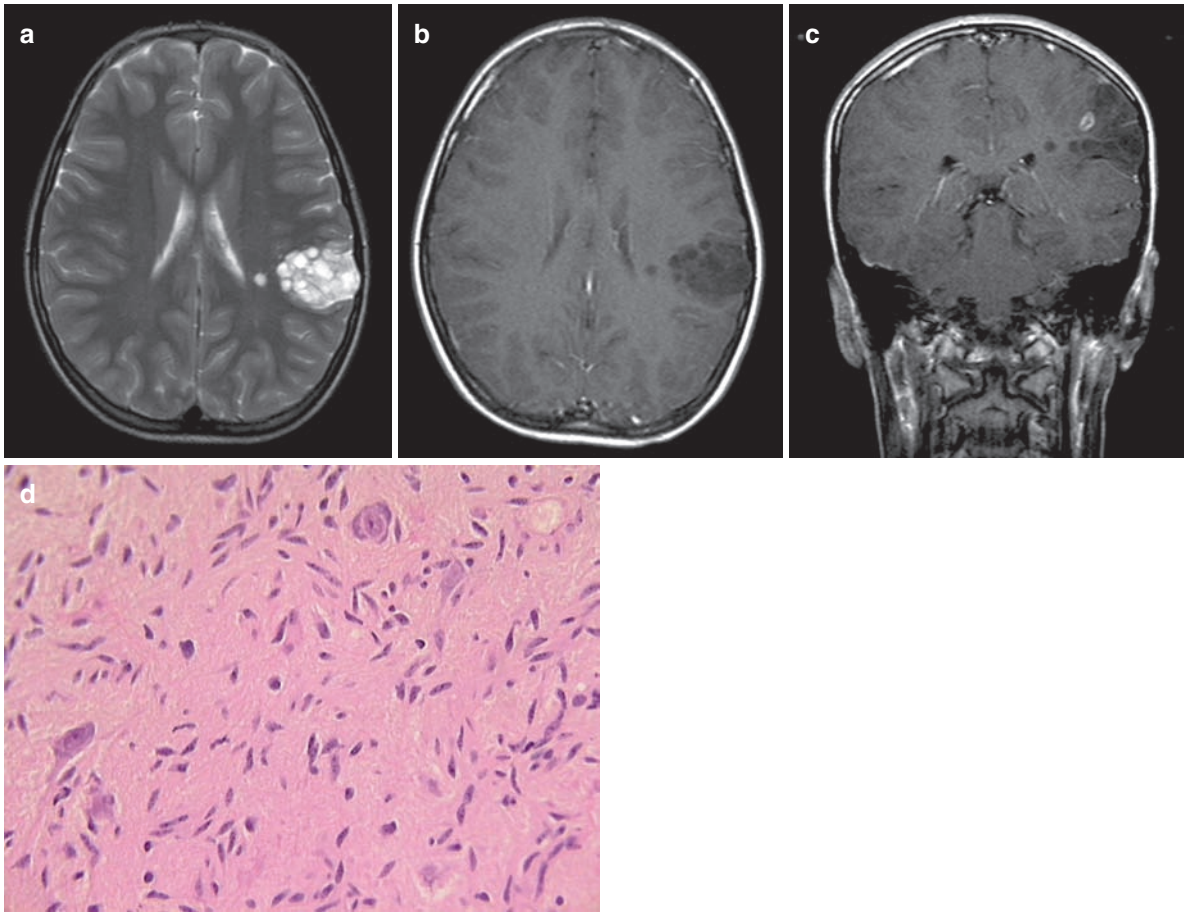

Figure 8.3

Dysembryoplastic neuroepithelial tumor (DNET). (**a**) T2-weighted axial MRI of a left parietal DNET demonstrates a typical "bubbly" appearance. The majority of the mass does not enhance following contrast (**b**), although a small focus of enhancement was noted along one margin of the tumor (**c**). No peritumoral edema is seen. (**d**) H & E staining in a complex form of DNET shows nuclear atypia of glioneuronal elements. Astrocytic, oligodendrocytic, and neuronal components are present to varying degrees

1994; Raymond et al. 1994). DNETs are classified as WHO Grade I.

8.2.2.3 Immunohistochemistry and Molecular Genetics

Neuronal elements stain positive for synaptophysin and neuronal nuclear antigen (NeuN) (Wolf et al. 1997; Brandes et al. 2000). Glial nodules stain positive for GFAP. The proliferation potential is very low and MIB-1 labeling indices vary from 0 to 8% (Prayson and Estes 1992; Daumas-Duport 1993; Taratuto et al. 1995). Specific cytogenetic or molecular findings have not been reported. DNETs have been reported in patients with neurofibromatosis type I (NF1), although the overall frequency is unknown. The molecular changes within the DNETs in these patients have not been characterized (Lellouch-Tubiana et al. 1995).

8.2.3 Clinical Features

DNETs are associated with chronic, intractable partial seizures, and are present in 25% of all lesions resected for medically refractory epilepsy (Wolf et al. 1993, 1995; Raymond et al. 1995; Pasquier et al. 1996). Most DNETs are located in the supratentorial region, especially the temporal lobe; however, other locations corresponding to the topography of the secondary germinal layers have been described, including basal ganglia, thalamus, cerebellum, and pons (Leung et al. 1994; Kuchelmeister et al. 1995; Cervera-Pierot et al. 1997). Multifocal locations have been described, including temporal lobe, third ventricle, and basal ganglia in one case and temporal lobe, thalami, cerebellum, and pons in a separate case (Leung et al. 1994).

8.2.4 Natural History

Without resection, medically intractable seizures are likely to persist. Tumor progression is rare with partially resected DNETs (Daumas-Duport et al. 1988; Daumas-Duport 1993; Leung et al. 1994; Raymond et al. 1994; Taratuto et al. 1995). Subtotally resected lesions can remain quiescent for extended periods of time.

8.2.5 Diagnosis and Neuroimaging

Appearance on unenhanced CT ranges from iso- to hypodense; often with calcifications and occasionally with true cyst formation. One-third of tumors show contrast enhancement and the overlying calvarium may be remodeled, consistent with the chronic nature of the tumor (Daumas-Duport 1993; Kuroiwa et al. 1995; Raymond et al. 1995). The DNETs are cortically based and may appear as macrogyri. Usually, the lesion involves the thickness of the normal cortex, although it can extend into the white matter. With MRI, the tumor is hypointense on T1-weighted and hyperintense on T2-weighted images (Fig. 8.3). No peritumoral edema or mass effect is seen. Enhancement is seen in one-third of tumors (Fig. 8.3c) (Koeller and Dillon 1992; Daumas-Duport 1993; Kuroiwa et al. 1995; Raymond et al. 1995).

A definitive diagnosis of DNET is difficult to obtain with neuroimaging alone. However, the combination of partial seizures before age of 20 years, lack of progressive neurologic deficit, cortical involvement on MRI, absence of mass effect or edema on CT or MRI, is highly suggestive of DNET (Daumas-Duport 1993; Lang et al. 1993; Fernandez et al. 2003).

8.2.6 Treatment

Surgical resection is curative. Recurrence has been rarely reported (Maher et al. 2008); therefore, radiation or chemotherapy is not indicated (Raymond et al. 1995). It is important to differentiate DNET from oligodendroglioma to avoid unnecessarily aggressive therapy.

8.2.7 Outcome

The DNETs are benign lesions. A high MIB-1 labeling index does not impact prognosis (Daumas-Duport 1993). Neither clinical nor radiographic tumor progression was observed in patients that underwent gross total or even subtotal resections (Daumas-Duport et al. 1988; Daumas-Duport 1993; Raymond et al. 1994; Taratuto et al. 1995). Resection results in a high rate of seizure control; 65–90% of patients are free of seizures after surgery. Incomplete resection

is a risk factor for poor-seizure control. Currently, no agreement exists over whether removal of the tumor alone (lesionectomy) or extended resection to include neighboring dysplastic cortex results in the best seizure control (Sutton et al. 1987; Nolan et al. 2004; Chan et al. 2006; Giulioni et al. 2006; Minkin et al. 2008).

8.3 Central Neurocytoma

8.3.1 Epidemiology

Central neurocytomas are rare neoplasms of the CNS. Central neurocytomas compromise only 0.25–0.5% of brain tumors and are tumors of adolescents and young adults (Hassoun et al. 1993). In a series of 207 cases, the mean age of presentation was 29 years, with a range of 8 days to 67 years (Hassoun et al. 1993). Most patients (72%) present between the ages of 20–40 years. The incidence is similar in males and females with a ratio of 1.02:1 (Hassoun et al. 1993).

8.3.2 Pathology

8.3.2.1 Gross Appearance

Central neurocytomas are lobulated, well-circumscribed masses that are gray in color, similar to normal cortex. They typically occur in close proximity to the foramen of Monro, and may be attached to the septum pellucidum. Necrosis and cyst formation are frequently seen, and some neurocytomas are very vascular. Intratumoral hemorrhage is unusual.

8.3.2.2 Histopathology

The histopathologic appearance of a central neurocytoma can be similar to that of an oligodendroglioma (von Deimling et al. 1990; Schild et al. 1997). Both neoplasms have small uniform cells with rounded nuclei and scant cytoplasm resembling perinuclear halos (the so-called fried egg appearance). It is quite likely that many intraventricular tumors previously diagnosed as oligodendrogliomas may actually have been central neurocytomas (von Deimling et al. 1990; Schild et al. 1997). The cytoplasm is ill-defined, and the nuclei are round to slightly lobulated (Fig. 8.4b). The tumor cells are dense in some areas and alternate with anuclear and less-dense tumor parts. In particular, the anuclear areas may have a fine fibrillary matrix. A delicate pattern of blood vessels forms a branching network in pattern similar to oligodendrogliomas. Focal calcification can be seen. Mitotic figures are absent or infrequent and endothelial proliferation and necrosis are uncommon. A variant, extraventricular neurocytoma (WHO grade II), usually occurs in adults and can be particularly difficult to distinguish from oligodendrogliomas (Mut et al. 2005).

8.3.2.3 Immunohistochemistry and Electron Microscopy

Immunostaining for neuron-specific enolase (NSE) and synaptophysin confirm the neuronal origin of these tumors (von Deimling et al. 1991). Positive staining with GFAP may represent neoplastic or reactive astrocytes. It has been suggested that central neurocytomas originate from bipotential (neuronal and astrocytic) progenitor cells in the periventricular region that persist into adulthood (von Deimling et al. 1991). An ultrastructural feature that sometimes distinguishes central neurocytomas from oligodendroglioma is the high degree of neuronal maturation. Electron microscopy demonstrates clear and dense core vesicles, microtubules, and synapse formation.

8.3.2.4 Cytogenetics and Molecular Genetics

Comparative genomic hybridization (CGH) analysis was used to identify losses and gains in DNA sequences in 10 histologically confirmed central neurocytomas (Yin et al. 2000). Genomic alterations were found in 6 tumors. Gain in genetic material was found for chromosomes 2p and 10q in 4 tumors, chromosome 18q in 3 tumors, and in chromosome 13q in 2 tumors. Gains in chromosome 7 were reported in 3 out 7 central neurocytomas using fluorescence in situ hybridization (FISH) (Taruscio et al. 1997). No specific gene alterations have been described in central neurocytoma. The *p53* tumor-suppressor gene was screened for mutations in central neurocytoma, but none were found (Ohgaki et al. 1993). Recently,

it was proposed that central neurocytoma originates from an adult neuronal progenitor cell. A significant overlap in the antigen profile and gene expression was observed in tumor specimens and native neuronal progenitor cells. *GDF8, PDGF-D, neuregulin 2 (NRG2), IGF2,* and *JAG1* were overexpressed in tumors, suggesting that central neurocytoma is characterized by the concurrent overactivation of these pathways, which may drive neurocytoma expansion, while restricting tumor progenitor phenotype (Sim et al. 2006).

8.3.3 Clinical Features

Patients present with symptoms attributable to raised intracranial pressure secondary to obstructive hydrocephalus. As expected, these consisted of headaches and visual changes; the duration of clinical symptoms and signs is typically less than 6 months. Ninety-three percent of patients complained of headaches, 37% had visual changes, and 30% experienced nausea and vomiting at presentation. Patients complained less commonly of paresthesias (19%), lethargy (11%), balance problems (11%), and tinnitus (7%) (Schild et al. 1997). The most common presenting signs were papilledema and ataxia.

8.3.4 Natural History

While most central neurocytomas are benign, they can recur and even disseminate along the CSF pathways (Yasargil et al. 1992; Eng et al. 1997). Although anaplasia has been demonstrated in central neurocytomas, the influence of this feature on prognosis is uncertain (von Deimling et al. 1990, 1991; Yasargil et al. 1992; Chang et al. 1993). An increase in GFAP positivity and vascular proliferation might suggest a more malignant course (Elek et al. 1999).

Most reports indicate that central neurocytomas have limited growth potential (Soylemezoglu et al. 1997; Sharma et al. 1998). Markers of proliferation have been studied in order to clarify the biological behavior of neurocytomas. In one study of 36 central neurocytomas, it was proposed that a MIB-1 LI of 2% might predict recurrence (Soylemezoglu et al. 1997). Patients with a MIB-1 LI under 2% had a 22% relapse rate compared to a relapse rate of 63% when the MIB-1 LI was over 2% for the observation period of 150 months (Soylemezoglu et al. 1997). Interestingly, a MIB-1 LI above 2% correlated with microvascular proliferation. In another study comparing histological atypia, proliferation, and clinical outcome, an elevated MIB-1 LI was felt to be indicative of biological activity (Mackenzie 1999). With longer follow-up, it is possible that some tumors with a low MIB-1 LI might relapse. This is illustrated in a recent case report of a patient with a recurrent central neurocytoma that had a four-fold increase in MIB-1 LI after a 9-year disease-free interval (Christov et al. 1999).

8.3.5 Diagnosis and Neuroimaging

CT scans demonstrate an iso- or slightly hyperdense mass within the body of the lateral ventricles near the foramen of Monro. Areas of hypodensity represent cystic degeneration. About half of central neurocytomas demonstrate calcification on CT imaging (Hassoun et al. 1993). These tumors are thought to arise from septal nuclei, and have broad-based attachments to the superior and lateral walls of the ventricle. Obstruction of the interventricular foramen of Monro by tumor mass usually results in hydrocephalus. Contrast enhancement is mild to moderate for most central neurocytomas.

MRI reveals an isointense mass on T1-weighted images (Wichmann et al. 1991; Chang et al. 1993). Of 13 central neurocytomas, 85% contained cysts, 69% contained calcification, and 62% had flow voids from tumor vessels resulting in a heterogeneous imaging appearance (Chang et al. 1993). Most central neurocytomas are isointense on T2-weighted images. Moderate gadolinium enhancement is seen (Fig. 8.4a) (Wichmann et al. 1991). Catheter angiography is rarely performed for central neurocytomas, but if obtained, shows a homogenous vascular blush. On occasion, tumors can be avascular (Goergen et al. 1992; Hassoun et al. 1993; Taratuto et al. 1995; Ashkan et al. 2000). Arterial supply is from the posterior and anterior choroidal, pericallosal, and lenticulostriate vessels.

Central neurocytomas in the lateral ventricle of young adults must be distinguished from

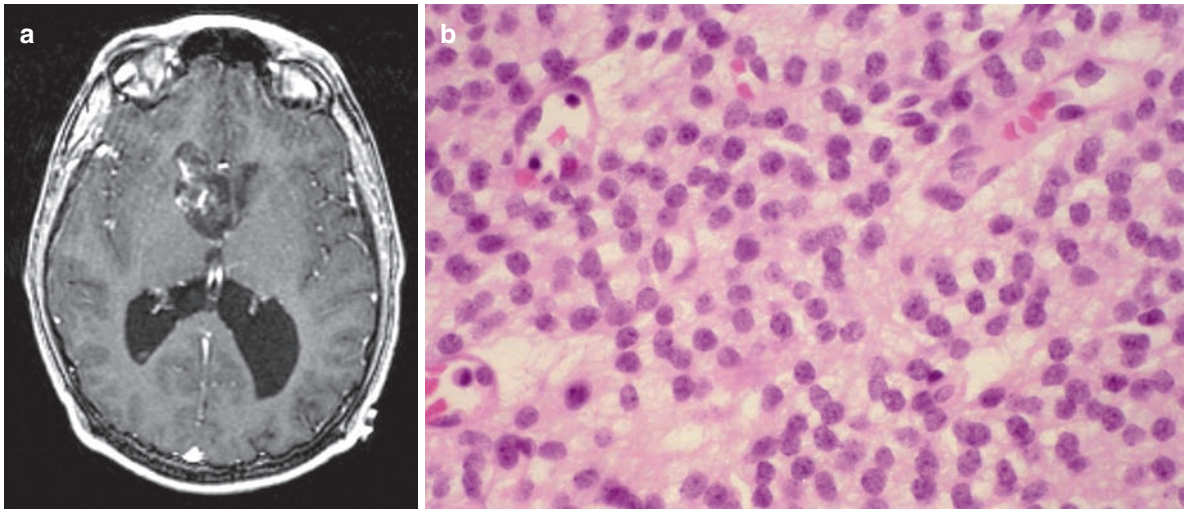

Figure 8.4

Central neurocytoma. (**a**) T1-weighted axial MRI with gadolinium of a typical central neurocytoma arising in the frontal horn of the right lateral ventricle. A heterogeneous pattern of enhancement is seen. (**b**) H & E staining demonstrates cells with uniform, round to oval nuclei with speckled chromatin and occasional nucleolus. Anaplastic features are not seen

oligodendroglioma, subependymal giant cell astrocytoma, ependymoma, and low-grade or pilocytic astrocytoma. The typical central neurocytoma is located in the supratentorial ventricular system in the anterior half of the lateral ventricle.

8.3.6 Treatment

8.3.6.1 Surgery

Complete surgical resection is the treatment of choice, and also has the benefit of reopening CSF pathways in patients with hydrocephalus. Clinical reports indicate that gross total resection confers long-term control for most central neurocytomas (Yasargil et al. 1992; Maiuri et al. 1995; Schild et al. 1997). In series of 32 patients with central neurocytoma, 5-year local control and survival rates of 100 and 80%, respectively, were seen after gross total resection without adjuvant therapy (Schild et al. 1997). However, tumor recurrence after gross total resection has been reported in 3/9 patients, 3–6 years after surgery (Yasargil et al. 1992).

Preoperative CSF shunting is rarely indicated, but if the patient continues to have hydrocephalus postoperatively, a permanent shunt is required. A third ventriculostomy can be useful in patients with noncommunicating hydrocephalus and was successful in 86% of patients with intraventricular tumors (Buxton et al. 2001). After completion of tumor resection, CSF should be drained via an external ventricular drain until nearly clear.

8.3.6.2 Radiation Therapy and Radiosurgery

The role of postoperative radiotherapy has been investigated in several case reports and clinical series (Nakagawa et al. 1993; Kim et al. 1997; Schild et al. 1997). Radiotherapy after gross total resection is not indicated, as surgery results in long-term tumor control for most patients. The use of radiation for residual tumor after subtotal resection is controversial. In a retrospective analysis of 15 patients with central neurocytoma, radiation appeared to have an effect on tumor control (Kim et al. 1997; Sharma et al. 2006). Five patients with subtotal resection

received fractionated radiation. Tumor shrinkage was observed in 3 patients, and the residual tumor disappeared in 2 patients. One patient experienced delayed radiation toxicity. The authors cautioned that radiation in subtotally resected tumors can result in delayed radiation toxicity, and noted that the 3 patients with residual tumor, who did not receive radiation, remained stable. Schild et al. demonstrated a 5-year local control rate for residual central neurocytoma of 100% with radiation compared to 50% without radiation (Schild et al. 1997).

More recently, the use of radiosurgery for the treatment of central neurocytomas has been reported in several case studies (Anderson et al. 2001; Cobery et al. 2001; Kim et al. 2007; Yen et al. 2007). In all of these reports, radiosurgery appeared to be efficacious. About half of patients had disappearance of their tumors, whereas the remainder had some shrinkage. Although it is not a first-line option, radiosurgery should be considered for residual or recurrent tumors, or for those patients whose tumors are located in regions that preclude open surgical resection.

8.3.6.3 Chemotherapy

The experience with chemotherapy for central neurocytoma is more limited. A variety of agents has been used, and responses to chemotherapy have not been well documented (Dodds et al. 1997; Schild et al. 1997; Sgouros et al. 1998; Brandes et al. 2000; von Koch et al. 2003). In the series of Schild et al., 4 patients received chemotherapy after radiation and none experienced tumor progression (Schild et al. 1997). Various combinations of carmustine, lomustine, prednisone, vincristine, and cisplatin were used. A case report of a 15-year-old patient with a large central neurocytoma who underwent a subtotal resection followed by four cycles of carboplatin, etoposide, and ifosfamide noted the tumor responded significantly, but eventually the patient required reoperation and radiation therapy (Dodds et al. 1997; Sgouros et al. 1998). Another study used chemotherapy in the treatment of recurrent/progressive central neurocytoma in 3 patients (Brandes et al. 2000). Stabilization was observed in two of them and the other had a complete remission. Follow-up was limited to 15, 18, and 36 months, but the responses were maintained.

8.3.7 Outcome

Central neurocytomas have a favorable prognosis, but in some cases, the clinical course can be more aggressive. Histological features of anaplasia do not predict biologic behavior; proliferation markers might be more useful in predicting relapse. The most important therapeutic modality remains surgery. A safe maximal resection confers the best long-term outcome. In cases of subtotal resection, standard external beam radiation can be used, or radiation can be delayed until tumor progression occurs. Most studies indicate that radiation improves local control, but not overall survival (Rades et al. 2004). One large series of 50 patients found that the 10-year survival rate was about 83% and the local control rate was 60% (Leenstra et al. 2007). These authors found that patients whose tumors have a low mitotic index (e.g., less than 3 per 10 high-power fields) have much higher survival and local control rates compared to those whose tumors have a higher mitotic index. Smaller residual or recurrent tumors can be treated with stereotactic radiosurgery. Reoperation for recurrence should be considered if the procedure can be performed safely. Chemotherapy may be useful for recurrent central neurocytomas that cannot be resected and have been radiated, although long-term responses have not been reported for chemotherapy. Despite good outcomes, long-term follow-up is important as recurrence can occur long after surgery (Bertalanffy et al. 2005).

8.4 Conclusions

Neuronal tumors are rare, and usually carry a good prognosis. Gangliocytomas, gangliogliomas, and DNETs present in late childhood or early adulthood and are commonly accompanied by intractable epilepsy. Complete surgical resection is curative and results in improved seizure control. It is important to distinguish these tumors from low-grade astrocytomas to prevent aggressive management. However,

malignant transformations have been seen with gangliogliomas, arising from the glial component.

Central neurocytomas are seen in early adulthood and present with hydrocephalus due to ventricular outflow obstruction. Although rare, tumor recurrence and progression is seen and adjuvant therapy such as chemotherapy, radiation therapy, or radiosurgery may be necessary in addition to surgical resection.

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Choroid Plexus Tumors

Nalin Gupta

Contents

9.1 Introduction

The choroid plexus has the highly specific function of producing cerebrospinal fluid (CSF). It is anatomically localized to the parenchymal/ventricular junction in all four ventricles. The choroid plexus is derived from the specialization of ventricular epithelium along certain segments of the neural tube, and there is a common ontogeny between choroid epithelium and cells of glial origin. This can, and does lead to diagnostic confusion in certain cases. Tumors arising from the choroid plexus can display a benign or malignant phenotype, but conversion to a malignant phenotype is a rare event (Chow et al. 1999; Jeibmann et al. 2007). Guerard was the first to describe a choroid plexus tumor in 1833. The first surgical resection was reported by Bielschowsky and Unger in 1906. Thereafter, both Cushing and Dandy reported their experiences with this unusual tumor (Dandy 1922; Davis and Cushing 1925).

9.2 Epidemiology

Choroid plexus papilloma (CPP) and choroid plexus carcinoma (CPC) are uncommon, comprising only 0.5–0.6% of all brain tumors. Although found in all age groups, choroid plexus neoplasms are primarily a tumor of childhood. Laurence in his review of all published cases prior to 1974 reported that 45% presented in the first year of life, while 74% were in the first decade (Laurence 1974). As expected, reviews from pediatric centers report that a higher percentage (1.8–2.9%) of their cases are choroid plexus tumors (Asai et al. 1989; Ellenbogen et al. 1989; Sarkar et al.

1999). In two reviews describing tumors occurring in the first year of life, choroid plexus tumors comprised 14 and 12.8% of all cases (Galassi et al. 1989; Haddad et al. 1991). The majority of the series noted here have not reported any predilection for right or left ventricle, or sex. Laurence did report that 50% of cases reviewed were situated in the lateral ventricles, 37% in the fourth ventricle, 9% in the third ventricle, and the remainder in other locations. Other series have confirmed this geographic distribution. CPCs, while rare, comprise 29–39% of all choroid neoplasms (Ellenbogen et al. 1989; Johnson 1989; St Clair et al. 1991).

9.3 Pathology

9.3.1 Gross Appearance

CPP is frequently described as "cauliflower-like." Indeed, these tumors are similar to the soft fronds of normal choroid, as found in the ventricles. The shape is roughly globular, with an irregular surface and intervening encapsulated areas. Old hemorrhage is sometimes apparent. Since papillomas are benign, they tend to expand the ventricle rather than invade the adjacent brain. Nevertheless, the proximity of these tumors to deep-seated structures such as the internal cerebral veins and limbic structures can make their removal difficult.

9.3.2 Histopathology

CPP is a WHO grade I tumor, and its microscopic appearance recapitulates the normal choroid plexus. There are many papillae covered with a simple cuboidal or columnar epithelia. The stroma of these fibrovascular structures is composed of connective tissue and small blood vessels. The presence of the connective tissue stroma is notable mainly because it allows one to distinguish between CPP and papillary forms of ependymoma (whose stroma is composed of fibrillary neuroglia). In addition, choroid epithelial cells do not contain cilia or blepharoplasts as do ependymal cells. Mitotic figures are rare.

Villous hypertrophy of the choroid plexus is a poorly defined entity. Characteristically, the choroid plexus of both lateral ventricles is enlarged and is associated with hydrocephalus from birth. Russell and Rubinstein comment that the hydrocephalus is related to hyperactivity of the choroid while the cytological appearance of the tissue is normal (Bigner et al. 1998). Other authors have used villous hypertrophy synonymously with bilateral CPP, but this is not accurate in the strictest sense if histologic evidence of neoplastic growth is not present, and expansion of the choroid plexus occurs diffusely (Hirano et al. 1994).

CPCs are WHO grade III tumors and are diagnosed on the basis of their microscopic appearance (Gopal et al. 2008). Two major features accompany malignancy. First is the presence of brain invasion by the tumor. This usually involves transgression of the ependymal lining and extension into the paraventricular parenchyma. Second, cytological criteria of malignancy – nuclear atypia, increased nuclear to cytoplasmic ratio, prominent mitotic figures, and necrosis – are present in association with a loss of normal papillary architecture. Rarely, if a tumor demonstrates some atypical features without evidence of invasion, it can be designated as an atypical papilloma. The epithelial nature of the frank malignancy can create confusion, since other tumors such as metastatic adenocarcinoma, papillary meningioma, and atypical teratoid/rhabdoid tumors (ATRT) can be histologically similar. If the tumor arises in a young patient, then chances of the tumor being metastatic are extremely low. Electron microscopy can reveal details such as cilia, which are normally not present in choroid plexus tumors. Grossly, these tumors tend to be softer and more friable than papillomas. While carcinomas rarely metastasize from the intracranial or intraspinal compartment, they can disseminate throughout the CSF pathways (McComb and Burger 1983).

An intermediate entity, the atypical CPP, is identified as a WHO grade II neoplasm but the diagnostic criteria are poorly defined (Paulus and Brandner 2007). The number of mitotic figures in a high-power field, or two other cytological features such as increased cellularity, nuclear pleomorphism, and/or necrosis, have been proposed as characteristics of atypical papillomas but this requires validation (Jeibmann et al. 2007). It is likely, however, that a biological

spectrum exists for tumors identified as papillomas and the clinician should be alert to unusual pathologic features that would prompt closer surveillance imaging in the postoperative period.

9.3.3 Immunohistochemistry

Only a few immunohistochemical stains have been found to be helpful. The calcium-binding protein S-100 is positive in the vast majority of choroid tumors (Paulus and Janisch 1990; Ho et al. 1991). This is of limited value since glial tissues and normal choroid express S-100 in a parallel fashion with glial fibrillary acid protein (GFAP). Other markers such as vimentin, GFAP, and cytokeratins can be positive but they also lack specificity (Mannoji and Becker 1988; Cruz-Sanchez et al. 1989). Pre-albumin, or transthyretin (TTR), was initially believed to be a specific marker, but another report noted that 20% of choroid tumors were TTR- negative (Herbert et al. 1990; Paulus and Janisch 1990). These investigators did find that prognostic information could be gleaned from immunohistochemical data. A poor prognosis was found in those tumors with less than 50% of the cells in a given tumor heavily stained for S-100. In addition, absence of TTR-positive cells correlated with a poor prognosis. Cellular proliferation, as measured by Ki67/MIB-1 labeling, is low with papillomas and significantly higher for carcinomas (Vajtai et al. 1996).

Using a microarray approach, Hasselblatt et al. identified a number of genes that appeared to be overexpressed in choroid plexus tumors (Hasselblatt et al. 2006). Two in particular, Kir7.1 (a potassium channel gene) and stanniocalcin-1, demonstrated high specificity and were proposed as markers for these tumors, but require confirmation by other groups. Finally, Judkins et al. noted that the BAF47 clone of the INI1 gene product was expressed in the majority of CPCs, but not in atypical teratoid/rhabdoid tumors, so this marker may be useful to distinguish between these tumor types (Judkins et al. 2005).

9.3.4 Genetics

The cause of choroid plexus tumors is unknown. One report has mentioned two cases occurring in one family, but a hereditary basis has not been observed for most cases (Zwetsloot et al. 1991). There is some evidence linking SV40, a primate DNA virus, with choroid plexus tumor etiology. Large T antigen, the major regulator of late viral gene products of the SV40 virus, when expressed in mice induces the formation of choroid plexus neoplasms (Brinster et al. 1984). The large T antigen is expressed only in the choroid plexus and appears to interact with the product of the *p53* gene (Marks et al. 1989). Using PCR, SV40 DNA sequences were demonstrated in 50% of choroid plexus tumors and the majority of ependymomas (Bergsagel et al. 1992). Active T antigen and p53 complexes have also been demonstrated in brain tumors (Zhen et al. 1999). Positive nuclear staining for the *p53* tumor suppressor gene was identified in 10 of 11 CPCs, but in only 1 of 12 CPPs (Carlotti et al. 2002). A *p53* mutation in this setting leads to a loss of normal gene function but an increased half-life of the protein. Germline mutations in *p53* can also lead to the development of CPCs (Krutilkova et al. 2005).

Experiments in mice showed that the expression of transgenes of the viral oncoproteins E6 and E7 from human papilloma virus produced tumors in 71% of offspring, and 26% of the tumors were choroid plexus tumors (Arbeit et al. 1993). Finally, mice that overexpress the *E2F1* gene in glial cells develop tumors such as medulloblastoma, CPCs, and primitive neuroectodermal tumors (PNETs) at an early age (Olson et al. 2007).

A subset of central PNETs, CPCs, and medulloblastomas were recently shown to have frequent mutations in the *hSNF2/INI1* gene, which encodes for a component of the ATP-dependent chromatin remodeling complex (Sevenet et al. 1999a). The same authors have proposed that constitutional mutations in this gene lead to a greater incidence of renal and extrarenal malignant rhabdoid tumors, CPCs, central PNETs, and medulloblastomas: a complex they have coined the "rhabdoid predisposition syndrome" (Sevenet et al. 1999b). The penetration of the disease is high, with many probands developing malignant tumors before 3 years of age. Some pathologic data also suggest a connection between malignant rhabdoid tumors and CPCs (Wyatt-Ashmead et al. 2001).

A number of chromosomal abnormalities have been identified in both CPP and CPC. Tumors with a gain of 9p and loss of 10q are associated with longer survival (Rickert et al. 2002). Surprisingly, even benign CPP (32 of 34 cases) demonstrated chromosomal aberration. The patterns of aberrations in CPP differ from those observed in CPC.

9.4 Clinical Features

Hydrocephalus is the presenting symptom in the vast majority of patients with choroid plexus tumors. It is caused by both overproduction of CSF and, in certain cases, the obstruction of CSF pathways, although it appears that overproduction is the major factor (Eisenberg et al. 1974). Resolution of hydrocephalus has been reported after complete tumor removal, suggesting that CSF hypersecretion was responsible for ventriculomegaly (Matson and Crofton 1960; Wilkins and Rutledge 1961; Gudeman et al. 1979). Variations are likely to exist since a normal rate of CSF production has been reported in a patient with a papilloma (Sahar et al. 1980).

The most common presentation of choroid plexus neoplasms is related to increased intracranial pressure secondary to obstructive hydrocephalus and/or CSF overproduction (Laurence 1974; Humphreys et al. 1987; Ellenbogen et al. 1989). Since the majority of cases occur in infants and young children there are characteristic features of raised ICP; Ellenbogen described the usual presenting signs and symptoms (Ellenbogen et al. 1989). The most common symptoms described were nausea/vomiting, irritability, headache, visual difficulty, and seizure. As expected, the most common signs were craniomegaly, papilledema, and decreased level of consciousness. The duration of symptoms reported in this series varied from 2 months in those patients younger than 2 years of age to 6 months on average in those patients older than 2 years. Although choroid neoplasms are viewed as slow-growing tumors, the presence of stupor or coma as the presenting sign in 25% of children suggests a more acute clinical course in some patients. Rapid decompensation can occur either from massive hydrocephalus or from tumoral hemorrhage. Of 21 patients who had CSF examined, 2 were found to have grossly bloody fluid. Lateralizing signs are found in a minority of patients and are usually related to asymmetrical ventricular dilatation. Hydrocephalus was present in 78% of cases at the Hospital for Sick Children, and in 95% of cases at the Children's Hospital in Boston (Humphreys et al. 1987; Ellenbogen et al. 1989).

9.5 Diagnosis and Neuroimaging

Since most patients present with hydrocephalus and increased intracranial pressure, there is no role for sampling CSF at diagnosis. There is little information that can be gained from CSF sampling, and there are reports of disastrous outcomes in some patients following lumbar puncture (Laurence 1974). No specific laboratory tests are available to diagnose these tumors. Other benign lesions of the choroid plexus such as choroid plexus cysts, villous hyperplasia, and lipomas can usually be distinguished on the basis of their appearance on magnetic resonance (MR) imaging (Naeini et al. 2009).

9.5.1 Computed Tomography

The typical features of CPP are present on a computed tomography (CT) scan. The mass is well-demarcated from the brain, lobulated, and often has punctate calcification. These tumors enhance homogeneously after contrast, reflecting a luxuriant blood supply (Laurence 1974). Since they arise from the choroid plexus, their location is almost always intraventricular. An enlarged choroidal artery leading into the tumor mass can sometimes be seen in postcontrast images. At times, the massive size of these lesions may obscure the site of origin. Some carcinomas display a diffuse border between tumor and normal brain that may reflect areas of brain invasion. On the basis of CT, certain features distinguish a suspected choroid tumor from other possibilities. Cerebellar astrocytomas tend to be less homogeneously staining and often have cystic areas. Medulloblastomas are characterized by a more heterogeneous appearance, although they also

stain vividly with contrast and may cause confusion with a fourth ventricle choroid papilloma. Finally, ependymomas arise physically in similar locations but tend to enhance inhomogeneously.

9.5.2 Magnetic Resonance Imaging

Papillomas are isointense to brain on T1-weighted images (Fig. 9.1a). Areas of high signal indicate hemorrhage or necrosis. Following gadolinium administration, the tumor enhances brightly (Fig. 9.1b, c), although this can be patchy in nature, reflecting areas of high flow. T2-weighted images demonstrate an intermediate to high signal intensity with areas of heterogeneous internal signal (Coates et al. 1989). With CPC, the boundary between the tumor and surrounding brain can be indistinct in areas, but this is not a universal finding (Meyers et al. 2004). Brain edema surrounding a CPC is often observed.

MR spectroscopy of CPP and CPC is characterized by a prominent choline peak and absence of *N*-acetyl aspartate (Horska et al. 2001). Myo-inositol level is also reported to be specifically increased in CPPs (Krieger et al. 2005). As with CT, an enlarged choroidal artery is often noted, especially with larger tumors. The vascularity of these tumors is easily demonstrated with specific perfusion sequences (Fig. 9.2).

9.6 Treatment

9.6.1 Preoperative Planning

Since most patients present with symptoms of intracranial hypertension, the order and type of treatment is directed at relieving hydrocephalus, determining the diagnosis, and removing the tumor. Unless the patient is rapidly deteriorating, urgent CSF drainage is not necessary. At the time of surgery, a ventricular drain is placed in order to reduce brain tension and allow sufficient retraction. An external ventricular drain may be left in place after surgery in order to monitor ICP and to determine if shunting is required in the early postoperative period. Matson and others have reported that the successful removal of a tumor obviates the need for shunting. However, it is likely that other factors such as ventricular bleeding, postoperative changes, or meningitis can also render the patient shunt-dependent. Ellenbogen's series noted that 37% of surviving patients required shunting (Ellenbogen

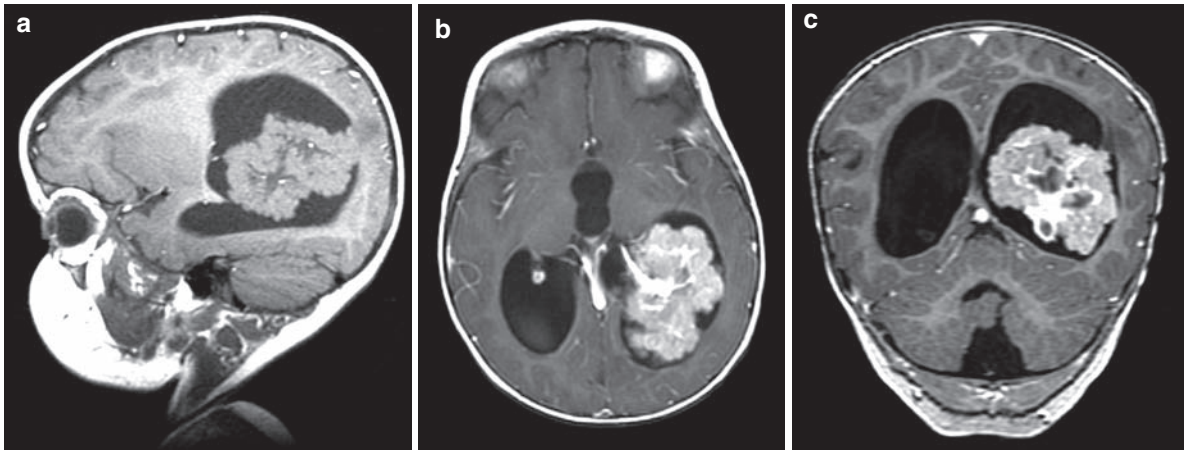

Figure 9.1

A large choroid plexus papilloma. (**a**) A sagittal precontrast T1-weighted MRI demonstrates a large lobulated mass within the lateral ventricle with associated enlargement of the ventricle. (**b**, **c**) Following contrast, the mass enhances brightly. Note that the papilloma is well demarcated from the ventricular wall

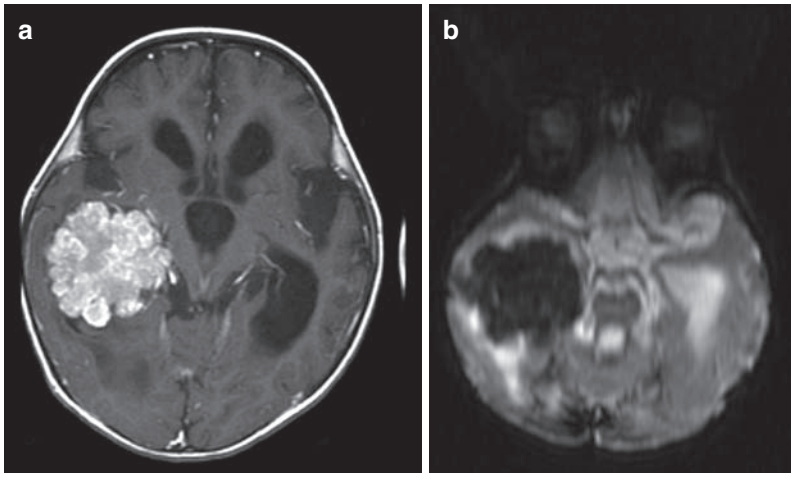

Figure 9.2
(**a**) An axial postcontrast image shows a large choroid plexus papilloma within the temporal horn of the lateral ventricle. (**b**) The perfusion sequence results in a "negative" image with increased vascularity depicted as a dark area. The mass is considerably darker than the adjacent brain tissue

et al. 1989). Two other series reported much higher rates of shunt dependency, ranging from 57 to 78% of cases reported (Humphreys et al. 1987; Lena et al. 1990). Raimondi and Gutierrez have recommended that third and fourth ventricle tumors require immediate shunt placement followed by a delay of 7–14 days prior to surgery (Raimondi and Gutierrez 1975). This method, while acceptable, can be substituted by performance of both procedures at the same time, if permitted by the condition of the patient.

Conventional catheter angiography is not required for diagnosis. Rather, its primary role is as a preoperative adjunct to define the blood supply and can be combined with embolization to reduce tumor vascularity. Angiography clearly indicates that the vascular supply of papillomas is from normal choroidal vessels, which often enlarge as the tumor grows. Tumors of the lateral ventricle or third ventricle are generally supplied by branches of the anterior or posterior choroidal arteries. Mass effect tends to displace the internal occipital artery and the basal vein of Rosenthal in an inferior direction. A fourth-ventricle tumor receives its blood supply from medullary or vermian branches of the posterior inferior cerebellar artery.

9.6.2 Operative Treatment

The goal of surgery is gross total resection (GTR), as measured by postoperative MR imaging. As with most intracranial tumors, the exact approach is determined by avoiding eloquent tissue (primary motor or sensory cortex, speech centers, and visual cortex). The two features of choroid plexus tumors that can make resection exceedingly difficult are: (1) profuse vascularity and (2) large size. The tumor's arterial vessels arborize rapidly, and so control of hemorrhage within the tumor requires slow and tedious dissection. The most effective strategy focuses on initial exposure of the feeding artery and its ligation (Fig. 9.3). In general, en bloc excision is recommended (Raimondi and Gutierrez 1975). For lateral ventricle papillomas, a cerebral incision posterior to the angular gyrus allows access to the entire trigone and permits the pedicle of the tumor to be identified and coagulated. For more anteriorly located tumors, an incision can be made in the frontal convolutions and the lateral ventricle approached from an anterolateral direction. Lateral ventricle tumors can also be approached through a cerebrotomy through the superior or middle temporal gyrus.

Third-ventricle tumors are rare and are approached via a midline transcallosal route. The anterior aspect of the ventricle is entered through a generous opening in the corpus callosum extending from the rostrum to the supraoptic recess. In this way, the tumor can be separated from the choroid of the tela choroidea where it is usually attached and the accompanying bridging vessels can be identified and divided.

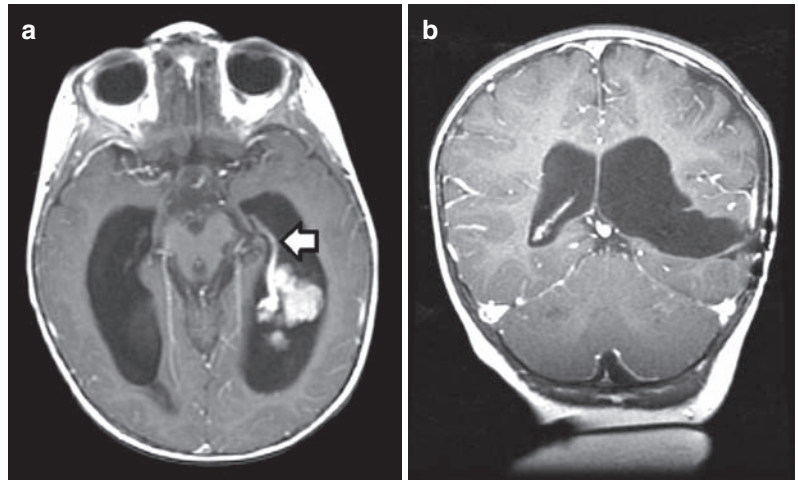

Figure 9.3
The same case as shown in Fig. 9.1. (**a**) The axial T1-weighted image clearly shows an enlarged choroidal artery leading into the tumor. (**b**) The postoperative coronal MRI image shows the route through the temporal lobe used to access initially the feeding artery and then the tumor itself. Once the blood supply was interrupted, the tumor removal proceeded uneventfully

Fourth-ventricle tumors almost always produce triventricular obstructive hydrocephalus, and may require preoperative shunting and stabilization as noted earlier. Tumors in this location arise from the caudal part of the roof of the fourth ventricle and may extend into the lateral recesses, or through the foramen of Magendie. The approach is via a standard midline posterior fossa craniectomy or craniotomy exposing the vermis and tonsils. The blood supply from branches of the PICA are visualized from a medial vantage.

9.6.3 Treatment of Choroid Plexus Carcinomas

Overall, reported results confirm that GTR has a favorable impact upon survival for carcinomas (see Outcome section). For this reason, aggressive surgical treatment with GTR should be the primary objective. Nevertheless, GTR with carcinoma is achieved in less than 50% of cases. Combined with adjunctive therapy, either radiation or chemotherapy, survival following GTR ranges from 67 to 91% (Fitzpatrick et al. 2002). Technical considerations with CPC include the expected increased tumor vascularity, as well as additional difficulties relating to the lack of a well-developed plane between the brain and tumor, and excessive friability of the tumor tissue. The rate of recurrence associated with GTR alone suggests that adjunctive therapy is useful, although definitive guidelines are not available (Fitzpatrick et al. 2002).

Most chemotherapy regimens rely upon cyclophosphamide, etoposide, vincristine, and a platinum agent (St Clair et al. 1991; Packer et al. 1992; Berger et al. 1998). Wolff et al. noted that only 8 of 22 carcinomas responded to chemotherapy, a disappointing observation (Wolff et al. 2002). Use of combination chemotherapy (ifosfamide, carboplatinum, and etoposide) after an initial surgical procedure was found to reduce tumor volume and allow a more complete resection during a second-stage operation (St Clair et al. 1991; Razzaq and Cohen 1997). Importantly, the vascularity of the tumor appeared to be greatly reduced, as measured blood loss during the second procedure was on an average, 15% of blood volume, compared to an average of 64% of blood volume during the first procedure. Recent meta-analyses have noted that administration of chemotherapy resulted in a survival advantage for patients with completely or incompletely resected carcinomas, and that second-look surgery is of benefit for those patients with incompletely resected CPCs (Wrede et al. 2005, 2007). Chemotherapy was also beneficial in the subgroup of patients who did not receive radiation. These observations, although retrospective in nature, suggest that aggressive therapy including chemotherapy and further attempts to remove any remaining tumor should be pursued when possible.

Postoperative radiation is usually recommended if the child is over 3 years of age, although this therapy has not been subjected to a clinical trial. Radiation is also used in the presence of leptomeningeal dissemination, subtotal resection (STR), and drop metastases. In one series, 10 patients with CPC were treated with either chemotherapy and/or craniospinal radiation (Chow et al. 1999). Some of these patients demonstrated no evidence of disease following chemotherapy alone, but others required radiation to achieve disease control. The authors do suggest that radiation can be used as salvage therapy, but whether radiation for all patients with carcinoma would reduce the relapse rate remains unclear. Certainly, this should be judiciously used in children under 3 years of age. Fitzpatrick et al. noted that following STR, radiation therapy, either alone or in combination with chemotherapy, offered a survival advantage (Fitzpatrick et al. 2002). The question of which adjunctive therapy to use following GTR remains unclear, although the presence of relapse despite chemotherapy and radiation suggests that surgery alone is not sufficient for CPC. Wolff et al. support this view and state that GTR alone is insufficient for carcinoma, and should be supplemented with radiation (Wolff et al. 1999). The role of conformal radiation and radiosurgery is unknown, nor is the role of intrathecal chemotherapy. The experience reported by Packer suggests that disease relapse confers a poor prognosis (Packer et al. 1992).

9.7 Outcome

The vast majority of patients with CPP can expect an excellent long-term survival. The survival for CPC, however, is much worse. In a recent meta-analysis, the 1-, 5-, and 10-year survival for papilloma was 90, 81, and 77%, compared to only 71, 41, and 35% for carcinoma (Wolff et al. 2002). In another large series of grade I CPPs, 12 of 124 patients recurred during a mean follow-up period of 59 months (Jeibmann et al. 2007). Of the 124 papillomas, 21 were described as having atypical histology. Six of these 21 tumors recurred, compared to 6 of the 103 tumors with normal histology. In the same series, 2 of the 103 papillomas progressed to carcinomas. The extent of surgery is the most important treatment variable impacting long-term survival for both papilloma and carcinoma patients (Ellenbogen et al. 1989; Packer et al. 1992; Wolff et al. 2002). The overall crude survival rate in Ellenbogen's series was 88% for patients with papillomas and 50% for those with carcinomas (Ellenbogen et al. 1989).

Packer et al. reported that GTR for carcinoma without adjunctive therapy offers the highest likelihood of success (Packer et al. 1992). Four of five patients who underwent GTR remained disease-free at a median of 45 months after diagnosis. Five of six patients who had a STR suffered a relapse.. Two other reports, however, noted that 5-year survival following GTR of carcinomas ranged from 26 to 40% (Berger et al. 1998; Pencalet et al. 1998). Berger et al. also noted that surgery was the most important prognostic factor for CPC. The meta-analysis by Wrede et al. confirmed the utility of chemotherapy and/or radiation for CPC (Wrede et al. 2007). A brief report noted that the 5-year survival for patients with carcinoma who were treated with GTR followed by radiation was 68%, compared to 16% for those not irradiated (Wolff et al. 1999). The two groups were not exactly comparable, but the clear suggestion is that surgery alone is insufficient to prevent recurrence of carcinomas.

Although papillomas are histologically benign and potentially curable, morbidity and mortality are significant concerns. With respect to operative mortality, modern series provide figures of 8–9.5% (Humphreys et al. 1987; Lena et al. 1990). In the series from the Hospital for Sick Children the cumulative mortality was 36%, the majority of which (6 of 8) occurred in patients below 12 months of age. Morbidity remains an important problem. In one series 33% of patients with papillomas had persisting motor sequelae and psychomotor retardation (Lena et al. 1990). In another series, 26% of patients were classified as having a fair or poor recovery (Ellenbogen et al. 1989).

As noted earlier, the treatment of hydrocephalus goes hand-in-hand with the treatment of choroid neoplasms, and associated complications can occur. One significant complication is the presence of large subdural collections that may develop following tumor resection, caused by a persistent venticulosubdural

fistula. Boyd and Steinbok appear to have dealt with this problem by applying pial sutures at the conclusion of the procedure (Boyd and Steinbok 1987). The role of preoperative shunting in the causation of this entity is unclear.

9.8 Conclusions

Choroid plexus tumors represent a well-defined subset of brain tumors that occur mainly in young children. Surgical resection for papilloma is usually curative, while adjunctive therapy for carcinoma should include chemotherapy and/or radiation. The long-term survival for carcinoma remains poor. The overall functional outcome can be excellent, but the potential for neurologic morbidity should be recognized early even for benign tumors.

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Intramedullary Spinal Cord Tumors

Isaac Yang • Andrew T. Parsa

Contents

10.1 Introduction

Intramedullary spinal cord tumors (IMSCT) are rare and account for only 5–6% of all central nervous systems (CNS) tumors (Sloof and McCarthy 1964; Goh et al. 1997; Houten and Weiner 2000). These tumors can occur at any age, but most are identified during the first three decades of life. Approximately 100–200 cases of pediatric IMSCT are diagnosed each year in the United States (Constantini and Epstein 1996). Primary glial tumors such as ependymomas, astrocytomas, and gangliogliomas account for at least 80% of IMSCTs (Cooper 1989; McCormick et al. 1990b; Sandler et al. 1992; Epstein et al. 1993; Cristante and Herrmann 1994; Hoshimaru et al. 1999), and nearly 60% occur in the cervical and cervicothoracic region (Cooper 1989).

The presenting symptoms are usually minimal, and parents typically report symptoms for months or years prior to diagnosis (Kothbauer 2007). The common clinical features are pain, weakness, paresthesias, spinal deformity, sphincter disturbance, and cervicomedullary symptoms (Goh et al. 1997). Slow progressive deterioration of neurologic function can also occur (Constantini and Epstein 1996; Kothbauer 2007). The surgical objective for primary IMSCTs is gross total resection, but in some cases, achieving this goal may leave a patient with severe neurologic deficits. The location of the tumor, age of the patient, pathology, and ability to achieve a gross total resection usually determine whether radiation or chemotherapy will be used.

10.2 Ependymoma

10.2.1 Epidemiology

Ependymomas are thought to arise from the ependymal lining of the ventricles and central canal and can occur both in the brain and spinal cord. The majority of ependymomas are sporadic, but they can also be associated with neurofibromatosis. In children, ependymomas usually arise in the cervical region and occur less frequently then astrocytomas (McCormick et al. 1990b; Brotchi et al. 1991; Fine et al. 1995; Goh et al. 1997; Miller 2000; Schwartz and McCormick 2000; Hanbali et al. 2002). Miller identified only 16 ependymomas out of 117 (14%) cases of pediatric IMSCTs (Miller 2000). Although intramedullary ependymomas are the most common spinal cord tumor in adults (Mork and Loken 1977; Sonneland et al. 1985; Helseth and Mork 1989; Whitaker et al. 1991; Clover et al. 1993; Hulshof et al. 1993; Hoshimaru et al. 1999; Schwartz and McCormick 2000; Chang et al. 2002; Hanbali et al. 2002; Parsa et al. 2004), they are less common in the pediatric population (Constantini and Epstein 1996; Constantini et al. 1996; Miller 2000). In their series of pediatric IMSCTs, Constantini and colleagues did not find any ependymomas in children less than 3 years of age (Constantini et al. 1996).

10.2.2 Pathology

10.2.2.1 Grading

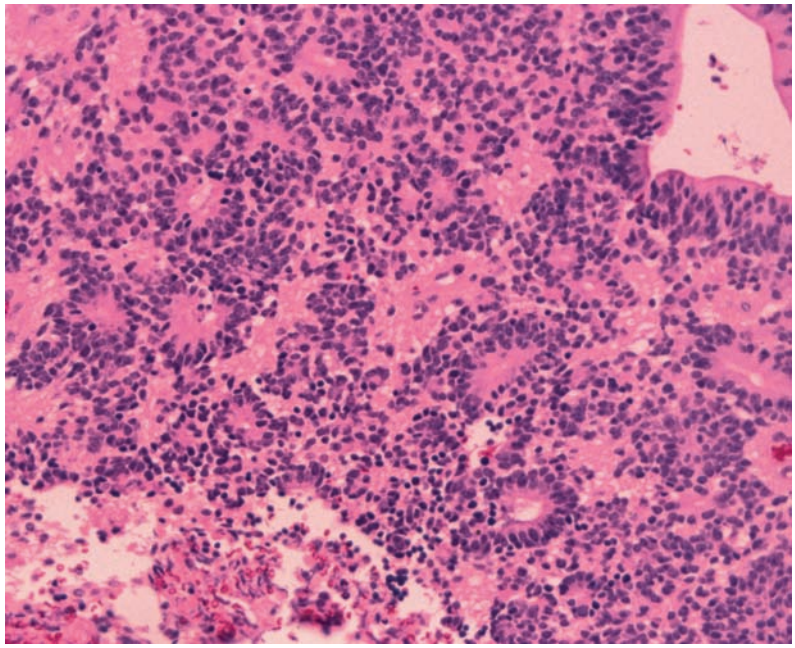
The World Health Organization (WHO) classification of CNS tumors (Louis DN et al. 2007; Kleihues et al. 2002) divides ependymomas into four types: subependymoma (grade I), myxopapillary ependymoma (grade I), benign or "classic" ependymoma (grade II), and anaplastic ependymoma (grade III). Subependymomas are considered benign, slow-growing, intraventricular tumors and have a good prognosis, although they are rarely encountered in the spinal cord. Myxopapillary ependymomas are unique tumors because they usually arise from the filum terminale or conus medullaris (Sonneland et al. 1985). Nearly all are histologically benign and are associated with a good prognosis (Mork and Loken 1977; Cooper 1989; Russell and Rubenstein 1989; McCormick et al. 1990b; Epstein et al. 1993; Chang et al. 2002; Hanbali et al. 2002). Although most spinal cord ependymomas in children are grade II tumors, anaplastic ependymomas do occur infrequently, and are believed to arise from the malignant transformation of lower-grade tumors (Kleihues et al. 2002).

10.2.2.2 Histopathology

Subependymomas are characterized by clusters of glial cells in a dense fibrillary matrix, and are often associated with small cysts. Ependymomas are highly cellular tumors, irrespective of their grade. Myxopapillary ependymomas are characterized by cuboidal or elongated tumor cells arranged in a papillary and radial pattern around the vascular and stromal cores. Little mitotic activity is present, but a matrix of abundant mucin can accumulate between myxopapillary ependymoma cells and vessels.

The gross appearance of grade II spinal cord ependymomas is that of a soft, red or grayish-purple, somewhat friable mass (McCormick et al. 1990b; Schwartz and McCormick 2000; Sun et al. 2003). Cystic degeneration and hemorrhage is common in these vascular tumors (Sun et al. 2003). Although unencapsulated, these tumors are usually well-circumscribed and do not infiltrate adjacent spinal cord tissue (Goh et al. 1997; Parsa et al. 2004, 2005). Microscopic features include pseudorosettes and perivascular clustering and cuffing, and immunoreactivity for glial fibrillary acidic protein (GFAP). Pseudorosettes are formed by clustering of cuboidal or columnar cells in a radial pattern around blood vessels (Fig. 10.1). True rosettes, which appear as a ring of several nuclei from which interlacing neurofibrils converge in the center, can also be present (Schwartz and McCormick 2000). Mitotic figures are rare, but an occasional nonpalisading focus of necrosis can be found in low-grade ependymomas. As measured by MIB-1 immunohistochemistry, the proliferative activity of spinal cord ependymoma is significantly lower than that of intracranial ependymoma. Proliferative indices greater than 2.0% may be associated with an increased risk of recurrence (Iwasaki et al. 2000). The

Figure 10.1
Histological features of ependymoma. This image illustrates the ependymal rosettes which are formed from columnar cells arranged around a central lumen. Also in the top right hand corner, a pseudorosette, cells arranged radially around a blood vessels, can be appreciated



atypical variants clear cell ependymoma and tanycytic ependymoma can mimic oligodendroglioma and astrocytoma, respectively (Goh et al. 1997).

Anaplastic ependymomas differ from grade II ependymomas. While grade II ependymomas morphologically appear similar to nonneoplastic ependymal cells, anaplastic ependymomas demonstrate clear evidence of malignancy such as increased mitotic activity, increased cellularity with microvascular proliferation, and pseudopalisading necrosis. Anaplastic ependymomas can be extremely invasive and are poorly differentiated.

10.2.2.3 Molecular Biology and Genetics

Myxopapillary ependymomas have a much higher propensity for aneuploidy or polyploidy, especially of chromosome 7, when compared to other ependymomas (Gilhuis et al. 2004; Santi et al. 2005). Anaplastic ependymomas (WHO grade III) of the spinal cord are rare, and genetic alterations remain largely undefined (Ebert et al. 1999).

The molecular and genetic events that lead to the formation of a spinal ependymoma may differ from those leading to ependymomas arising within the brain. In a recent study, Ebert and colleagues analyzed 62 ependymal tumors, including myxopapillary ependymomas, subependymomas, classic ependymomas, and anaplastic ependymoma. They showed informative allelic loss of chromosomes 10q (5 out of 56) and 22q (12 out of 54) (Ebert et al. 1999). Somatic mutations of the neurofibromatosis type 2 (NF2) gene were detected in six of the tumors examined, and in each case the tumor was from a grade II spinal cord ependymoma. These results were confirmed by another group which found mutations in the *merlin* gene, which causes neurofibromatosis Type 2 (NF2). In addition, loss of heterozygosity (LOH) of 22q was present in all spinal intramedullary ependymomas ($n=6$) (Lamszus et al. 2001). Allelic loss on 22q was also frequently observed, and was more common in intramedullary spinal ependymomas than in tumors in other locations (Lamszus et al. 2001).

In a report of 22 pediatric ependymomas, Kramer et al. report a LOH at chromosome 22 in two cases, deletions of chromosome 17 in another two cases, and the deletion or rearrangement of chromosome 6 in another five cases (Kramer et al. 1998). In addition,

a low-penetrance ependymoma susceptibility locus has recently been mapped to chromosome 22q11 (Hulsebos et al. 1999; Ammerlaan et al. 2005), suggesting the role of alternative predisposing genes apart from *NF2*.

Overall, 75% of all ependymomas display chromosomal aberrations or rearrangements over several different chromosomes, the most frequent LOHs being found on the long arms of chromosomes 6 (30.3%), 9 (27.3%), and 17 (Huang et al. 2003). In 18 pediatric ependymomas, von Haken and colleagues reported a 50% incidence of allelic mutations on the short arm of chromosome 17 (von Haken et al. 1996). LOH was also detected on 3p14 (13.3%), 10q23 (10.3%), and 11q (18.2%). Monosomy of chromosome 22 is present in approximately 30% of ependymomas (Scheil et al. 2001), with aberrations or alterations of 22q existing in up to 40% of all ependymomas. It is important to note that although chromosome 22q abnormalities and *NF2* mutations are common in spinal ependymoma, they are not exclusive to ependymoma.

Another distinction between spinal and cranial ependymoma may lie in the methylation of particular tumor-related genes. A recent study examining the methylation of a putative tumor suppressor gene, *HIC-1* on chromosome 17p13.3, showed a significant correlation between hypermethylation of *HIC-1* and cranial localization ($p = 0.019$, $n = 52$) (Waha et al. 2004). Losses in chromosomes 1p and 16q, which occur in other CNS tumors, have not been found in ependymoma (Bijlsma et al. 1995). The apparent genetic differences between ependymomas in the brain and those in the spine suggest that different molecular mechanisms exist that lead to the pathogenesis of each. Because primary brain and spine tumors are rarely, if ever, associated with each other, these distinctions may indicate the need to reclassify spinal ependymoma separately from intracranial ependymoma.

10.2.2.4 Association with Neurofibromatosis Type 2

NF2 is an autosomal dominant genetic disorder associated with tumors of the CNS (Mulvihill et al. 1990). NF2 is rare, with a prevalence of 1 in 40,000 individuals (Evans et al. 1992), and is caused by a mutation of a tumor-suppressor gene called *merlin* or *schwannomin* located on chromosome 22 (Rouleau et al. 1987, 1993; Trofatter et al. 1993). Patients with NF2 have a high incidence of several CNS tumors, including vestibular schwannomas and meningiomas (Martuza and Eldridge 1988). Several authors have also noted an association between NF2 and intramedullary spinal cord ependymomas (Rodriguez and Berthrong 1966; Martuza and Eldridge 1988; Mautner et al. 1993; Lee et al. 1996; Lamszus et al. 2001). NF2 patients represent approximately 2.5% of patients with IMSCTs, yet only 0.03% of the population (Lee et al. 1996). In addition, in one small study, 71% of patients with intramedullary spinal cord ependymomas and no evidence of NF were shown to possess mutations in the *NF2* gene (Birch et al. 1996).

10.2.3 Clinical Features

Arising from ependymal cells lining the central canal, intramedullary ependymomas are well-circumscribed, slow-growing tumors usually located in the center of the cervical spinal cord and cause symmetric expansion of the cord (McCormick et al. 1990a; Brotchi et al. 1991; Fine et al. 1995; Goh et al. 1997; Miller 2000; Schwartz and McCormick 2000; Hanbali et al. 2002). Patients typically complain of dysesthesia correlating to the level of the tumor for months to years prior to diagnosis. Other symptoms include paresthesia, radicular pain, bowel and bladder dysfunction, and other sensory disturbances (Rawlings et al. 1988; McCormick and Stein 1990; McCormick et al. 1990b; Clover et al. 1993; Epstein et al. 1993; Hulshof et al. 1993; Asazuma et al. 1999; Hoshimaru et al. 1999; Schwartz and McCormick 2000; Chang et al. 2002; Hanbali et al. 2002; Peker et al. 2004; Shrivastava et al. 2005). Children most often present with pain, weakness, gait abnormality, torticollis, or progressive kyphoscoliosis (Constantini and Epstein 1996; Constantini et al. 1996, 2000). Hydrocephalus also is more common in pediatric patients with intramedullary spinal cord ependymomas than in adult patients, and may require cerebrospinal fluid (CSF) shunting (Houten and Cooper 2000; Houten and Weiner 2000). A sudden decline in neurological function may occur

Table 10.1. Presenting symptoms of intramedullary spinal cord tumors in children

Pain
Motor regression
Weakness
Gait abnormality/ deterioration
Torticollis
Progressive kyphoscoliosis
Hydrocephalus
Sphincter disturbance
Reflex changes
Sensory impairment

following intratumoral hemorrhage (McCormick et al. 1990b). Motor impairment usually occurs late in the disease progression as the expanding tumor thins the surrounding spinal cord to a few millimeters (Epstein et al. 1993) (Table 10.1). This differs from intramedullary astrocytomas, which tend to present with pain and progressive motor dysfunction over a shorter time (Epstein et al. 1993).

10.2.4 Diagnostic Imaging

A precise histological diagnosis is usually not possible with imaging studies alone (Kothbauer 2007). The anatomical features of spinal cord tumors, however, are best evaluated with magnetic resonance imaging (MRI) (Miyazawa et al. 2000; Sun et al. 2003). Intramedullary spinal cord ependymomas are classically centrally located lesions with sharply defined rostral and caudal margins, enhancing borders, and typically spanning 3–4 vertebral body segments (Baleriaux 1999; Miyazawa et al. 2000). Spinal cord ependymomas commonly demonstrate symmetric enlargement of the spinal cord, unlike astrocytomas, which exhibit a nodular or asymmetric pattern of growth (Kopelson and Linggood 1982; McCormick et al. 1990a; Hulshof et al. 1993; Minehan et al. 1995; Lee et al. 1996; Innocenzi et al. 1997; Iwasaki et al. 2000; Miyazawa et al. 2000; Jallo et al. 2001).

Spinal cord ependymomas are isointense on T1-weighted MR images and slightly hyperintense on T2-weighted MR images (Miyazawa et al. 2000; Sun et al. 2003) (Table 10.2). However, signal heterogeneity can occur with cyst formation, necrosis, or hemorrhage (Miyazawa et al. 2000). A "cap sign" is typically associated with spinal cord ependymomas and represents areas of low signal density on either border of the tumor mass itself. This "cap" hypointensity at the tumor margin is often due to hemosiderin deposits from secondary, chronic hemorrhage (Baleriaux 1999; Miyazawa et al. 2000; Chang et al. 2002). Almost all intramedullary ependymomas enhance with contrast, but to a lesser degree than intracranial ependymomas (Sun et al. 2003) (Fig. 10.2). Occasionally, these spinal cord ependymomas can present with subarachnoid hemorrhage.

Spinal cord ependymoma-related cysts are common, and are classified into three types: cystic tumors from tumor necrosis and hemorrhage, syrinx

Table 10.2. Magnetic resonance imaging of intramedullary spinal cord tumors

	Ependymomas	Astrocytomas
Location	Centrally located; mostly in the cervical spine but in children also present in the conus	Eccentrically located; usually widens the spinal cord; 75% of astrocytomas in the cervical and thoracic regions; 20% in the distal cord; 5% in the filum terminale
T1	Isointense/hypointense	Isointense/hypointense
T1 with contrast	Axial view – cord symmetrically expanded. Enhances with contrast but less than astrocytomas	Ill-defined borders Axial view – cord asymmetrical, "lumpy"; Heterogeneous, moderate, partial contrast enhancement

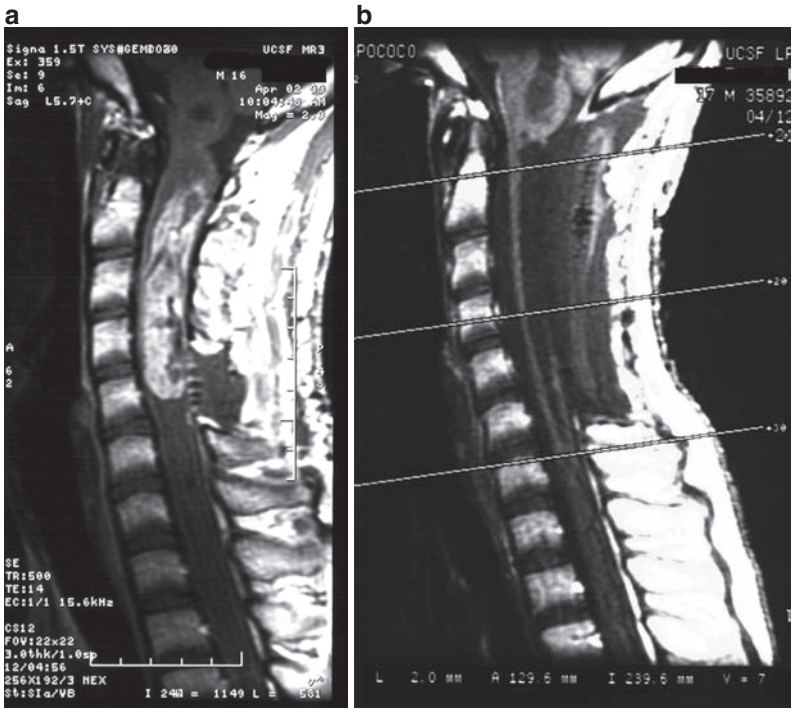


Figure 10.2

A 17-year-old male presented with left-arm numbness and tingling. (**a**) The preoperative MRI scan reveals an intramedullary cervical cord mass in the sagittal T1-weighted image with contrast. Gross total resection was achieved, and pathology was consistent with a grade II ependymoma. (**b**) A postoperative MRI showed resection of the mass with no evidence of residual tumor as demonstrated in the sagittal T1-weighted image with contrast

formation from disturbances of CSF formation, and rostral and caudal cysts from reactive products of IMSCTs (Sun et al. 2003). Ependymoma-associated cysts appear hypointense on T1-weighted MR images and hyperintense on T2-weighted images (Sun et al. 2003). These cysts are also centrally located and cause symmetric expansion of the spinal cord (Sun et al. 2003). A tumor-associated syrinx has similar MR characteristics to CSF and is present in over 50% of spinal cord ependymomas (Chang et al. 2002). Syringes are more commonly associated with ependymomas than with spinal cord astrocytomas (Chang et al. 2002; Sun et al. 2003). The majority of rostral and caudal cysts are also hypointense on T1-weighted MR images and hyperintense on T2-weighted MR images (Sun et al. 2003).

10.3 Astrocytoma

Astrocytomas are the most common type of IMSCT in children (Epstein and Epstein 1981; Reimer and Onofrio 1985; Rossitch et al. 1990; Epstein et al. 1992, 1993). These tumors are commonly associated with intratumoral cysts and are most likely to occur in the thoracic spine. Secondary cysts as well as associated hydromyelia can also occur (Baleriaux 1999). The most common astrocytoma subtype in children is the pilocytic astrocytoma. High-grade spinal cord astrocytomas are much less common.

10.3.1 Epidemiology

Juvenile pilocytic astrocytomas (JPA) of the spinal cord often occur in the first two decades of life. In the adult population, they occur in young patients (mean age 29 years) with a slightly higher predilection for males (Baleriaux 1999). Intramedullary spinal cord astrocytomas can be clustered with inherited syndromes such as Li–Fraumeni syndrome, Turcot's syndrome, tuberous sclerosis complex (TSC), Maffucci/Ollier disease, and NF (Mellon et al. 1988; Frappaz et al. 1999; van Nielen and de Jong 1999).

10.3.2 Pathology

10.3.2.1 Grading

Grading of spinal cord astrocytomas is based on the region of the tumor with the highest degree of histologic anaplasia. Grade I astrocytomas are the most common subtype in the pediatric population (Lee et al. 1996; Allen et al. 1998; Baleriaux 1999). Grade II astrocytomas are diffusely infiltrative, grade III astrocytomas are anaplastic, and grade IV astrocytomas are defined as glioblastoma multiforme (GBM).

10.3.2.2 Histopathology

JPAs are characterized by elongated, "hair-like" cells with cytoplasmic Rosenthal fibers and granular eosinophilic bodies. Although occasional cellular pleomorphism, mitoses, vascular proliferation, and invasion of meninges can be detected, these histopathologic findings have not been determined to be prognostic, and are not considered to be malignant findings.

Grade II diffuse astrocytomas of the spinal cord are infiltrative and produce a fusiform, enlarging process of the tumor. Typically these lesions are characterized by hypercellularity, nuclear pleomorphism, and a diffuse infiltrative growth pattern in the spinal cord. Diffuse spinal cord astrocytomas are differentiated by a fibrillary or gemistocytic neoplastic astrocyte with a background of loosely structured microcystic matrix. Higher-grade intramedullary spinal cord astrocytomas have increased cellularity, anaplastic features, mitotic activity, vascular proliferation, and areas of necrosis.

10.3.2.3 Molecular Biology and Genetics

Intramedullary spinal cord astrocytomas are thought to arise from glial cell predecessors. These tumors are usually sporadic and are rarely associated with other genetic syndromes (Mellon et al. 1988; Frappaz et al. 1999; van Nielen and de Jong 1999). Genetic analyses of JPAs have found numerous genetic aberrations, but previously no specific tumor suppressor or oncogene was identified (Ransom et al. 1992).

Although a novel gene fusion at the *BRAF* locus was recently identified in (Jones et al. 2008), there is little genetic data available for spinal cord astrocytomas. Nevertheless, it is likely that some of the genetic alterations described in intracranial astrocytoma play a role in the progression of intramedullary spinal cord astrocytoma. Three general pathways for glioma progression are proposed: (1) astrocyte to astrocytoma, (2) astrocytoma to anaplastic astrocytoma, and (3) anaplastic astrocytoma to glioblastoma. In the first mutations in *p53* and losses of chromosome 17p and 22q have been implicated. Recently, Rubio and colleagues have shown that the *NF2* gene was not mutated in 30 astrocytomas examined, making it an unlikely candidate for the 22q locus lost during this transition (Rubio et al. 1994). In the progression from astrocytoma to anaplastic astrocytoma, genetic defects include retinoblastoma (Rb) gene mutations, chromosome 13q loss, P16 gene deletions, chromosome 9p loss, and chromosome 19q loss (von Deimling et al. 1995). The transition from anaplastic astrocytoma to glioblastoma has been shown to involve chromosome 10 loss and epidermal growth factor receptor (EGFR) gene amplification (Liu et al. 1997).

Several studies have identified the *PTEN* gene (also known as MMAC and TEP1) as one of the candidate chromosome 10 genes lost in glioblastoma (Liu et al. 1997; Parsons 2004). The gene encodes a tyrosine phosphatase, which is consistent with a tumor suppressor phenotype. When phosphatase activity is lost as a result of genetic mutation, signaling pathways can become activated constitutively, resulting in aberrant proliferation.

10.3.2.4 Association with Neurofibromatosis

There are two distinct types of neurofibromatosis, each affecting cells derived from the neural crest. Neurofibromatosis type 1 (NF1) is characterized by autosomal dominant inheritance with almost complete penetrance and variable expressivity (Ward and Gutmann 2005). NF1 is at least ten times more

common than NF2. Spinal cord tumors in NF1 patients are usually astrocytomas, while ependymomas usually occur in patients with NF2 (Dow et al. 2005). In one small cohort of neurofibromatosis patients with IMSCTs, 3 had NF1, 5 had NF2, and 1 had an uncertain type (Lee et al. 1996). The reported incidence of IMSCTs in the total neurofibromatosis population was approximately 19% (9 out of 48). In 1997, Yagi and colleagues described a cohort of 44 adult patients with IMSCTs, 2 of whom had NF1 (Yagi et al. 1997). In both cases, the pathology of the lesion was astrocytoma (anaplastic astrocytoma and glioblastoma).

10.3.3 Clinical Features

Children with intramedullary spinal cord astrocytomas present with symptoms similar to those of patients with spinal cord ependymomas (Table 10.1). The typical symptoms include gait disturbance, pain, reflex changes, motor or sensory symptoms, and bowel or bladder sphincter dysfunction (Steinbok et al. 1992; Constantini and Epstein 1996; Constantini et al. 1996; Houten and Cooper 2000; Houten and Weiner 2000). Spinal deformity can be present in up to 30% of patients (Epstein and Epstein 1981; Epstein et al. 1992; Steinbok et al. 1992). Intramedullary tumors involving the cervicomedullary junction can present with a myriad of symptoms, such as vomiting, choking, dysphagia, frequent respiratory infections due to chronic aspiration, dysarthria and dysphonic speech, and sleep apnea, and failure to thrive (Abbott 1993; Robertson et al. 1994). A tumor in the cervical spinal cord can cause chronic neck pain, torticollis, progressive motor weakness, sensory changes, hyperreflexia, and, rarely, hydrocephalus (Abbott 1993; Robertson et al. 1994). Chronic pain at the level of the tumor can be present for months or years (Houten and Cooper 2000; Houten and Weiner 2000).

10.3.4 Diagnostic Imaging

As with all spinal cord tumors, MRI is the diagnostic tool of choice (Miyazawa et al. 2000; Sun et al. 2003). Astrocytomas are commonly located eccentrically within the spinal cord and there is often heterogeneous contrast enhancement following injection of gadolinium (Osborn 1994; Baleriaux 1999) (Figs. 10.3 and 10.4). Approximately 75% of astrocytomas occur in the cervicothoracic region, 20% in the distal spinal cord, and 5% in the filum terminale (Osborn 1994). Unlike ependymomas, which typically span 3–4 vertebral bodies, intramedullary spinal cord astrocytomas are more extensive (Osborn 1994; Baleriaux 1999). Although MRI has improved our ability to identify the exact location of IMSCTs, a precise histopathologic diagnosis requires tissue biopsy (Kopelson and Linggood 1982; McCormick et al. 1990a; Hulshof et al. 1993; Minehan et al. 1995; Lee et al. 1996; Innocenzi et al. 1997; Jallo et al. 2001).

10.4 Von Hippel–Lindau Disease and Spinal Hemangioblastoma

Hemangioblastomas are benign (WHO grade I) vascular tumors predominantly found in the cerebellum and spinal cord. First described by Arvid Lindau as cystic lesions in the cerebellum, CNS hemangioblastomas are usually sporadic, but 20–30% of cases occur in association with von Hippel–Lindau (VHL) disease (Glasker 2005). VHL is an autosomal dominant disorder with 90% penetrance attributable to loss of a tumor-suppressor gene on chromosome 3p25-26 (Kley et al. 1995). The *VHL* gene encodes for a protein required for oxygen-dependent degradation of hypoxia-inducible factor-1 alpha (HIF-1α). Dysfunction or absence of the *VHL* gene product leads to constitutive overexpression of HIF-1α, which then leads to increased levels of vascular endothelial growth factor (VEGF) and other proangiogenic signals (Kim and Kaelin 2004). Additional information is provided in Chapter 12.6.

Lesions associated with VHL include CNS hemangioblastoma, retinal angioma, renal cysts, renal cell carcinoma, pancreatic cysts, pheochromocytoma, and epididimal cystadenoma (Glavac et al. 1996). VHL families can be grouped according to the presence

Figure 10.3

A 3-year-old girl presented with 6 months of intermittent, worsening back pain. (**a**) The MRI scan revealed a large intramedullary mass extending from T3 to T7, shown here in a sagittal T2-weighted image. The histology was consistent with a juvenile pilocytic astrocytoma. (**b**) The postoperative MRI scan demonstrates removal of the centrally located tumor. Nodular enhancement in the area of the surgery, is seen in a sagittal T2-weighted image. Although nodular enhancement was present in the first imaging, subsequent MRIs showed complete resolution 6 months after resection

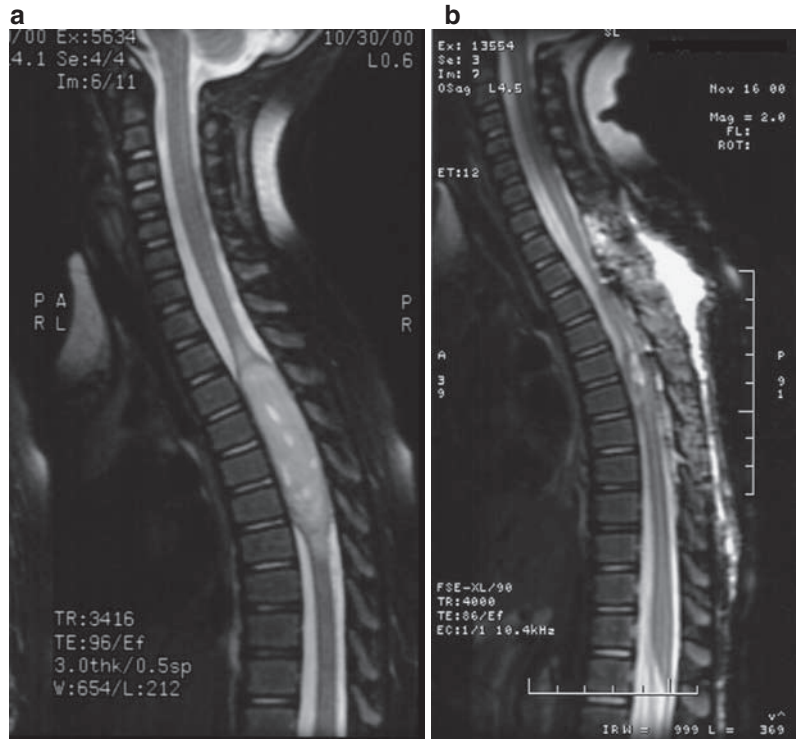
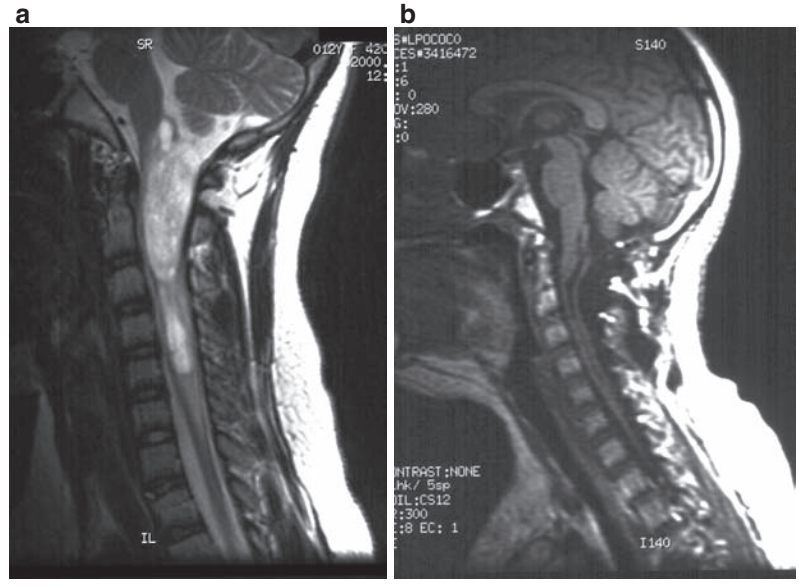


Figure 10.4

A 12-year-old girl presented with a 3-month history of progressive right arm weakness and clumsiness. (**a**) The preoperative MRI scan revealed an intramedullary spinal cord tumor extending from the cervicomedullary junction to C4, as shown in sagittal T2-weighted image. Histology was consistent with a juvenile pilocytic astrocytoma. (**b**) The postoperative MRI demonstrates that the enhancing mass has been resected, as shown in the sagittal T1-weighted image



or absence of pheochromocytomas (Neumann et al. 1995). Nearly all families with pheochromocytomas have missense mutations of the VHL gene. Using tissue microdissection, Vortmeyer and colleagues have demonstrated consistent LOH at the VHL gene locus in the stromal cells, implicating these cells in the pathogenesis of hemangioblastoma (Vortmeyer et al. 1997).

CNS hemangioblastoma occurs in both Type I (without pheochromocytoma) and Type II (with pheochromocytoma) VHL disease. Common sites include the posterior fossa (80%) and the spinal cord (20%). VHL-related hemangioblastomas have been reported to harbor germline mutations (94%) and LOH (62%) at the *VHL* gene (Glasker et al. 1999, 2001; Glasker 2005). Over 150 different germline mutations have been identified and include deletion and missense and nonsense frameshift mutations. The resultant biallelic inactivation of the *VHL* gene suggests a "2-hit" model of tumor-genesis in VHL patients. VHL patients are usually heterozygous for the germline VHL mutant, and a "second hit" at the remaining wild-type *VHL* gene then causes neoplastic progression. In contrast, sporadic hemangioblastomas contain only 50% LOH and 23% germline mutations at the *VHL* gene, suggesting alternate pathways to biallelic inactivation and tumor genesis in sporadic cases (Glasker 2005).

Other mutations and sites of LOH have been implicated in the development of sporadic hemangioblastomas. LOH of chromosome 22q13 was found in 5 of 8 patients with non-VHL-related hemangioblastoma, with only 3 of 8 patients harboring LOH at chromosome 3p21-23 (Beckner et al. 2004). Differences in the molecular and genetic origins of hemangioblastoma may indicate differences between patients with VHL disease and CNS hemangioblastomas and those with sporadic CNS hemangioblastomas.

10.5 Other Intramedullary Spinal Cord Tumors and Lesions

Inclusion tumors and cysts, metastases, nerve sheath tumors, neurocytoma, and melanocytoma account for much of the remainder of intramedullary mass lesions. Approximately 4% of apparent IMSCTs are nonneoplastic lesions (Lee et al. 1998). Lipomas are the most common developmental lesion and account for about 1% of all intramedullary spinal cord masses (Lee et al. 1998).

10.6 Treatment

Surgery is the treatment of choice for IMSCTs and excellent results are associated with gross total resection (Houten and Weiner 2000; Iwasaki et al. 2000). Although the outcome for low-grade spinal cord astrocytomas is better in children than in adults, the prognosis for spinal cord astrocytomas is not as favorable as that of ependymoma (Goh et al. 1997; Houten and Cooper 2000; Houten and Weiner 2000; Iwasaki et al. 2000; Hanbali et al. 2002). The clinical benefits of radical surgical resection for low-grade spinal cord astrocytoma has yet to be proven (Houten and Cooper 2000; Houten and Weiner 2000).

10.6.1 Surgery

10.6.1.1 Surgical Principles

Surgery may be less effective for diffusely infiltrating spinal cord astrocytomas and often a tissue diagnosis is all that can be safely accomplished (Houten and Cooper 2000; Houten and Weiner 2000). Juvenile pilocytic spinal cord astrocytomas, however, can be completely resected. The goal of surgery for intramedullary ependymoma is gross total resection (GTR) and preservation of neurologic function (Cooper 1989; McCormick et al. 1990a, b; McCormick and Stein 1990; Epstein et al. 1993; Cristante and Herrmann 1994; Chang et al. 2002; Peker et al. 2004). Ependymomas are typically noninfiltrative lesions that cause compression of the adjacent cord parenchyma and the presence of a well-defined interface between the spinal cord and the tumor facilitates surgical resection (Sandalcioglu et al. 2005). An adequate myelotomy is necessary to fully expose the tumor and allow an accurate tissue diagnosis

(Hanbali et al. 2002). An intraoperative frozen section diagnosis consistent with ependymoma should prompt an attempt at GTR. Conversely, identification of a malignant tumor signals an end to the procedure since surgery will be of little benefit (Kopelson and Linggood 1982; Cohen et al. 1989; Cooper 1989). The presence of a syrinx may improve the chances of a GTR, but it cannot be used as an independent predictor of outcome (Samii and Klekamp 1994; Chang et al. 2002; Peker et al. 2004).

10.6.1.2 Surgical Approach

Removal of the bony lamina to expose the dura and spinal cord, or laminectomy is centered on the solid portion of the tumor as indicated on preoperative MRI. Osteoplastic laminotomy, or removal and replacement of the posterior bony elements, restores the normal anatomical structures (Houten and Cooper 2000; Houten and Weiner 2000), and may reduce the incidence of postoperative spinal deformities (Constantini and Epstein 1996; Constantini et al. 1996, 2000). Intraoperative ultrasonography improves the accuracy of surgical exposure and identification of the intramedullary tumor, which in turn reduces the size of the laminotomy, dural opening, and myelotomy (Epstein et al. 1993; Maiuri et al. 2000; Hanbali et al. 2002).

The technique of tumor removal is determined by the surgical objective, tumor size, and gross and histological characteristics of the tumor. If no physical plane is present between the tumor and surrounding spinal cord, then it is likely that an infiltrative tumor is present. A biopsy is performed to establish a histological diagnosis. If an infiltrating or malignant astrocytoma is identified and is consistent with the intraoperative findings, further tumor removal may not be warranted. Ependymomas appear with a smooth, reddish-gray glistening tumor surface, which is sharply demarcated from the surrounding spinal cord. Large tumors may require internal decompression with an ultrasonic aspirator or laser.

In contrast to ependymoma, most intramedullary spinal cord astrocytomas are infiltrative tumors without an identifiable margin. If tumor is easily identified, then continued removal is reasonable. A reduction of motor or sensory evoked potentials (Asazuma et al. 1999; Quinones-Hinojosa et al. 2005), or uncertainty of spinal cord-tumor interface should signal an end to tumor resection (Asazuma et al. 1999).

10.6.1.3 Postoperative Management

Postoperatively, early mobilization is encouraged to prevent complications of recumbency such as deep venous thrombosis and pneumonia (Smith et al. 2004). Patients with severe motor deficits are particularly vulnerable to thromboembolic complications. Compression stockings are routinely used and subcutaneous heparin (Epstein 2005) is begun on the second postoperative day in these patients. Orthostatic hypotension may occasionally occur following removal of upper thoracic and cervical intramedullary neoplasms. This is usually a self-limiting problem that can be managed with liberalization of fluids and more gradual mobilization. A posterior fossa syndrome occasionally occurs following removal of a high cervical intramedullary neoplasm. Neck pain and stiffness can be managed with steroids and anti-inflammatory medications, although a lumbar puncture may sometimes be required to exclude a diagnosis of meningitis (Cooper and Epstein 1985; McCormick and Stein 1990).

Early and aggressive use of physical and occupational therapy results in a better functional recovery. Despite evidence to support a gross total resection, there is a risk of recurrence (Whitaker et al. 1991; Chang et al. 2002). Long-term clinical and radiographic follow-up is warranted in these patients (Sandalcioglu et al. 2005). An early postoperative MRI establishes the completeness of resection and serves as a baseline against which further studies can be compared. GTR is defined as more than 90% tumor removal, subtotal resection as 50–90%, and partial as less than 50%. Serial gadolinium-enhanced MRIs are obtained because radiographic tumor recurrence usually precedes clinical symptoms (Chang et al. 2002; Hanbali et al. 2002).

10.6.2 Radiation

Radiation therapy has played a limited role in the primary management of pediatric IMSCTs. Its principle role is in the treatment of incompletely resected low-grade astrocytomas and malignant tumors (Isaacson 2000). Radiotherapy in young children is associated with significant adverse effects and a general trend has emerged among oncologists to avoid or delay radiation therapy as long as possible (Rousseau et al. 1994; Perilongo et al. 1997; Prados et al. 1997; Gornet et al. 1999; Zuccaro et al. 1999; Grill et al. 2001; Teo et al. 2003; Valera et al. 2003).

GTR of grade II intramedullary ependymomas provides better long-term tumor control compared to subtotal resection and radiation therapy (McCormick et al. 1990b; Epstein et al. 1993; Hulshof et al. 1993; Cristante and Herrmann 1994; Hoshimaru et al. 1999). Although some authors recommend that radiation therapy is unnecessary following gross total resection (Cooper and Epstein 1985; Cooper 1989; McCormick et al. 1990b; Epstein et al. 1993; Hulshof et al. 1993; Samii and Klekamp 1994; Isaacson 2000; Kothbauer 2007), some studies have reported a 5–10% recurrence rate following surgery (Guidetti et al. 1981; Cooper 1989; Hulshof et al. 1993; Chang et al. 2002).

Subtotal resection, as expected, has a very high recurrence rate (Cooper 1989; Linstadt et al. 1989; Chang et al. 2002). The data supporting postoperative radiation after subtotal resection is largely based on studies with small patient populations, limited follow-up, and inadequate controls treated without radiation therapy (Isaacson 2000). Despite these limitations, the overall results suggest that radiation may be beneficial after subtotal resection of spinal cord ependymomas (Kopelson and Linggood 1982; Garcia 1985; Shaw et al. 1986; Cooper 1989; Linstadt et al. 1989). The usual dose delivered is approximately 5000 cGy in 180–200 cGy fractions using external beam radiation therapy. In some cases, reoperation and another attempt at gross total resection should be considered if a recurrent tumor is more accessible or better defined from the normal spinal cord (Cooper 1989; Chamberlain 2002b; Hanbali et al. 2002).

Patients who present with focal disease usually recur locally and do not manifest late dissemination (Chamberlain 2002a, b). Craniospinal radiation is only indicated for the rare patient who presents with multifocal disease (Garrett and Simpson 1983; Linstadt et al. 1989; Hulshof et al. 1993). Although the outcome is worse for this subgroup, good control rates have been reported (Garcia 1985; Linstadt et al. 1989).

10.6.3 Chemotherapy

Chemotherapy in patients who receive surgery and/or radiotherapy is not standardized and has not been completely defined for its role in the treatment of IMSCTs. Adjuvant chemotherapy has been used in the treatment strategy of recurrent ependymomas (Gornet et al. 1999). Massimino et al. have recently described their effective treatment of childhood low-grade gliomas using a multiagent regimen of chemotherapy (Massimino et al. 2002; Valera et al. 2003). This regimen has been effectively used as a neoadjuvant for treating supratentorial ependymoma (Valera et al. 2003). Platinum-based regimens in conjunction with nitrosourea-based regimens appear to show the most promise (Gornet et al. 1999; Chamberlain 2001). The effect of chemotherapy on survival and functional outcome is still unclear. The prospect of preoperative chemotherapy for second-look surgery has been explored in small trials with mixed results (Foreman et al. 1996; Schiffer and Giordana 1998; Chamberlain 2001; Valera et al. 2003). Also, because of the desire to avoid radiation therapy or delay it in young children, adjuvant chemotherapy may play an important role in children less than 3 years of age as a method of delaying radiation therapy (Prados et al. 1997).

Chemotherapy guidelines for pediatric IMSCTs have been mainly derived from the clinical experience with intracranial ependymomas and low-grade astrocytomas. No randomized clinical trials have been performed (Kothbauer 2007). Etoposide, a topoisomerase II inhibitor, has been used to treat recurrent intramedullary ependymomas. This drug appeared to be well-tolerated with modest toxicity

(Chamberlain 2002a, b). Further trials are needed to determine the efficacy of this potential therapy for recurrent and refractory intramedullary ependymomas. Two recent reports of chemotherapy as an adjuvant treatment for pediatric spinal cord astrocytomas demonstrated good clinical results, indicating that chemotherapy may have a valuable role in the future treatment of IMSCTs (Lowis et al. 1998; Hassall et al. 2001).

10.7 Outcome

10.7.1 Disease Control

The histological grade of the tumor is a significant prognostic factor in the outcome of patients with IMSCTs (Cristante and Herrmann 1994). Sandler reported a 5-year survival of 57% in patients with Grade I or II spinal cord astrocytomas (Sandler et al. 1992). Children with JPAS have better prognoses than those with diffuse spinal cord astrocytomas (Houten and Weiner 2000). Patients with malignant astrocytomas do very poorly, with no correlation between the extent of resection and survival (Fig. 10.5).

The most important determinant in the treatment of ependymomas is the extent of resection (Nazar et al. 1990; Rousseau et al. 1994; Pollack et al. 1995; Perilongo et al. 1997; Schiffer and Giordana 1998; Souweidane et al. 1998; Chamberlain 2001; Grill et al. 2001; Teo et al. 2003; Valera et al. 2003). It should be noted that late recurrences can occur, even up to 12 years after surgery (Linstadt et al. 1989). As noted earlier, gross total resection results in cure or long-term control more frequently than subtotal resection and radiation. Regardless of whether radiation is used following surgery, long-term imaging surveillance is required.

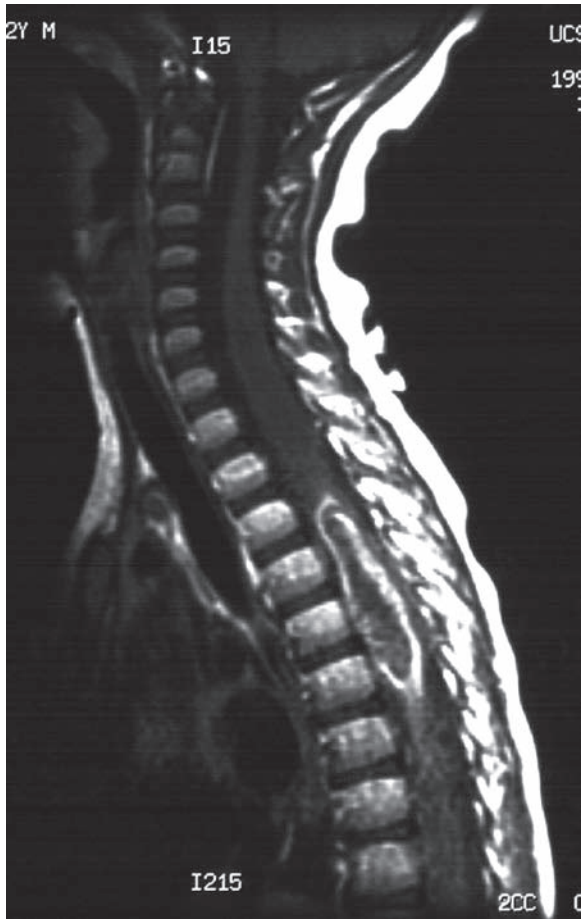


Figure 10.5

A 2-year-old boy presented with several weeks of slowly progressive disuse of his lower extremities. The preoperative MRI demonstrated a 6-cm intramedullary thoracic cord mass from T3 to T7 with marked edema spanning the entire length of the spinal cord. Histopathology showed the tumor to be a grade III oligoastrocytoma. The patient's tumor progressed despite treatment

10.7.2 Functional Outcome

The strongest predictor of postoperative functional outcome is preoperative functional ability (Cooper 1989; McCormick and Stein 1990; McCormick et al. 1990b; Epstein et al. 1993; Cristante and Herrmann 1994; Hoshimaru et al. 1999; Chang et al. 2002; Sandalcioglu et al. 2005). Significant improvement of a severe or long-standing preoperative neurologic deficit rarely occurs, even following a successful surgical excision (Chang et al. 2002). Surgical morbidity

is also greater in patients with more significant preoperative deficits (Hoshimaru et al. 1999; Chang et al. 2002; Hanbali et al. 2002; Peker et al. 2004). A shorter duration of preoperative symptoms, however, may favor improvement even in patients with a significant preoperative deficit (Hoshimaru et al. 1999). In general, most patients note sensory loss in the early postoperative period, most likely as a result of the midline myelotomy, transient edema, or vascular compromise (McCormick and Stein 1990; Epstein et al. 1993). These deficits usually resolve within 3 months (Hoshimaru et al. 1999; Peker et al. 2004), although sensory ability may not return to preoperative baseline (McCormick and Stein 1990).

Additional surgical morbidity is directly related to the location of the tumor and the presence of spinal cord atrophy and arachnoid scarring (Cooper 1989; McCormick and Stein 1990; Cristante and Herrmann 1994; Samii and Klekamp 1994; Hoshimaru et al. 1999). A thoracic location has been correlated with a decline in postoperative function (Cristante and Herrmann 1994; Hoshimaru et al. 1999; Hanbali et al. 2002; Sandalcioglu et al. 2005), perhaps due to a more tenuous blood supply in this region.

10.8 Conclusions

Early diagnosis of IMSCTs plays an important role in the management of these lesions and as a factor in long-term outcome. Because preoperative functional status is a significant prognostic factor, early diagnosis and surgical intervention is critical to the successful treatment of these tumors. Unexplained and chronic spine pain in a child should be investigated immediately with a high-quality MRI with gadolinium. For intramedullary ependymomas, the extent of surgical resection is the strongest predictor of long-term survival. Adjuvant therapy should be reserved for malignant, disseminated, or progressive subtotally resected tumors.

A postoperative MRI scan and serial imaging are important for long-term follow-up of patients who have an IMSCT. New adjuvant therapeutic agents will likely play an increasing role in the treatment of spinal cord astrocytomas in children. Finally, improved knowledge of the genetic and molecular features of these tumors made possible through analysis of small tissue specimens will allow the identification of new therapeutic targets.

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Rare Tumors

Sunanda Pejavar • Daphne Haas-Kogan

Contents

11.1 Meningioma

11.1.1 Epidemiology

Meningiomas are mostly benign tumors that arise from arachnoid cap cells of the meninges. They occur most frequently during the fifth or sixth decades of life and account for 15–25% of all primary intracranial neoplasms (Germano et al. 1994). These tumors are rare in children and adolescents, comprising only 1–3% of all meningiomas (Tufan et al. 2005) and less than 5% of all pediatric intracranial neoplasms (Di Rocco and Di Rienzo 1999; Tufan et al. 2005; Amirjamshidi et al. 2000). Unlike adult series, in which the female-to-male ratio is 2:1, most series on pediatric meningiomas report either a male preponderance (Sano et al. 1981; Baumgartner and Sorenson 1996; Erdincler et al. 1998) or no gender predilection (Di Rocco and Di Rienzo 1999; Amirjamshidi et al. 2000).

Most children with meningiomas are diagnosed in the first or second decades of life (Erdincler et al. 1998), and median age at presentation is 13 years (Greene et al. 2008). Although many of these tumors develop spontaneously, risk factors include prior radiation therapy and diagnosis of neurofibromatosis type 2 (NF2). Patients with NF2 have mutations on chromosome 22 that lead to the dysfunction of the *NF2* tumor-suppressor gene (Gutmann et al. 1997). The incidence of neurofibromatosis in children with meningiomas ranges from 13–41% in various series (Deen et al. 1982; Germano et al. 1994; Baumgartner and Sorenson 1996; Erdincler et al. 1998; Amirjamshidi et al. 2000). Patients with radiation-induced or neufibromatosis-associated meningiomas are generally diagnosed at a later age than

those with spontaneously occurring tumors (Greene et al. 2008).

Most pediatric meningiomas are found in supratentorial locations, but they may also be infratentorial, intraorbital, or intraventricular. Infratentorial meningiomas are noted in 19% of cases found in children under the age of 15 (Erdincler et al. 1998). The incidence of intraventricular tumors in children is 10% (Germano et al. 1994) compared with only 5% in adults (Rohringer et al. 1989). Rarely, they may occur in the third ventricle, arising from the ventricular floor, choroid plexus, or velum interpositum (Huang et al. 1993; Pau et al. 1996; Erdincler et al. 1998). The orbital location is associated exclusively with neurofibromatosis in one series (Greene et al. 2008). Meningiomas without dural attachment are also common in children, as are tumors with large cystic components (Drake et al. 1985; Ferrante et al. 1989; Tufan et al. 2005).

11.1.2 Histopathology

The World Health Organization (WHO) Classification of Tumours of the Central Nervous System (Louis et al. 2007) separates meningiomas into three grades (Table 11.1). Meningiomas in children and adolescents are known to have higher rates of atypical and malignant features than those in adults (6–10%) (Arivazhagan et al. 2008). One series noted that pediatric meningiomas are phenotypically and genotypically more aggressive than tumors in adults and exhibit high frequencies of brain invasion (Perry et al. 2001). Immunohistochemical staining shows higher MIB-1 labeling indices in atypical and malignant meningiomas than in those tumors without atypia (Sandberg et al. 2001). Of benign meningiomas, fibrous (24%), transitional (12%), and meningothelial (12%) subtypes are the most common. Other histological variants include psammomatous, fibroblastic, clear cell, and vascular. The significance of meningioma subtype on outcome is not known.

Table 11.1. World Health Organization (WHO) classification for meningiomas (Louis et al. 2007)

WHO grade I	Benign meningiomas: with low risk of recurrence and/or low risk of aggressive growth
WHO grade II	Atypical meningiomas: with increased mitotic activity or three or more of the following features: increased cellularity, small cells with high nucleus-to-cytoplasm ratio, prominent nucleoli, uninterrupted patternless or sheetlike growth, and foci of spontaneous or geographic necrosis
WHO grade III	Anaplastic (malignant) meningiomas: exhibit frank histologic features of malignancy far in excess of the abnormalities present in atypical meningiomas

11.1.3 Clinical Features

Children with meningiomas often experience insidious, nonspecific symptoms and signs related to increased intracranial pressure. Therefore, they generally present with a relatively long duration of symptoms (average 6–10 months) and with large tumors at diagnosis (Arivazhagan et al. 2008).

Headache (91%) and vomiting (70%) are the most common presenting complaints in adolescents (Tufan et al. 2005; Arivazhagan et al. 2008). In infants, a tense or bulging fontanel can be seen (Erdincler et al. 1998; Di Rocco and Di Rienzo 1999; Amirjamshidi et al. 2000). Other patients present with distinct neurologic symptoms related to tumor location. Motor deficits or hemiparesis is often observed (20%) (Erdincler et al. 1998). A large number of patients develop visual deficits (51%) or cranial neuropathies (64%) due to the high incidence of skull base and infratentorial tumors (Arivazhagan et al. 2008). Epilepsy is relatively uncommon in the pediatric population and occurs in 20–30% of patients (Erdincler et al. 1998; Amirjamshidi et al. 2000).

11.1.4 Diagnosis and Neuroimaging

Magnetic resonance imaging (MRI) is the mainstay of diagnosis of intracranial meningioma. Tumors show intense enhancement upon administration of gadolinium contrast agent and are frequently cystic and calcified. An enhancing dural tail can be seen (Fig. 11.1), but is less common in children than in

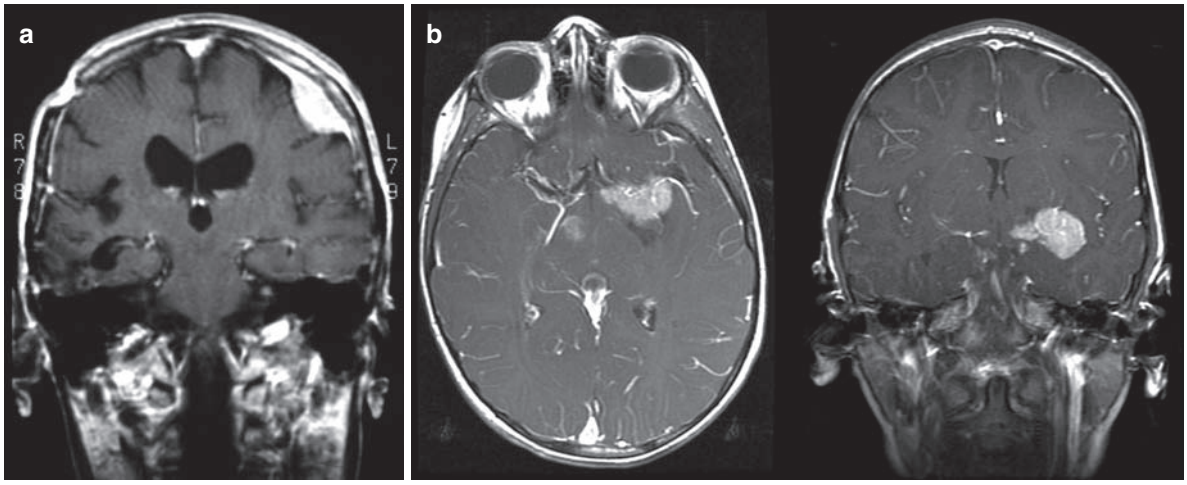


Figure 11.1

(**a**) A T1-weighted MR image following contrast administration showing a dural-based convexity meningioma with an enhancing "tail." (**b**) T1-weighted postcontrast MR images (axial and coronal) of a 6-year-old girl with a very unusual meningioma located in the Sylvian fissure without a defined dural attachment point. No obvious syndrome was identified

adults (Sano et al. 1981; Turgut et al. 1997; Di Rocco and Di Rienzo 1999; Yoon et al. 1999; Im et al. 2001). Other studies, including contrast-enhanced computed tomography (CT) scans and plain films, may serve to confirm the diagnosis. On a head CT scan, a meningioma appears as a dural-based tumor that usually compresses, but does not invade the brain. They are usually intensely and homogenously enhancing and may be surrounded by extensive edema. On a plain radiograph, intracranial calcifications and hyperostosis may be seen.

Conventional catheter angiography typically shows a delayed vascular blush and "sunburst" pattern of feeding meningeal arteries. This modality was used in the past for diagnosis; however, it is now limited to those cases in which preoperative embolization is being considered. Catheter angiography, magnetic resonance arteriography (MRA), and magnetic resonance venography (MRV) are important tools in planning surgery by determining vascularity of the tumor, impingement on critical vascular structures, and patency of involved dural sinuses.

11.1.5 Treatment

Surgical gross total resection (GTR) is the primary treatment modality. In various series, GTR was accomplished in 65–86% of cases (Erdincler et al. 1998; Tufan et al. 2005; Arivazhagan et al. 2008). Specific surgical challenges in children include the proximity of the tumor to vital structures, larger tumor size at diagnosis, and lower blood volume. Multiple-staged resections are sometimes necessary, particularly when significant perioperative blood loss occurs.

Preoperative embolization of meningiomas is shown to decrease tumor vascularity and reduce blood loss during surgery in adults, although there is no data specifically pertaining to children (Oka et al. 1998). Pediatric patients may have an increased risk of morbidity from this procedure due to their smaller caliber vessels.

Adjuvant chemotherapy and radiotherapy have limited roles in the treatment of pediatric meningioma. In adults, postoperative radiation therapy has been shown to increase survival in those patients with subtotal resection (Goldsmith et al. 1994). Due to the long-term risks of radiation in young children and

the usually benign nature of meningiomas, however, radiation therapy is rarely used in very young children (<3 years of age).

11.1.6 Outcome

Although most meningiomas are slow-growing and benign tumors, the prognosis in children remains unclear (Chan and Thompson 1984; Drake et al. 1985; Germano et al. 1994). With advances in medical technology, more modern series show improved outcome. A review of the literature on infantile meningiomas reports that 91% of patients diagnosed after 1980 are alive 15 years later, versus only 50% of patients diagnosed between 1970 and 1980.

Tumor location, extent of tumor resection, and pathological grade are described as the most significant prognostic factors (Sheikh et al. 1996; Erdincler et al. 1998; Di Rocco and Di Rienzo 1999). Patients with neurofibromatosis-associated tumors generally experience worse outcomes than those with sporadic tumors, due to the complex natural history of the disease (Erdincler et al. 1998). However, spontaneously arising meningiomas tend to exhibit higher rates of recurrence than radiation-induced or neurofibromatosis-related tumors (Greene et al. 2008). This observation may be related to the fact that malignant meningiomas in children tend to arise spontaneously (Greene et al. 2008). Histological subtype may also play a role in outcome. Meningeal sarcomas, hemangiopericytomas, and angioblastic or melanocytic tumors are more aggressive than classic meningiomas, and have worse prognoses.

11.2 Pediatric Pituitary Adenoma

11.2.1 Epidemiology

Pituitary adenomas account for only 1–10% of all childhood brain tumors, and between 3–6% of all surgically treated pituitary tumors (Gold 1981; Kane et al. 1994; Mindermann and Wilson 1995). Variation in reported incidence is related to the lack of consensus on an age cutoff for pediatric tumors. The majority of children present with hormone-secreting tumors. Nonfunctioning adenomas are rare in children and only make up 3–6% of tumors in this population, compared with one third of adenomas found in adult series (Partington et al. 1994; Mindermann and Wilson 1995).

The most common functioning adenomas in children are prolactinomas (45–53%), followed by adrenocorticotropic hormone (ACTH)-secreting adenomas or corticotroph adenomas (25–33%), and finally growth hormone (GH)-secreting adenomas or somatotroph adenomas (8–15%). Thyroid hormone-secreting tumors or thyrotroph adenomas are extremely rare, and only a few pediatric cases have been reported in the literature. The vast majority of cases present in adolescence (Haddad et al. 1991; Partington et al. 1994; Pau et al. 1996); only 25% of pediatric patients with pituitary adenomas are under the age of 12 (Mindermann and Wilson 1995). When stratified into prepubescent (age 0–11), pubescent (age 12–17), and postpubescent (age 18–19) groups, there is a characteristic distribution by tumor type (Table 11.2).

Table 11.2. Occurrence of pediatric pituitary adenoma by age group (Kunwar and Wilson 1999)

Adenoma Subtype	No. of patients (%)			
	Age 0–11	Age 12–17	Age 18–19	Total
Prolactinoma	5 (16.1)	61 (59.8)	12 (70.6)	78 (52.0)
Corticotroph adenoma	22 (71.0)	31 (30.4)	3 (17.6)	56 (37.3)
Somatotroph adenoma	2 (6.4)	8 (7.8)	2 (11.8)	12 (8.0)
Endocrine inactive	2 (6.4)	2 (2.0)	0	4 (2.7)
Total[a]	31 (20.7)	102 (68.0)	17 (11.3)	150 (100)

[a] Numbers represent total of each age group. Percentages represent the number out of 150 patients

Corticotroph adenomas are most commonly seen in the youngest age group, found in over 50% of prepubescent children diagnosed with pituitary adenomas. Somatotroph adenomas are equally distributed amongst the three age groups. The distribution of the various adenomas in the postpubescent group mimics that in adults.

Multiple series have shown a female preponderance in pediatric pituitary adenomas (Maira and Anile 1990; Kane et al. 1994; Mindermann and Wilson 1995; Webb and Prayson 2008). The vast majority of prolactinomas occur in females (83% females vs. 17% males) and slightly more corticotroph adenomas occur in females than in males (55% females vs. 45% males; Fraioli et al. 1983; Maira and Anile 1990; Partington et al. 1994; Mindermann and Wilson 1995). On the other hand, pure somatotroph adenomas are more common in males (57% males vs. 43% females).

11.2.2 Histopathology

Most pituitary adenomas are benign tumors arising from epithelial cells of the adenohypophysis. Tumor development occurs as a monoclonal process influenced by a multitude of factors, including hormones, gene mutations, or heredity. The exact pathophysiologic mechanism, however, is unknown. Pituitary adenomas can occur sporadically or as components of hereditary syndromes. Prolactinomas, corticotroph adenomas, and somatotroph adenomas are common in patients with multiple endocrine neoplasia syndrome type 1 (MEN-1). Somatotroph adenomas are also associated with several other hereditary conditions, including McCune Albright syndrome or the Carney complex (Lafferty and Chrousos 1999).

There is some discrepancy among the series regarding the ratio of macroadenomas (>1 cm) to microadenomas. Most studies document either equal distribution between the two types or a slightly higher incidence of macroadenomas in the pediatric population (range 36–78%). The size of the tumor appears to be related to secretory function, with the vast majority of somatotroph and thyrotroph adenomas presenting as macroadenomas and corticotroph adenomas presenting as microadenomas. Hormonally inactive adenomas often present as macroadenomas.

11.2.3 Clinical Features

Presenting symptoms in patients with pituitary adenomas depend both on tumor size and on secretory capability. Headaches and visual deficits are common in children with macroadenomas. Because pediatric patients have a preponderance for functioning adenomas, the majority of children also present with endocrine dysfunction (75%) (Pandey et al. 2005). This dysfunction manifests as specific clinical signs related to hormone hypersecretion from the tumor, as well as disruptions in growth or sexual maturation related to compression of normal pituitary tissue. The pituitary gland shows a predictable sequence of secretory failure (Kunwar and Wilson 1999). GH-releasing cells are extremely vulnerable to compression and are almost always the first cells to exhibit hormone hyposecretion. Therefore, children with adenomas other than somatotroph adenomas usually present with short stature or growth retardation. Gonadotropin-releasing cells are also susceptible to compression, although to a lesser degree than GH-secreting cells, and menstrual irregularity is a common complaint in adolescent girls with pituitary adenomas. Thyroid stimulating hormone (TSH) is affected late and only with relatively large tumors.

Prolactinomas can present with different signs and symptoms depending on the age and sex of the child. Prepubertal children present with nonspecific symptoms of headache, visual disturbance, and growth failure, mentioned earlier. Common complaints by postpubertal females are amenorrhea (83%) and galactorrhea (36%). These tumors are rare in males, but may present with pubertal arrest, hypogonadism (23%), or gynecomastia (23%). Because prolactinomas arise from cells in the same lineage as somatotropes and thyrotropes, these tumors may also stain for and secrete GH and TSH.

Cushing syndrome is the most common presentation of corticotroph adenomas. Approximately 90% of children over the age of 5 years diagnosed with Cushing syndrome have ACTH-secreting adenomas (Lafferty and Chrousos 1999). These patients experience weight gain (50%) with purplish striae, easy bruising, moon facies, growth retardation, and sometimes hypertension and insulin resistance. Prepubertal children may

present with hirsutism and premature pubarche, while postpubertal children often have pubertal arrest. Unlike adults, proximal myopathy is uncommon in children, and weight gain tends to be generalized rather than centripetal (Lafferty and Chrousos 1999). Neuropsychiatric problems such as compulsive behavior and overachievement in school tend to dominate in the pediatric population, as opposed to depression and memory loss which are common in adults.

Somatotroph adenomas generally cause rapid growth and gigantism in children with open epiphyseal plates. Occasionally, these tumors also cause weight gain, premature puberty, or menstrual irregularities. In older children, who have undergone epiphyseal fusion, symptoms tend to mimic those in adults. These patients may present with glucose intolerance, acromegalic features such as coarse facies and enlarged hands and feet, nausea, and respiratory difficulty.

Nonfunctioning adenomas, which are uncommon in children, present with generalized symptoms of headache, visual disturbance, growth retardation, and pubertal arrest. Thyrotroph adenomas, which are exceedingly rare, may present with hyperthyroidism, or nonspecific findings similar to those patients with nonfunctioning adenomas.

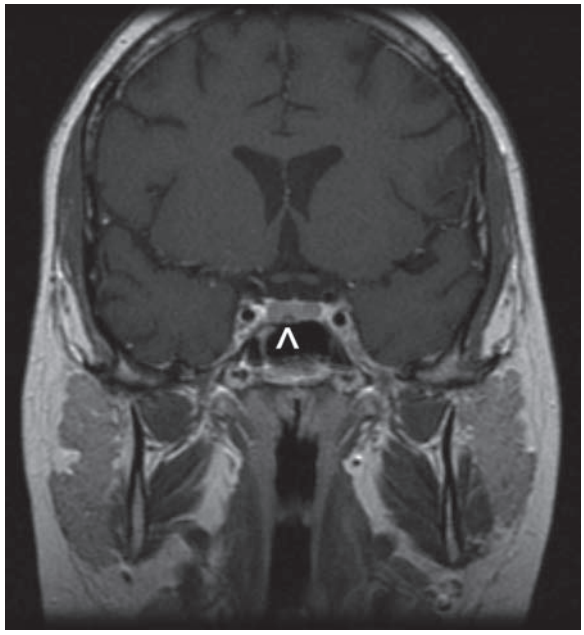


Figure 11.2

A teenage girl presenting with Cushing's disease secondary to a hormone secreting corticotroph microadenoma. A T1-weighted coronal MR image shows a small lesion (*arrrowhead*) that is hypointense relative to the pituitary gland. The normal pituitary gland is usually brighter than a small pituitary adenoma following contrast

11.2.4 Diagnosis and Neuroimaging

11.2.4.1 Imaging

Pituitary adenomas are diagnosed by both imaging and biochemical studies. MRI with gadolinium is the imaging modality of choice and has 72% sensitivity in the diagnosis of adenomas (Devoe et al. 1997). On T1-weighted images, pituitary adenomas are hypoenhancing, compared with normal anterior pituitary tissue that appears slightly hyperintense relative to the rest of the brain (Fig. 11.2). Nonspecific signs may include a deviation of the pituitary stalk or an increase in the vertical height of the gland, although a normal pituitary gland in adolescent girls may appear enlarged and convex superiorly. Physiologic enlargement of the pituitary gland during puberty is frequently mistaken for a macroadenoma. Although MRI provides superior soft tissue contrast and resolution of the sella compared with CT, this modality is still only able to detect less than one-half of microadenomas.

Newer imaging studies with promise include positron emission tomography (PET) scans and ultrasound, although these have not been used yet in primary diagnosis. Ultrasound has shown promise during transsphenoidal surgery, particularly in patients with corticotroph adenomas (Ram et al. 1999). This modality provides good contrast between tumor and normal pituitary gland and has the potential to identify sellar or suprasellar structures with invasion or damage. In postoperative patients, PET can help differentiate recurrence from scarring. Radiolabeled octreotide scans, which use in-diethylenetriamine pentaacetic

acid-labeled octreotide as a receptor ligand, have been tried for tumor localization, but results have been disappointing (Colao et al. 1999; Kwekkeboom et al. 1999).

11.2.4.2 Biochemical Tests

Hematologic tests depend on clinical presentation. Prolactin levels are checked in any patient with a suspected prolactinoma. A single elevated level of greater than 200 in a patient with a 1cm pituitary mass on imaging is adequate for a diagnosis of prolactinoma. Because moderately elevated levels can signify either a microadenoma or secondary hyperprolactinemia due, for example, to functional pituitary stalk disconnection, a second, fasting level may be checked for confirmation and is usually drawn an hour after placing an indwelling cannula.

Suspected corticotroph adenomas warrant a work-up that confirms the presence of Cushing's disease. Multiple 24 hour urine free cortisol (UFC) levels are checked and adjusted for the child's body surface area. In addition, a dexamethasone suppression test can be administered and is positive for Cushing's disease if the patient's serum cortisol fails to drop the morning after receiving a dose of dexamethasone. Once Cushing's disease is diagnosed, further tests are ordered to confirm that the etiology is a corticotroph adenoma. A high-dose dexamethasone suppression test is positive if a patient's serum cortisol drops by 50% the morning after a high dose of dexamethasone is administered and has 85% sensitivity for diagnosis of corticotroph adenoma (Lafferty and Chrousos 1999). Additional tests involve injecting ovine corticotropin-releasing hormone and measuring ACTH simultaneously from central and peripheral sites. If ACTH is stimulated, the test has 97% sensitivity for corticotroph adenoma. Alternatively, bilateral inferior petrosal sinuses can be sampled and detection of ACTH both confirms the diagnosis and lateralizes the tumor with 75% accuracy.

Biochemical tests for somatotroph adenomas include random measurements of GH and insulin-like growth factor (IGF-1). Elevations in both markers suggest a diagnosis of somatotroph adenoma, although IGF-1 can sometimes be elevated during normal puberty. An oral glucose tolerance test, during which GH shows failed suppression or a paradoxical rise, is also positive for a somatotroph adenoma. This test, however, has a high false-positive rate (Holl et al. 1999) and should be used in conjunction with other laboratory testing. Somatotroph adenomas also frequently express thyrotropin-releasing hormone (TRH) receptors, and therefore the diagnosis can be confirmed by measuring GH stimulation after TRH administration.

Several tests may be used to help confirm the presence of a thyrotroph adenoma. Elevated free T4 and T3 without suppression of TSH support the diagnosis. However, additional tests differentiate an adenoma from central T4 resistance. Thyrotroph adenomas do not respond to TRH stimulation, and this test has a sensitivity of 71% and specificity of 96%. In addition, elevated alpha-glycoprotein subunit is a positive test and has 75% sensitivity and 90% specificity.

11.2.5 Treatment

11.2.5.1 Surgery

Surgical treatment for pituitary adenomas has been widely used during the past 50 years. Surgery has the advantage of rapidly lowering hormone levels in functioning adenomas and improving visual symptoms in patients with optic chiasm compression. Two general surgical approaches are used: transcranial/subfrontal or transsphenoidal. In some situations with very large tumors, a combination of approaches is needed. At present, the preferred technique is the transsphenoidal route in both adults and children. In several series, transsphenoidal surgery was used in children as the initial approach. This technique yielded positive results, and very few patients suffered postoperative complications or required a second intracranial procedure (Maira and Anile 1990; Partington et al. 1994). The transsphenoidal route has been used in children as young as 4 years old without difficulty (Haddad et al. 1991; Ludecke and Abe 2006).

In patients with larger tumors, the transcranial route is often used. Specific indications include dumbell-shaped tumors with extensive suprasellar

component, multicompartmental tumors, and unclear diagnoses (Pandey et al. 2005). However, morbidity is often higher in patients operated on via this route, and postoperative visual deterioration is more common.

Surgery as primary therapy is recommended for all pituitary adenomas except prolactinomas. Corticotroph adenomas usually present as microadenomas, and therefore hemihypophysectomy is often curative. However, this approach entails confirmation of which half of the anterior pituitary gland contains the microadenoma. If the tumor is not visible on routine sellar MRI scans, selective venous sampling is required. In a patient with a lateralizing ACTH gradient of 2:1 or greater, removal of the appropriate half of the pituitary will be curative in 80% of cases (Kunwar and Wilson 1999). Similarly, 83% of patients with acromegaly due to a somatotroph adenoma will be cured following surgery (Mindermann and Wilson 1995). Although surgery is the preferred treatment for thyrotroph adenomas, these tumors are often large and invasive and therefore require adjuvant radiation therapy (Kunwar and Wilson 1999). While adult patients with asymptomatic, nonfunctioning adenomas are usually observed, pediatric patients are almost always treated surgically. This approach is primarily due to the fact that nonfunctioning adenomas are extremely rare in children and difficult to discern from craniopharygiomas.

In children with prolactinomas, medical rather than surgical therapy is recommended as the initial treatment. Surgery is reserved for individuals who have rapid visual decline (Fig. 11.3), are intolerant of the side effects of medication, or are unwilling to comply with life-long pharmacologic therapy. Pediatric patients that do undergo surgery for prolactin-secreting tumors experience an 82% cure rate (Mindermann and Wilson 1995).

11.2.5.2 Medical Therapy

Prolactinomas are the only adenomas that can be managed initially with medical therapy. Dopamine agonists such as bromocriptine, pergolide, and cabergoline are effective for shrinking the tumor and normalizing prolactin levels. Side effects of these medicines, however, include gastrointestinal upset and orthostatic hypotension. In addition, elimination of the entire tumor has not been reported; therefore, these patients will require medical treatment for their entire lives.

For other types of pituitary adenomas, medical therapy is indicated only in nonsurgical candidates or if surgical management is inadequate in controlling hormone levels. Adrenal blockade with ketoconazole is often required in patients with corticotroph adenomas, but is only used if surgery and postoperative radiation have failed. Somatostatin analogs such as octreotide and lanreotide have been used in adults with GH-secreting tumors, although there is limited experience with these drugs in the pediatric population. These drugs show variable effects on both tumor shrinkage and hormone suppression. Octreotide causes a significant reduction in tumor size in 40% of patients, although this effect is not sustained after discontinuation of the medication (Ezzat et al. 1994). This medication results in suppression of GH to less than 5 μg/L in 65% of patients, and normalization of IGF-1 in 56% of patients. Lanreotide, which is a longer-acting analog, is effective in suppressing GH and IGF-1 levels, but only provides significant tumor shrinkage in 15% of patients (Caron et al. 1997). Dopamine agonists have been explored as treatment for somatotroph adenomas, but result in tumor shrinkage and normalization of hormone levels in only 10–20% of patients (Jaffe and Barkan 1992). In thyrotroph adenomas, octreotide has been shown to normalize thryoid hormone levels in 80–90% of patients, and decreases tumor size in 50% of patients (Chanson et al. 1993; Fukuda et al. 1998; Brucker-Davis et al. 1999).

11.2.5.3 Radiation Therapy

Radiation therapy as primary treatment for pituitary adenomas is not recommended in children due to the risk of long-term sequelae from radiation to the pituitary gland and normal brain. Moreover, normalization of hormone levels is usually suboptimal after radiation and requires years to take effect. This modality is indicated postoperatively for residual or unresectable pituitary adenomas (Jennings et al. 1977; Fraioli et al. 1983; Pandey et al. 2005; Mehrazin

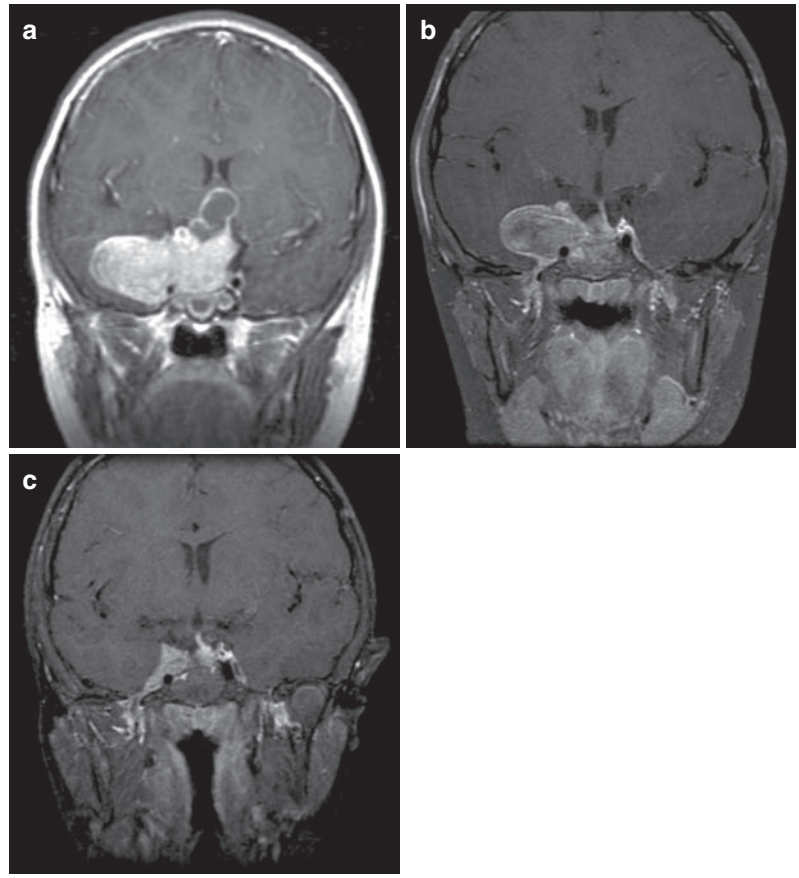


Figure 11.3
A 5-year-old boy who presented with visual loss from a very large prolactinoma. The tumor was treated with subtotal surgical resection to decompress the optic chiasm and preserve visual function. The pre-operative T1-weighted coronal MR image (**a**) shows a large multilobulated mass with poor visualization of the chiasm. The immediate postoperative scan (**b**) shows excellent decompression of the suprasellar tumor although the lateral portion remains. Two years later (**c**), after taking oral cabergoline, a much smaller residual tumor remains adjacent to the cavernous sinus. The patient has a partial GH deficiency but otherwise has normal visual and endocrine function

2007). In children with corticotroph adenomas, treatment with radiation doses of 35–50 Gy at standard fractionation has been shown to result in cure rates of 70–80% at 2 years (Jennings et al. 1977).

Recently, radiosurgery has been used to treat residual or unresectable pituitary adenomas. Doses of 25–30 Gy for functioning tumors and 20 Gy for nonfunctioning tumors have provided effective tumor control, as well as faster normalization of hormone levels than conventional radiation techniques (Jackson and Noren 1999).

11.2.6 Outcome

Pediatric pituitary adenomas are rarely fatal but can have significant effects on quality of life and sometimes lead to long-term complications caused by endocrine dysfunction. Treatment is almost always recommended for functional or symptomatic nonfunctional adenomas, but optimal management remains unknown.

Children who undergo surgical resection for functioning adenomas have cure rates of 80–90% (Partington et al. 1994; Mindermann and Wilson 1995). Recurrence depends largely on the extent of resection (total vs. subtotal). Pediatric patients who undergo GTR have local recurrence rates of 1–5% (Kane et al. 1994; Partington et al. 1994; Mindermann and Wilson 1995; Webb and Prayson 2008), while patients who undergo subtotal resections have recurrence rates greater than 60% (Webb and Prayson 2008).

When surgery is undertaken successfully, patients will often require hormone supplementation such as thyroid hormone or hydrocortisone for the duration of their lifetime. Surgical complications such as visual deficits or diabetes insipidus are rare and usually transient. However, pituitary apoplexy, a complication caused by sudden tumor hemorrhage or pituitary infarction, is found relatively often in pediatric patients after surgery, radiation, or medical therapy (Yousem et al. 1989; Bills et al. 1993; Knoepfelmacher et al. 2004; Semple et al. 2005). Apoplexy typically occurs in macroadenomas, can involve both functional and nonfunctional adenomas and has been reported to occur up to two years after surgical resection (Yousem et al. 1989; Knoepfelmacher et al. 2004; Semple et al. 2005; Nielsen et al. 2006; Mehrazin 2007).

11.3 Primary Central Nervous System Lymphoma

11.3.1 Epidemiology

Primary central nervous system lymphoma (PCNSL) accounts for 4–7% of all primary intracranial neoplasms and 1–2% of all lymphomas (Maher et al. 1990; Corn et al. 1997). The incidence of this tumor has increased tenfold over the last three decades in both immunocompetent and immunocompromised individuals (Corn et al. 1997). The PCNSL occurs between the fourth and sixth decades of life, and most series report a male predominance (Mendenhall et al. 1983; Jack et al. 1988).

This neoplasm is extremely rare in the pediatric population, with an estimated incidence of only about 14 cases annually (Abla et al. 2006). Children with congenital or acquired immunodeficiency are at an increased risk of developing this tumor (Roychowdhury et al. 2003; Newell et al. 2004), although there have been several sporadic cases of pediatric PCNSL reported in the literature. In immunocompetent adults, sporadic cases of PCNSL have been reported in association with antecedent gastrointestinal or flu-like illnesses or demyelinating conditions such as Lyme disease (Hochberg et al. 1983; Brecher et al. 1998). In the pediatric population, the presence of this association is unknown.

11.3.2 Histopathology

The PCNSL most frequently arises from B lymphocytes, and the majority of cases (90%) are diffuse large B-cell lymphomas. The remaining 10% of tumors are low-grade lymphomas, Burkitt lymphomas, or T-cell lymphomas (Miller et al. 1994). The most common type, diffuse large B-cell lymphoma, is comprised of immunoblasts or centroblasts that cluster around small cerebral blood vessels. Reactive T-cell infiltrates are commonly seen in immunocompetent patients but are rare in individuals with AIDS.

The frequency of PCNSL in immunodeficient individuals suggests that the immune system may play a role in the pathogenesis of the neoplams. Almost all patients with AIDS express Epstein–Barr viral genome in their tumors. Although the exact mechanism of tumorigenesis is not known, the tumor may arise from an Epstein–Barr virus-mediated malignant transformation and clonal expansion of B-cells. One series documented HHV-8 (Kaposi-sarcoma associated herpes virus) in 56% of immunocompetent and immunocompromised patients with PCNSL. Chromosomal abnormalities in both adults and children are not reported often. In one pediatric series, 2 of 3 patients with anaplastic T-cell lymphoma were found with t(2:5) translocations (Abla et al. 2006).

11.3.3 Clinical Features

PCNSL has been described as four distinct clinicopathologic entities: solitary or multiple intracranial lesions; diffuse periventricular or leptomeningeal disease; vitreous or uveal deposits; and intradural spinal cord tumors. In adults, signs and symptoms tend to correlate with location of involvement.

The majority of children present with intracranial, multifocal disease as opposed to solitary lesions. These patients may present with nonspecific symptoms related to increased intracranial pressure, such as headache, vomiting, or somnolence. Many children

also present with either ataxia or hemiparesis, and other presenting symptoms in various series include paresthesias, nystagmus, decreased visual acuity, panhypopituitarism, or personality change. The duration of symptoms varies depending on the series, and ranges from 1 day to 13 months (Abla et al. 2006).

11.3.4 Diagnosis and Neuroimaging

Diagnosis of PCNSL involves radiographic evaluation, cerebrospinal fluid testing, and histopathogic analysis. CT and MRI studies are used in both immunocompetent and immunocompromised patients with suspected PCNSL. Radiographic features seen in children are similar to those seen in adults (Schulman et al. 1991). In immunocompetent individuals, intracranial lesions appear as nonhemorrhagic masses in the deep white matter adjacent to the ventricular surfaces (Buhring et al. 2001). The tumors are generally hyperdense on CT images, hypointense on T2-weighted MR images, and homogeneously enhance after administration of contrast agent (Fig. 11.4). Surrounding edema, calcification, necrosis, and ring enhancement are relatively infrequent in PCNSL (Buhring et al. 2001). Leptomeningeal and vitreal disease are often missed on both CT and MRI.

Lumbar puncture is almost always performed on patients with suspected PCNSL if no mass effect is evident, and CSF evaluation includes cytology, flow cytometry, and immunophenotypic analysis. Elevated protein concentration and slight lymphocytic predominance are often seen. Glucose levels are usually normal, but may be low in patients with leptomeningeal disease. Although malignant lymphoid cells may be present in many patients, there is difficulty in differentiating between reactive and malignant cells or between medulloblastoma cells and malignant B-cells. Immunophenotype testing using antibodies against lymphocytic antigens is often useful in supporting the diagnosis of PCNSL and in distinguishing B-cell neoplasms from T-cell neoplasms. Stereotactic biopsy is the usual surgical technique used to establish a tissue diagnosis.

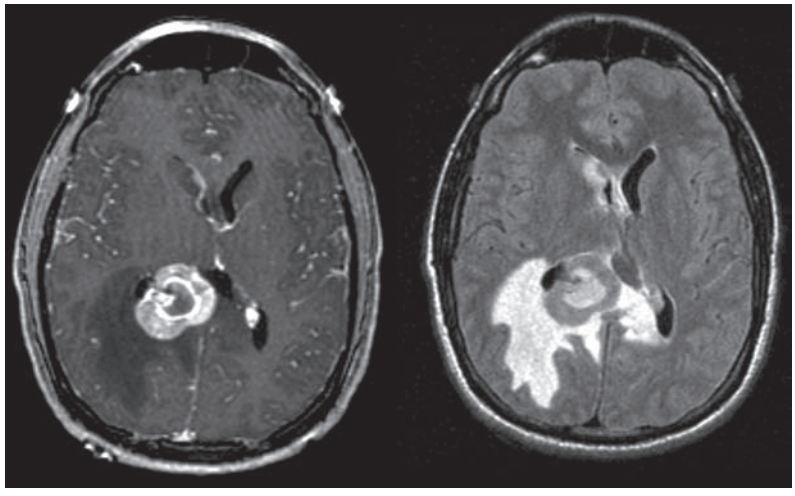
Systemic disease is rare in patients with PCNSL (7–10% incidence in adult series). Therefore, extensive staging with CT scans of the body or spinal MRI are not routinely recommended unless patients are symptomatic. Like adults, pediatric patients should undergo a complete assessment for immunosuppressive diseases, including HIV, autoimmune conditions, and congenital diseases.

11.3.5 Treatment

The role of surgery in the treatment of PCNSL is limited to stereotactic biopsy. Complete resection

Figure 11.4

Primary CNS lymphoma involving the right medial occipital lobe and corpus callosum. The tumor enhances (*left image*) but there is also a marked degree of white matter edema visible on the FLAIR image (*right image*)



is usually not possible because of the tumor's usual deep location, multifocality, and extensive infiltration into the surrounding brain. Moreover, patients treated with surgical excision alone have a poor prognosis, with a median survival of less than 5 months (Henry et al. 1974). Surgical intervention may be considered emergently in patients with impending herniation, significant mass effect, or hydrocephalus.

Patients with PCNSL respond dramatically to corticosteroids. This type of lymphoma appears to be more sensitive to the lymphocytotoxic effects of steroids than systemic lymphoma, and dexamethasone in particular has been shown to induce temporary complete remission in patients with PCNSL (Pirotte et al. 1997). Other series have reported response rates of up to 70% after treatment with steroids alone (Hochberg et al. 1983; Ferracini 1997). The clinical and radiographic changes are almost always transient, however, and the tumor tends to recur within several months after discontinuation of the therapy.

Radiation with or without corticosteroids was historically the mainstay of treatment in adults with PCNSL. Lymphomas are extremely sensitive to radiation, and several series have shown rapid, complete radiographic and clinical responses in patients treated to doses between 30 and 40 Gy at standard fractionation. The majority of these patients, however, will have local recurrence within 1 year of treatment. Moreover, cranial radiation is associated with a high rate of cognitive impairment and leukoencephalopathy in these patients with no significant improvement in disease-free survival.

Because of the rarity of PCNSL in the pediatric population, the optimal therapeutic strategy is unknown. Several early series have documented an improvement in median survival time among children treated with radiation alone for PCNSL. After whole-brain radiation therapy, median survival ranged from 11.6 to 18 months (Nelson et al. 1992; Ishikawa et al. 2003; Shibamoto et al. 2005). Dose varied between 30 and 40 Gy, with an occasional boost of 10–20 Gy to the tumor bed (Nelson et al. 1992; Ishikawa et al. 2003; Shibamoto et al. 2005). One case report described a 9-year-old boy with PCNSL who was treated with 30 Gy of whole-brain radiation followed by a 20 Gy boost, and remained in complete remission 14 years later (Makino et al. 2006). Although overall response rate to radiation alone is 90% (Nelson et al. 1992), long-term remission is rare, and patients treated with radiation alone are generally found to have a high local recurrence rate. Moreover, the risks of cognitive dysfunction and second malignancy pose major concerns regarding the use of radiation in children.

More recently, treatment approaches in adults have been based on combination chemotherapy and cranial irradiation, or intensive chemotherapy alone. The effectiveness of cranial irradiation has been documented in adult patients with PCNSL (Brada et al. 1998; Deangelis and Iwamoto 2006). High-dose methotrexate is the chemotherapeutic agent with the highest antitumor activity against PCNSL. However, several adult series showed high rates of relapse, low response rates, and high incidences of progressive disease during therapy (Batchelor and Loeffler 2006; Herrlinger et al. 2005). The use of methotrexate-based regimens in conjunction with cranial radiation has improved median survival to 3 years with a cure rate of 30–40% in immunocompetent patients (Maher and Fine 1999; Ferreri et al. 2002). Pediatric patients have been treated with chemotherapy alone with positive long-term results (Cohen et al. 1986; Cairo et al. 2007). Although the optimal regimen is unknown, agents such as procarbazine, thiotepa, and nitrosourea have shown some efficacy when combined with methotrexate in adult patients (Freilich and DeAngelis 1995; Ferreri et al. 2002). In a pediatric series where patients were treated with high-dose methotrexate and cytarabine, the 5-year event-free survival rate was 70% (Abla et al. 2006). A case report described a patient treated with cytarabine and methotrexate, along with intrathecal methotrexate, cytarabine, and dexamethasone, who was tumor-free 68 months later (Medina-Sanson et al. 2006).

11.3.6 Outcome

The prognosis of PCNSL is poor in both adults and children, and the disease is rapidly fatal when untreated. Five-year event-free survival in pediatric patients treated for PCNSL ranges widely from 25 to

70% (McAllister et al. 2000; Abla et al. 2006). Young age has been shown to be a favorable prognostic factor in adults with PCNSL (Bessell et al. 2004). In addition, a series that evaluated chemotherapy alone in pediatric patients showed favorable long-term outcome, suggesting that children may have more chemosensitive tumors, better tolerance of aggressive chemotherapeutic regimens, or biologically different tumors than adults.

11.4 Hemangioblastoma

11.4.1 Epidemiology

Hemangioblastomas are benign, highly vascular tumors arising in the central nervous system. They are uncommon in the general population, accounting for just 1–3% of all intracranial neoplasms, and usually occur between the third and fifth decades of life (De la Monte and Horowitz 1989; Neumann et al. 1989; Glasker and Van Velthoven 2005). In children under the age of 18, these tumors are extremely rare with an incidence of less than 1 per 1,000,000 (Ries et al. 2000; Fisher et al. 2002).

Although hemangioblastomas can occur as sporadic lesions, up to 50% of cases are associated with von Hippel–Lindau disease (VHL) (Latif et al. 1993). This hereditary, autosomal dominant syndrome results from germline mutations on chromosome 3 that cause loss of function of the *VHL* tumor-suppressor gene (Zagzag et al. 2005). This condition predisposes patients to a variety of malignant and benign tumors, including hemangioblastomas, renal cysts and carcinomas, neuroendocrine tumors, and cystadenomas of the reproductive organs. In adults, the average age at diagnosis of VHL-associated hemangioblastomas is about 10 years less than that of sporadic cases (Maher et al. 1990). Therefore, the presence of multiple hemangioblastomas at a young age is highly suggestive of VHL.

11.4.2 Histopathology

Hemangioblastomas are vascular tumors and are composed mainly of normal-appearing capillary endothelial cells. Two additional distinct cellular types are often found, a perivascular endothelial cell with sparse cytoplasm and compact nuclei and a stromal cell with multiple vacuoles and lipid-rich eosinophilic cytoplasm. Two histological subtypes of hemangioblastomas have been described: cellular and reticular. The reticular subtype is more common, but the cellular subtype has been found to have a higher incidence of recurrence (Hasselblatt et al. 2005).

11.4.3 Clinical Features

Most hemangioblastomas are found in the posterior fossa, although children and adolescents with VHL also frequently present with additional tumors in the spinal cord. Symptoms are generally a function of tumor size and anatomical location. Cerebellar lesions may cause ataxia and loss of coordination, brainstem tumors may cause cranial neuropathies or motor deficits, and spinal cord neoplasms initially cause pain followed by neurologic dysfunction. Both intracranial and intraspinal hemangioblastomas occasionally cause spontaneous hemorrhage (Glasker et al. 1999), but the risk of bleeding with tumors smaller than 1.5 cm is virtually zero.

Symptoms are frequently related to the development of tumor-associated pseudocysts. The pathogenesis of these pseudocysts is not known, but it is postulated to be a result of transudation of fluid from tumor capillaries along gray matter near the central canal (Van Velthoven et al. 2003).

11.4.4 Diagnosis and Neuroimaging

Contrast-enhanced MRI is the gold standard for diagnosis of hemangioblastoma (Lee et al. 1989). The tumor is usually hypointense or isointense on pregadolinium T1-weighted studies, and hyperintense on T2-weighted images (Fig. 11.5). Characteristic appearance on contrast CT scan is a uniformly enhancing tumor nodule adjacent to a hypodense cyst. Cerebral and spinal angiography reveals a tumor blush, which may be useful to surgeons in determining vascular supply to the tumor.

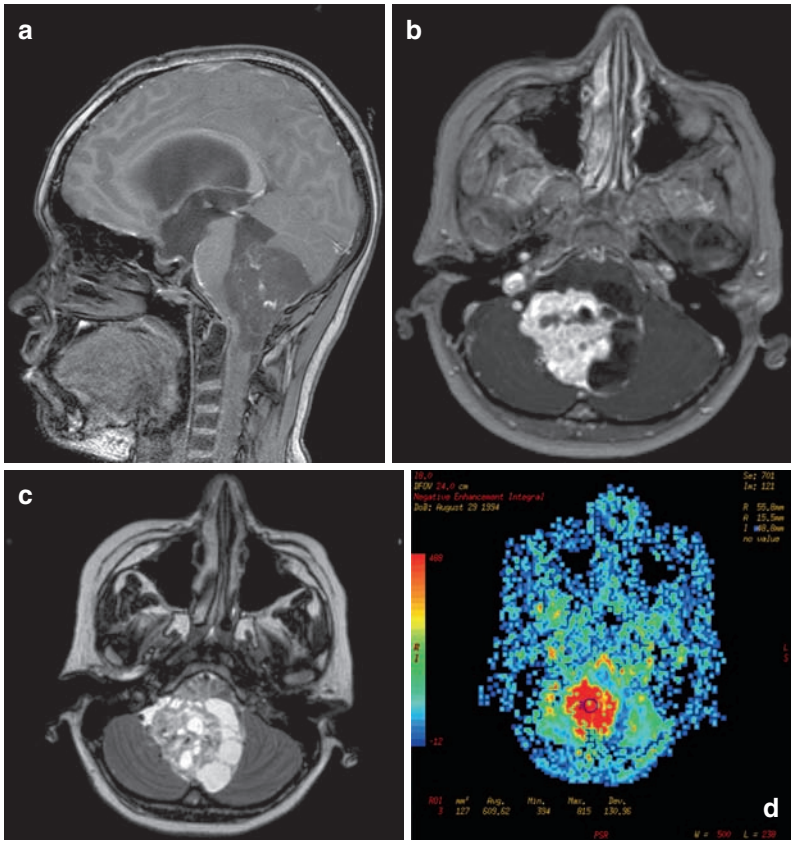


Figure 11.5

A posterior fossa hemangioblastoma in an 8-year-old boy who presented with worsening headaches. (**a**) On this sagittal T1-weighted image, the tumor is noted to fill and obstruct the fourth ventricle and cause hydrocephalus. (**b**) A post-contrast T1-weighted axial image shows a well defined mass arising in the cerebellum. There is a cyst associated with the medial border of the tumor. (**c**) Prominent flow voids which represent large blood vessels are seen along the lateral border of the tumor in this T2-weighted axial image. (**d**) The vascularity of these tumors is emphasized by a perfusion sequence

Because of the high incidence of VHL in pediatric patients with hemangioblastoma, these patients should undergo complete neural axis imaging in order to rule out multiple lesions. It is recommended that they undergo genetic testing for germline mutations of the VHL gene, as this will have consequences for further treatment planning. In addition, abdominal imaging, ophthalmological evaluation, urine analyses for catecholamines, and urological assessment are recommended in order to identify other sequelae of the VHL disease complex.

11.4.5 Treatment

Because hemangioblastomas are generally benign, microneurosurgery is considered the standard of care in adults. Children and adolescents with VHL syndrome, however, may present with multiple tumors that affect the brain and spinal cord, and are therefore rarely cured with surgery. Currently, there is no data on adequate management of these patients. Staged surgical procedures are sometimes recommended in those with symptomatic lesions or tumors with radiographic progression.

Preoperative endovascular embolization in used in adults in order to decrease tumor vascularity and risk of hemorrhage during surgery (Eskridge et al. 1996; Takeuchi et al. 2001); however, this procedure may pose an increased risk of morbidity in children due to smaller vessel caliber. Stereotactic radiosurgery and antiangiogenic therapy have recently been described in adult patients (Niemela et al. 1996; Patrice et al. 1996; Chang et al. 1998; Pan et al. 1998), but no data are available in the pediatric population.

11.4.6 Outcome

Long-term results of hemangioblastoma management are generally favorable. Postoperative outcome for intramedullary and brainstem tumors highly depends on preoperative neurologic status (Lonser et al. 2003; Weil et al. 2003). In one series, surgical morbidity was extremely low in the pediatric population, with no permanent neurologic sequelae sustained (Vougioukas et al. 2006). Complete surgical resection generally results in cure, and partially resected tumors can be controlled with radiosurgery or conventional radiation. In adults, the overall risk of local recurrence is low. However, children and patients with known VHL have higher rates of recurrence after surgical resection. Histological subtype also correlates with hemangioblastoma recurrence, with an 8% recurrence rate among reticular tumors and a 25% recurrence rate in the cellular subtype (Hasselblatt et al. 2005).

11.5 Conclusions

Many rare and unusual CNS tumors arise in children. While their location often determines the presenting symptoms and surgical management, definitive treatment must be individualized. In certain situations, the exact pathologic diagnosis is impossible to determine and treatment is extrapolated from a related tumor type. Caution must be used when stating the prognosis of rare tumors.

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Neurocutaneous Syndromes and Associated CNS Tumors

Sabine Mueller • Daphne Haas-Kogan

Contents

12.1 Introduction

In the Greek language, *Phakos* means spot, mole, or lentil, and phakomatosis suggests the presence of a congenital lesion or birthmark (Berg 1991). Historically, this term was applied to a group of genetic disorders defined by the involvement of the central nervous system (CNS), skin, and one or more body systems. Over time, this group expanded to include over 40 entities, each with its own specific features (Chalhub 1976). This chapter reviews six of the more common neurocutaneous syndromes and the current designation for these disorders, with a particular emphasis on the CNS tumors occurring in each disease: neurofibromatosis types 1 (NF1) and 2 (NF2), tuberous sclerosis (TS), ataxia-telangiectasia (AT), von Hippel–Lindau (VHL), and Sturge–Weber syndrome (SWS). Other comprehensive reviews discuss each entity in detail (Joerger et al. 2005; Korf 2005; Frappart and McKinnon 2006; Pearce 2006; Farrell and Plotkin 2007; Sathornsumetee et al. 2007; Osborne et al. 2008; Savar and Cestari 2008). More up-to-date information on current molecular genetics is also available through the Online Mendelian Inheritance in Man website (http://www.ncbi.nlm.nih.gov/omim/).

Dysplasia caused by specific genetic alterations within normal ectodermal tissue is thought to give rise to the abnormalities seen in the skin and neural tissues of individuals with neurocutaneous syndromes. The same underlying molecular defects predispose affected individuals to further genetic alterations and increased risk of developing a neoplasm. The molecular mechanisms leading to marked variations in disease phenotype remain poorly understood. Clinical characterization of these syndromes has improved, accelerated by advances in imaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (MRI) (Kalantari and Salamon 2008; van Engelen et al. 2008). Imaging is now essential to identify major and minor criteria used to diagnose neurocutaneous syndromes. In many patients, the neuroradiographic features often precede clinically significant findings or patient complaints. Insight into the molecular pathways involved in these disorders lead to multiple target-driven investigational therapies such as the use of rapamycin for seizure control in patient with TS.

Most oncologists should be familiar with the neurocutaneous syndromes for several reasons. First, these patients are at increased risk of developing CNS tumors. Second, the natural history of these tumors may differ from sporadically occurring versions of the same tumors (Listernick et al. 2007; Shamji and Benoit 2007). Finally, the incidence of these inherited syndromes is relatively high. Similar to other genetic syndromes and heritable diseases, great variability exists among patients with phakomatoses due in part to mosaicism, expressivity, and genetic penetrance. Such variability exists among patients afflicted with the same neurocutaneous syndrome, even within a single family. Genotype–phenotype correlation studies have given further insight into these diseases but have been disappointing with regard to predicting outcome based on specifically identified mutations (van Slegtenhorst et al. 1999; Becker-Catania et al. 2000). Further complexity is added by spontaneous mutations that result in neurocutaneous syndromes that lack a family history but incur subsequent risk for patients and their progeny.

12.2 Neurofibromatosis Type 1

12.2.1 Epidemiology

NF1, also known historically as von Recklinghausen's disease, is an autosomal dominant disease with an estimated incidence of 1:3000–4000, equal sex distribution, and no apparent ethnic predisposition (Szudek et al. 2000; Korf 2002). It is one of the most common single-gene disorders, with as many as 50% of cases arising sporadically due to new mutations. The disorder has a high phenotypic inheritance, and therefore, unaffected parents have a low risk of recurrence. Most cases of NF1 can be detected in infancy based on skin abnormalities, which, although subtle, usually intensify with age, especially after puberty. NF1 exhibits nearly 100% penetrance by 8 years of age (DeBella et al. 2000).

12.2.1.1 Genetics and Molecular Biology

The *NF1* gene maps to Chromosome 17q11.2 and consists of 57 constitutive exons spread over 350 kb of genomic DNA. More than 200 different mutations have been observed in patients with NF1 (Pros et al. 2008). The *NF1* gene encodes for a 2818-amino-acid protein referred to as neurofibromin; is expressed in Schwann cells, oligodendrocytes, and neurons; and acts as a tumor-suppressor gene. The protein contains a large amino-acid segment exhibiting homology to the functional domain of the p21ras-GTPase activating protein. p21ras-GTPase inactivates the oncogene p21ras by stimulating its GTPase activity, thus converting the active form of p21ras into its inactive form. Mutations of neurofibromin leading to low or absent expression allow constitutive activation of p21ras and probably account for the many phenotypic abnormalities seen in NF1, including benign and malignant neoplasms. Germline mutation in the *NF1* gene constitutes the first hit in the 2-hit cancer theory. Malignant transformation occurs with additional genetic changes such as *p53* mutation. It has been suggested that such molecular signaling abnormalities may also underlie the learning disabilities well-described in approximately half of all patients with NF1 (Szudek et al. 2000).

12.2.2 Diagnostic Criteria and Clinical Features

The clinical features of NF1 are divided into major and minor subgroups (Table 12.1). The most recognizable clinical feature of NF1 is the café au lait spot, a smooth, nonraised, brown discoloration of the skin, which appears before adulthood in 95% of patients with NF1. Dermal neurofibromas, which arise from Schwann cells occur in >99% of patients. These tumors appear during adolescence and increase in number and size with age. Other manifestations seen in patients with NF1 include axillary freckling, Lisch nodules (pigmented hamartomas of the iris), optic gliomas, and bone dysplasias (Szudek et al. 2000; Korf 2002). Other associated symptoms include macrocephaly, vascular changes, short stature, scoliosis, and learning disabilities. As outlined in an earlier NIH meeting (NIH Consensus Development Conference, Neurofibromatosis: Conference Statement, 1988), the diagnosis of NF1 is made if a patient has met two or more of the following criteria:

Table 12.1. Major and minor features of NF1

Major features	Minor features
Café au lait spots and skin freckling	Macrocephaly
Peripheral neurofibromas	Short stature as growth hormone deficiency found in NF1 patients that do not even have hypothalamic lesions
Lisch nodules (iris hamartomas)	Hypsarrhythmia
Plexiform neurofibromas	Intellectual difficulties (e.g., learning difficulties)
CNS tumors (optic gliomas, spinal neurofibromas)	Epilepsy
Distinctive osseous lesions (ribbon ribs, sphenoid wing dysplasia, pseudoarthroses, or thinning of long bone cortex)	Hypertension – may be due to aortic coarctation, renal artery stenosis, or pheochromocytoma

NIH Consensus Development Conference, Neurofibromatosis: Conference Statement, 1988

1. Six or more café au lait spots (greatest diameter >5 mm if prepubertal, >15 mm if postpubertal)
2. Two or more neurofibromas of any type, or one or more plexiform neurofibromas
3. Freckling in the axilla or inguinal regions (Crowe's sign)
4. Two or more Lisch nodules (iris hamartomas)
5. An optic pathway tumor
6. A distinctive osseous lesion such as sphenoid wing dysplasia, or thinning of the cortex of the long bones with or without pseudoarthroses
7. First degree relative (parent, sibling, or offspring) with NF1 by the aforementioned criteria

There is an increased incidence of specific CNS neoplasms in patients with NF1 (Korf 2000; Rosser and Packer 2002). The most common NF1-associated tumors are optic gliomas, especially chiasmatic gliomas, the majority of which are diagnosed in childhood (Turgut et al. 1991; Balestri et al. 1993). Studies suggest that up to 30% of patients with optic pathway glioma have stigmata of NF1 (Dutton 1994) and 12–20% of patients with NF1 have signs of optic pathway glioma (Listernick and Charrow 2004), suggesting that many NF1 patients are asymptomatic and, therefore, might never be diagnosed. If symptomatic, these tumors may present with decreased visual acuity, visual field defects, proptosis, and precocious puberty due to hypothalamic compression. To date, there is no consensus regarding the frequency of follow-up MRIs required and it can vary from every 3 to 24 months (Listernick et al. 2007). Some studies argue that assessing the visual system is sufficient to follow these patients and that MRI studies are not indicated in patients with no clinical signs of disease progression (Listernick and Charrow 2004; Listernick et al. 2007).

In addition to optic gliomas, NF1 is associated with an increased incidence of parenchymal gliomas, particularly in the brainstem, cerebellar peduncles, globus pallidus, and midbrain. The biologic behavior of brainstem gliomas in patients with NF1 differs significantly from that of lesions with similar appearance in patients without NF1 (Pollack et al. 1996; Listernick et al. 1999). In general, patients with NF1 and brainstem gliomas have better outcomes than nonaffected children (Sevick et al. 1992; Listernick et al. 1994). A recent study identified 23 patients out of 125 with NF1 (18.4%) who presented with brainstem mass lesions. Reported outcome was favorable; 17/23 untreated and 6/23 treated patients were alive with stable or decreased disease burden on MRI at median follow-up of 67 and 102 months, respectively. Only one previously untreated patient experienced disease progression (Ullrich et al. 2007). Brainstem tumors should not be confused with nonspecific white matter changes, which are frequently found on MRI in patients with NF1 and are of unknown clinical significance (Sevick et al. 1992; van Engelen et al. 2008). These unidentified bright objects are normally not associated with mass effect, edema, or contrast enhancement and tend to decrease in size over time. Besides astrocytomas, CNS neoplasms that occur at higher rates in NF1 patients are ependymomas, meningiomas, and medulloblastomas.

NF1 patients develop not only CNS lesions, but also peripheral nervous system tumors. Neurofibromas and schwannomas arise most commonly from major peripheral nerves particularly radial and ulnar nerves. The incidence of symptomatic neurofibromas in NF1 patients is 4% and the incidence of asymptomatic but radiographically evident tumors is >25%. Malignant transformation leads to malignant peripheral nerve sheath tumors. These tumors occur in less than 5% of children with NF1, but are the leading cause of mortality in adults with NF1 (Rasmussen et al. 2001). Malignant peripheral nerve sheath tumors are chemoresistant sarcomas associated with poor 5-year survival rates despite aggressive therapy. The clinical signs associated with malignant transformation are rapid growth and/or pain. Surgical resection remains the mainstay of therapy. The other indication for surgical resection is a large tumor that creates a cosmetic problem. Patients with NF1 are also at risk for non-CNS tumors, including Wilm's tumor, rhabdomyosarcoma, leukemia, melanoma, medullary thyroid carcinoma, and pheochromocytoma.

12.2.3 Natural History and Prognosis

NF1 is a progressive disease that can affect almost any organ (Rasmussen et al. 2001; Korf 2002), and overall survival is less than that of the general population (Sorensen et al. 1986). The causes of death in NF1 patients include malignant peripheral nerve sheath tumors, CNS tumors, and systemic conditions such as hypertension due to the associated vasculopathies leading to renal artery stenosis. Patients with NF1 are 34 times more likely to have malignant connective tissue or soft tissue neoplasms than non-NF1 individuals (Rasmussen et al. 2001).

12.2.4 Laboratory Studies

A wide variety of mutations in the NF1 gene have been identified. Current molecular technology is

able to identify NF1 mutations in greater than 95% of cases (Messiaen et al. 2000). To date, the majority of cases are identified on a clinical basis, and therefore genetic testing should be reserved when there is uncertainty in the clinical diagnosis. Prenatal diagnosis is also available for couples with a positive family history of NF1.

12.2.5 Imaging Studies

On CT head scans, the characteristic features of an optic glioma are often visible. These include fusiform enlargement of the optic nerve(s), optic tract, and/or optic chiasm. Remodeling of the optic canal and medial sphenoid wing may also be present. Sphenoid wing dysplasia is usually associated with plexiform neurofibroma and bupthalmos (Balestri et al. 1993; Mukonoweshuro et al. 1999; Fischbein et al. 2000; Kornreich et al. 2001).

With MR brain imaging, optic nerve gliomas are easily visible with enlargement of the optic nerve(s), chiasm, and/or optic tract (Fig. 12.1). Asymptomatic optic gliomas are present in up to 20% of NF1 patients. The extent of involvement is often underestimated with T1-weighted images, while T2-weighted images provide better representation of the involved areas. Contrast enhancement can occur and may be heterogeneous or homogeneous. Brainstem gliomas are relatively common (Aoki et al. 1989; Balestri et al. 1993; Mukonoweshuro et al. 1999; Kornreich et al. 2001; Fischbein et al. 2000). Parenchymal tumors (usually astrocytomas) have a predilection for the thalami and basal ganglia and appear as T2 prolonging mass lesions with variable post gadolinium enhancement.

Nonenhancing foci of T2 prolongation within deep gray nuclei and the white matter may represent myelin vacuolization. These are most common in the globus pallidus, followed by the cerebellum and brainstem, internal capsules, centrum semiovale, and corpus callosum and occur in up to 60% of NF1 patients (Fig. 12.2). The T2-weighted signal characteristics are variable.

12.2.6 Treatment

Patients with NF1 should have a thorough annual physical examination including visual field testing. Although the value of screening imaging studies is not proven, most patients at some point undergo a screening MRI of the brain and spine. Even if a mass is identified, treatment focuses on symptomatic lesions (Turgut et al. 1991; Pollack et al. 1996). Most optic pathway gliomas associated with NF1 are asymptomatic and some have been noted to regress spontaneously (Parsa et al. 2001). Pathologically, these tumors are mainly pilocytic astrocytomas, classified as WHO grade I, with more indolent clinical courses than in non-NF1 patients. The role of surgery in patients with optic pathway gliomas remains controversial.

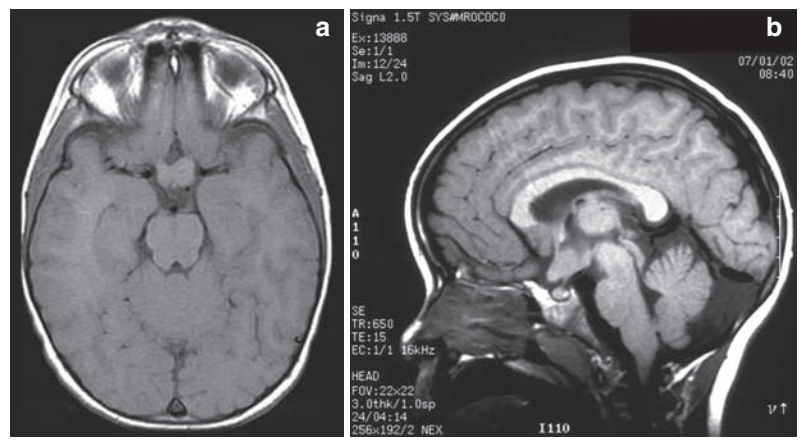

Figure 12.1
Optic pathway gliomas associated with NF1. (**a**) The T1-weighted axial images show asymmetry of the optic chiasm with the right optic nerve being larger than the left. The mass did not enhance following gadolinium administration. (**b**) A sagittal T1-weighted image shows the thickened chiasm directly above the pituitary gland

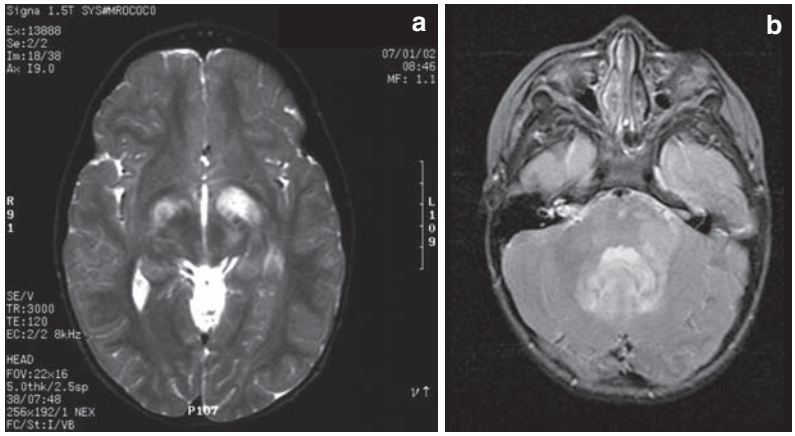

Figure 12.2

White matter lesions associated with NF1. These lesions are best seen on T2-weighted images. (**a**) In this axial image, there are bilateral lesions (larger on the patient's left side) within the basal ganglia that do not produce much mass effect. These lesions do not enhance following gadolinium administration. (**b**) Similar lesions may be seen in the posterior fossa. Here, the area of T2 prolongation extends from the cerebellar peduncle towards the pons

Consensus for surgical intervention exists for single-nerve lesions, which cause disfiguring symptoms for patients. Surgery might also be beneficial if there are signs of increased intracranial pressure, mass effect, or hydrocephalus (Medlock et al. 1997; Astrup 2003). Rapidly growing tumors, more frequently located in the hypothalamus and chiasm, benefit from early surgical resection to preserve vision and reduce mass effect (Listernick et al. 2007). Radiation therapy is discouraged in patients with NF1, mainly due to the development of neurovascular, endocrine, and neuropsychological side effects as well as the high risk of developing secondary malignancies (Grill et al. 1999; Sharif et al. 2006). One study showed that 3 out of 5 patients with NF1 and optic pathway glioma, who were treated with radiation therapy for disease progression developed a secondary CNS tumor, whereas none of the patients with sporadic tumors developed a secondary tumor (Singhal et al. 2002). Slow enlargement of optic pathway gliomas clearly demonstrated on serial imaging studies and accompanied by symptoms can be managed by systemic chemotherapy. A large Phase II study found that 22 NF1 patients with low-grade gliomas who were treated with chemotherapy had better overall survival than non-NF1 patients (Gururangan et al. 2002). Patients were treated if they met one or more of the following criteria: (a) >25% increase in the size of the tumor (Fig. 12.3a, b), (b) papilledema, (c) loss of vision, (d) increase in proptosis, or (e) increase in the diameter of the optic nerve >2 mm.

Usually, protocols tailored for low-grade astrocytic tumors are used (see Chap. 1). Surgery is often required for plexiform neurofibromas that have become disfiguring or painful, but new biologic-based approaches are currently under study (Babovic-Vuksanovic et al. 2007). See http://www.ctf.org for ongoing NF1 patient trials.

12.3 Neurofibromatosis Type 2

12.3.1 Epidemiology

NF2 is inherited in an autosomal dominant manner with an incidence of 1:37,000 and has no gender predilection (Mautner et al. 1993; Parry et al. 1994). Generally NF2 patients become symptomatic at puberty or thereafter, but age of onset is highly variable. The

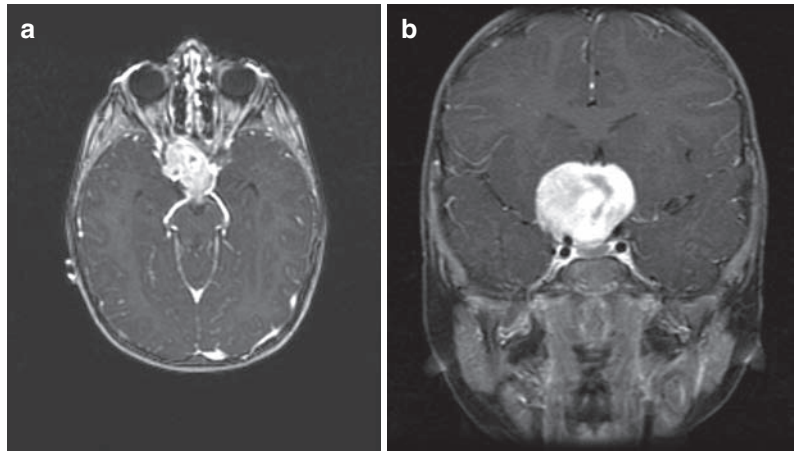

Figure 12.3

Large optic pathway glioma in a patient with NF1. This 3-year-old-girl presented with visual loss and was noted to have an extremely large optic glioma as seen on axial (**a**) and coronal (**b**) T1-weighted images following contrast administration. The optic chiasm and nerves cannot be differentiated from the tumor. Because of the degree of visual loss, the patient underwent biopsy to confirm the diagnosis and then was started on chemotherapy

mean age of onset of symptoms is approximately 17 years, usually with tinnitus and/or acute hearing loss due to vestibular tumors.

12.3.2 Molecular Biology and Cytogenetics

The *NF2* gene is located on Chromosome 22q12 and the protein consists of 595 amino acids. It was identified in 1993 in two different laboratories, and named *merlin* and *schwannomin* (Rouleau et al. 1993; Bianchi et al. 1994). The name merlin refers to a high degree of homology with a family of F-actin binding proteins including *m*oeisin, *e*zrin, and *r*adixin (De Vitis et al. 1996a, b) .

Merlin localizes at the cell membrane and acts as a membrane-cytoskeletal linker. It can revert Ras-induced malignant phenotypes, indicating that the *NF2* gene product is a tumor-suppressor protein. Despite considerable efforts to identify its functions, it remains unclear if any of the known merlin-regulated signaling pathways are keys to the development of NF2-associated tumors (Scoles 2008). Mutations leading to the loss of merlin expression are the most common gene defect in meningiomas. A total of 50–60% of all spontaneous meningiomas and NF2-associated meningiomas have mutations in the *NF2* gene. Schwannomas are caused by loss of merlin expression, whereas only 29–38% of ependymomas show alteration in merlin expression (Lamszus et al. 2001; Rajaram et al. 2005). Mutations of the *NF2* gene occur not only in neoplasms associated with NF2, but also in 30% of melanomas and 41% of mesotheliomas (De Vitis et al. 1996a, b). It remains unclear why *NF2* mutations predispose to the formation of bilateral vestibular schwannomas.

Recently, a third disorder within neurofibromatosis was distinguished as schwannomatosis. This disorder is characterized by the presence of schwannomas of cranial nerves other than the vestibular nerve. The gene has been mapped to chromosome 22 near the *NF2* locus but appears to be distinct from *NF2* (MacCollin et al. 2003).

12.3.3 Diagnostic Criteria and Clinical Features

Clinical criteria are used to diagnose NF2 (Table 12.2). Bilateral vestibular schwannomas, which are characteristic lesions in patients with NF2, usually present

Table 12.2. NF2 diagnostic criteria

Clinical features (one of the following)	Or, two of the following
Bilateral eighth cranial nerve masses (vestibular schwannomas) seen with imaging techniques	Multiple meningiomas
A first-degree relative with NF2 and unilateral vestibular schwannoma or any two of: neurofibroma, glioma, meningioma, schwannoma, juvenile posterior subcapsular lenticular opacity	Unilateral vestibular schwannoma Neurofibroma, schwannoma, glioma, cerebral calcification, or subcapsular lens opacity

NIH Consensus Development Conference, Neurofibromatosis: Conference Statement, 1988

with tinnitus and/or hearing loss (Uppal and Coatesworth 2003). These tumors are found in 96% of NF2 patients; bilateral in 90%, and unilateral in 6%. Vestibular schwannomas were formerly called acoustic neuromas, an inaccurate term because they arise from Schwann cells and typically involve the vestibular rather than the acoustic (cochlear) branch of the eighth cranial nerve. NF2 patients exhibit an overall predilection for tumors of the meninges and Schwann cells, and may also present with facial nerve, trigeminal nerve, and multiple spinal nerve schwannomas, as well as meningiomas and retinal hamartomas. Symptoms at time of presentation include hearing loss, tinnitus, and disequilibrium from vestibular schwannomas. Age at onset of symptoms ranges from 15 to 74 years. The NF2 patients under 10 years of age present most commonly with visual deficits or rapidly growing skin tumors.

NF2 patients develop other central neurofibromas including paraspinal tumors that may compress the spinal cord and present with myelopathy. These lesions are surprisingly common (67–90%) in patients with NF2 and are a source of major morbidity and mortality (Mautner et al. 1995; Dow et al. 2005). Additional lesions associated with NF2 include posterior subcapsular cataracts (63%), retinal hamartomas, optic nerve-sheath meningiomas, meningiomas, ependymomas (usually spinal cord), gliomas, and trigeminal schwannomas (Mautner et al. 1996).

12.3.4 Natural History and Prognosis

The mean age of onset of symptoms is 17 years, while the mean age of NF2 diagnosis is 22 years. Relentless progression of vestibular schwannomas and other tumors may lead to loss of vision, paresis, and eventual death from brainstem compression (Parry et al. 1994). The prognosis for *NF2* patients is variable, as a spectrum of phenotypes exists. The type of mutation in the *NF2* gene influences the disease severity. Constitutional nonsense and frameshift mutations that cause protein truncation confer a poorer phenotype (Baser et al. 2004). Early detection offers distinct advantages to the patients as hearing preservation remains a challenge. The diagnosis of NF2 increases the likelihood of developing CNS tumors (schwannomas, meningiomas, gliomas, and neuromas) that may involve the brain, cranial nerves, or spinal cord.

12.3.5 Laboratory Studies

Laboratory diagnosis relies on the presence of DNA mutation in the *NF2* gene, and requires linkage studies from DNA derived from at least two affected family members.

12.3.6 Imaging Studies

Schwannomas on CT head scanning are round or ovoid extra-axial masses. They are iso-to mildly hypodense on noncontrast CT scan, unless cystic or hemorrhagic. Meningiomas are dural-based, extra-axial masses, often with an associated dural tail. They are typically isodense to brain on nonenhanced CT scan (Aoki et al. 1989; Mautner et al. 1996; Fischbein et al. 2000).

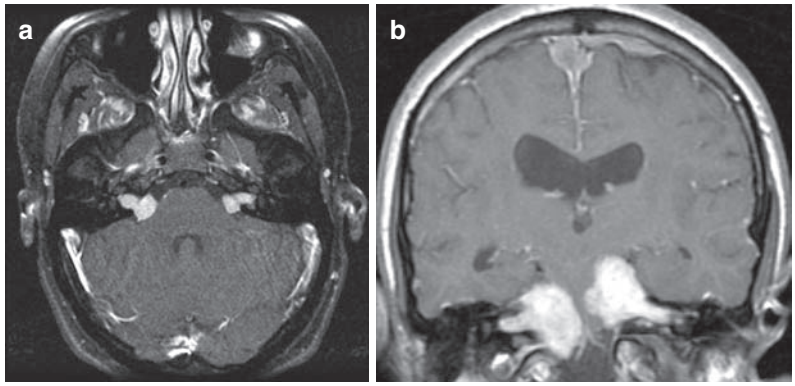

Figure 12.4

NF2 tumors. (**a**) Typical appearance of bilateral vestibular schwannomas in a teenage girl. On this fat-suppressed T1-weighted axial image, the tumors are clearly seen arising from the internal acoustic meatuses on either side. (**b**) This patient has much larger bilateral schwannomas although convexity and falcine meningiomas are also visualized

On MR imaging, schwannomas are iso- to mildly hypointense compared to brain parenchyma on T1-weighted images. They are iso- to hyperintense to brain parenchyma on T2-weighted images. Intense homogeneous enhancement after contrast administration is typically seen (Fig. 12.4a), although areas of cystic change or hemorrhage may lead to heterogeneous enhancement. Large lesions may cause brainstem compression and/or hydrocephalus. Similar to schwannomas, meningiomas are isointense to gray matter on T1- and T2-weighted images. They usually enhance intensely and homogeneously following gadolinium administration, and calcifications are common (Fig. 12.4b) (Mautner et al. 1996; Fischbein et al. 2000).

12.3.7 Treatment

The best approach to the management of schwannomas remains controversial. These tumors generally progress slowly, and if small and asymptomatic, patients can be followed by serial imaging studies. Any progression of symptoms such as hearing loss may be considered failure of conservative management. Vestibular schwannoma surgery is challenging and often is performed by multidisciplinary teams of neurosurgeons and neuro-otologists. Recently, radiosurgery has become more popular in the management of vestibular schwannomas. The main goal of radiosurgery is tumor control, which is accomplished in 89–100% of cases. Outcomes for hearing preservation are similar to those reported from surgical studies, ranging from 50 to 89% (Myrseth et al. 2007). A recent retrospective study (Moffat et al. 2003) spanning 17 years concluded that surgery unequivocally offered superior tumor control over stereotactic radiosurgery (Gamma Knife®, Elekta AB), when hearing preservation and facial nerve function were the endpoints studied. Half of the tumors in this study were treated conservatively with annual surveillance alone and did not require intervention. In another study (Samii 1995), the hearing preservation rate following surgical resection for 74 NF2 patients with bilateral tumors was 36%, while another group (Brackmann et al. 2001) reported 42.5% hearing preservation with early proactive surgical intervention. Others report that stereotactic radiosurgery is a safe and effective treatment for NF2 tumors, and may in fact have better rates of hearing preservation (approximately 43%) (Subach et al. 1999). Patients with small vestibular schwannomas can suffer deafness without imaging changes in tumor size (Walsh et al. 2000). Recently,

erlotinib, an EGFR inhibitor, has been reported to be effective in the treatment for progressive vestibular schwannomas (Plotkin et al. 2008). The use of EGFR inhibitors in the treatment of vestibular schwannomas is based on the finding that merlin associates with EGFR via a scaffold protein and prevents signaling. In patients with NF2 and mutated merlin, this pathway cannot be down regulated (Curto et al. 2007). At this time, more clinical experience is warranted to better define the most effective treatment(s) and key criteria for initiating therapy.

12.4 Tuberous Sclerosis Complex

12.4.1 Epidemiology

Tuberous sclerosis complex (TSC), previously known as Bourneville's disease, is an autosomal dominant disorder with a growing incidence currently estimated to be 1:6000 to 1:9000 due to improved diagnostic tests (Roach and Sparagana 2004). There is no race or gender predilection and onset of symptoms varies from infancy to late childhood (Roach et al. 1998; Sparagana and Roach 2000).

12.4.2 Molecular Biology and Genetics

TSC is genetically heterogeneous with two implicated genes: TSC1 on chromosome 9q34 encodes hamartin, a 130 kDa tumor-suppressor protein; and TSC2 on chromosome 16p13 encodes tuberin, a 200 kDa tumor-suppressor protein. Both proteins form a ubiquitous intracellular complex called the TSC complex, which is involved in many cell regulatory processes.

Through the GTPase-activating function of tuberin, the TSC tumor suppressor complex drives the small GTPase, termed Ras homolog enhanced in brain (Rheb), into the inactive guanosine diphosphate-bound state. Rheb in the guanosine triphosphate-bound active state is a positive effector of *m*ammalian *t*arget *o*f *r*apamycin (mTOR). Mutations in either hamartin or tuberin drive Rheb into the guanosine triphosphate-bound state, which results in constitutive mTOR signaling. mTOR appears to mediate many of its effects on cell growth through the phosphorylation of the ribosomal protein S6 kinases (S6Ks) and the repressors of protein synthesis initiation factor eIF4E, the 4EBPs. The S6Ks act to increase cell growth and protein synthesis, whereas the 4EBPs serve to inhibit these processes. mTOR interacts with the S6Ks and 4EBPs through an associated protein, raptor.

Mutation of tuberin or hamartin leads to constitutive activation of mTOR, which results in the hamartomatous lesions in the brain, kidney, heart, lung, CNS, and other organs of the body. More aggressive tumors, such as angiomyolipomas, can also arise. Such mutations are commonly found in patients with TSC, but one third of clinically diagnosed patients have no discernable mutation (Jones et al. 2000). This might be in part due to somatic mosaicism. Reasons for the clinical variability associated with identical mutations remain elusive. Recent reports suggest that patients with mutations in *TSC1* gene are less severely affected than patients with mutations in the *TSC2* gene, a finding that provides some help when counseling parents (Jansen et al. 2008).

12.4.3 Diagnostic Criteria and Clinical Features

TSC is characterized by seizures, behavioral problems, mental retardation, and development of benign tumors (hamartomas) in multiple organs. The classic TSC triad consists of seizures, mental retardation, and adenoma sebaceum (Hanno and Beck 1987; Curatolo 1996; Roach et al. 1998). Adenoma sebaceum are pathologically best characterized as facial angiofibromas. In infants, the combination of depigmented areas of skin, infantile spasms, and delayed development is diagnostic of TSC. The CNS lesions seen with TSC include cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas (SEGA). Cortical tubers present a hallmark for the disease. They form during development and represent a disorder of neural proliferation. A variety of clinical criteria are used to establish the diagnosis of TSC (Table 12.3). For a definite diagnosis of TSC, either two major features or one major feature and two minor features must be present. For a probable diagnosis of TSC, one major feature or two or more minor features must be present.

Table 12.3. Diagnostic criteria for tuberous sclerosis (Roach et al. 1998)

Major features	Minor features
• Facial angiofibromas or forehead plaque • Nontraumatic ungula or periungual fibroma • Hypomelanotic macules (≥3) • Shagreen patch (connective tissue nevus) • Multiple retinal nodular hamartomas • Cortical tuber – when cerebral cortical dysplasia and cerebral white matter migration tracts occur together, they should be counted as 1 rather than 2 features of TSC • Subependymal nodule • Subependymal giant cell astrocytoma • Cardiac rhabdomyomas, single or multiple • Lymphangiomyomatosis – when both lymphangiomyomatosis and renal angiomyolipomas are present, other features of TSC should be present before a definite diagnosis is assigned • Renal angiomyolipomas – when both lymphangiomyomatosis and renal angiomyolipomas are present, other features of TSC should be present before a definite diagnosis is assigned	• Multiple randomly distributed pits in dental enamel • Hamartomatous rectal polyps – histologic confirmation is suggested • Bone cysts – radiologic confirmation is sufficient • Cerebral white matter radial migration lines – radiologic confirmation is sufficient; one panel member felt strongly that ≥3 radial migration lines should constitute a major sign • Gingival fibromas • Nonrenal hamartoma – histologic confirmation is suggested • Retinal achromic patch • Confetti skin lesions • Multiple renal cysts – histologic confirmation is suggested • Cardiac rhabdomyomas: some neonates may present with congestive heart failure • Macrocephaly • Multiple ungual fibromas – fleshy lesions arising from around or underneath the nails; more in toes than fingers and more in girls than boys; seen in 15–20% of TSC patients, but usually not seen before adolescence • Retinal hamartomas • Renal angiomyolipomas and cysts

Epilepsy is the most common neurological symptom associated with TSC, present in 60–90% of cases, and often beginning in the first year of life (Jozwiak et al. 2000; Thiele 2004). In one analysis of 105 patients diagnosed with TSC, 47% had abnormal cognitive function that was associated with refractory seizures and mutations in the *TSC2* gene (Winterkorn et al. 2007). The prevalence of autism in TSC is estimated to be 1–4% and is greater in children that carry mutations in the *TSC2* gene (Holmes and Stafstrom 2007).

Hypomelanotic lesions, ash-leaf macule depigmented nevi resembling vitiligo may be noted at birth and can be seen in more than half of TSC patients before 2 years of age. These are best visualized with ultraviolet light (Wood lamp). Ash leaf spots are seen in up to 90% of patients with TSC. Facial angiofibromas (adenoma sebaceum) skin lesions consist of vascular and connective tissue elements. The red papular rash typically extends over the nose and down the nasolabial folds toward the chin, cheeks, and malar regions. Skin lesions gradually enlarge, manifesting in 12% of affected children by 1 year of age, 40% by 3 years of age, and ultimately in as many as 80% of TSC patients (Hanno and Beck 1987; Curatolo 1996; Roach et al. 1998).

12.4.4 Natural History and Prognosis

The leading cause of morbidity and mortality in TSC patients is caused by neurologic manifestation of the disease followed by renal complications (Franz 2004). Refractory epilepsy is common and leads to poor cognitive outcome (Winterkorn et al. 2007). SEGAs can cause hydrocephalus and require surgical intervention (Cuccia et al. 2003). Additional abnormalities occur in the eyes, skin, kidneys, bones, heart, and lungs. Prognosis varies with the individual manifestations of the disease. Major causes of death in a large TSC Scottish cohort were renal disease, followed by brain tumors, pulmonary lymphangiomyomatosis, status epilepticus, and bronchopneumonia (Shepherd and Stephenson 1992). In severe cases, death occurs in the second decade of life (Curatolo 1996; Webb et al. 1996; Sparagana and Roach 2000).

12.4.5 Laboratory Studies

Molecular genetic testing has become available in clinical practice over the last several years. Often molecular testing is helpful in young patients who are less than 2 years, since many of the clinical signs

are not present until later in life. Various molecular assays reveal the presence of a mutation in 62.4–80% of cases (Jones et al. 1999; Dabora et al. 2001; Au et al. 2004; Sancak et al. 2005).

12.4.6 Imaging Studies

Clinical criteria are commonly used to establish the diagnosis of TSC and a head CT scan is performed as a confirmatory test. Approximately, 95% of patients with clinical features of TSC have abnormalities on CT scans (Menkes and Maria 2000). Typically, there are hypodense subependymal nodules lining the ventricles (Fig. 12.5a), usually calcified after the first year of life, and 50% of affected individuals demonstrate calcified cortical hamartomas. SEGAs located at or near the foramen of Monro enhance brightly following contrast administration. Calcified subependymal and cortical nodules are seen in 95% of individuals with TSC, leaving CT as a simpler diagnostic tool than MRI by obviating the need for general anesthesia in children (Braffman et al. 1990; Menor et al. 1992; Mukonoweshuro et al. 1999; Fischbein et al. 2000).

Brain MRI is preferable for defining the exact number and location of cerebral cortical and subcortical tubers, white matter lesions, and areas of heterotopias (Braffman et al. 1990; Menor et al. 1992; Mukonoweshuro et al. 2001; Fischbein et al. 2000). Tubers or sclerotic white patches involving the gyri or white matter occur mostly in the cerebrum, while cerebellar, brainstem, and spinal cord lesions occur less commonly. Cortical tubers and hamartomas change in appearance as the brain myelinates. They are initially hyperintense on T1-weighted images and hypointense on T2-weighted images, but as brain myelination progresses, this imaging pattern reverses. White matter lesions appear as hyperintense

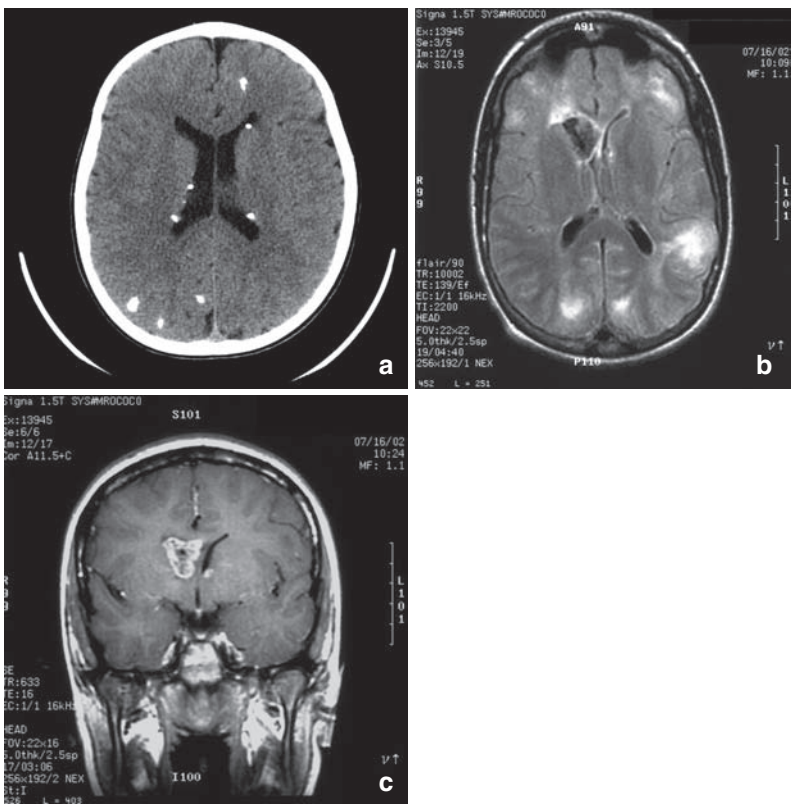

Figure 12.5

Tuberous sclerosis complex. (**a**) Axial CT image of multiple calcified subependymal nodules. Other calcifications are also seen within the cortex. (**b**) Bilateral cortical tubers of varying sizes and a frontal subependymal giant cell astrocytoma (SEGA) are seen on this T2-weighted image. (**c**) A postcontrast T1-weighted coronal image from the same patient demonstrates the proximity of the tumor to the foramen of Monro

linear bands in cerebrum and cerebellum. In infants, bands are hypointense to unmyelinated white matter on T2-weighted images and are hyperintense to white matter in older children and adults (Fig. 12.5b). SEGAs at or near foramen of Monro display intense postcontrast enhancement, although the pattern can be heterogeneous (Fig. 12.5c). MR spectroscopy can be useful to distinguish them from cortical tubers.

PET/MRI fusion imaging has been studied to identify epileptogenic tubers with great promise for improving surgical cure rates for intractable epilepsy (Chandra et al. 2006).

12.4.7 Treatment

TSC affects multiple organs and treatment recommendations vary according to each specific organ manifestation. Patients with TSC should undergo neuroimaging at time of diagnosis and every 1–3 years until the age of 20. Renal ultrasound to assess angiolipomas and renal cysts should be performed every 1–3 years (Roach et al. 1999). Other tests to consider include electrocardiogram, neuropsychological testing, chest CT scan, and ophthalmological examination. Medical management of TSC can prove challenging, with 75–90% of patients displaying focal or generalized seizures, many refractory to treatment. In addition to antiepileptic agents, surgical options for control of intractable seizures are gaining attention. In selected cases, surgical resection of dominant seizure foci that have an established concordance of neuroimaging and electrophysiological and clinical findings can be effective in achieving seizure control. SEGAs are in general slow-growing tumors, and mainly require intervention if they cause symptoms (e.g., hydrocephalus). Surgical resection remains the mainstay of therapy with good long-term survival rates. Clinical trials are ongoing to investigate the role of m-TOR inhibitors, including rapamycin and its derivatives temsirolimus and everolimus, in the treatment of these tumors as well as for seizure control. In a recent exciting publication, investigators from University of Cincinnati reported that rapamycin led to regression of astrocytomas associated with TSC. Five patients with TSC and either SEGAs ($n=4$) or pilocytic astrocytoma ($n=1$) were treated with oral rapamycin at standard immunosuppressive doses (serum levels 5–15 ng/mL) from 2.5 to 20 months. Although all lesions had shown growth on serial scans prior to initiation of therapy, treatment with rapamycin resulted in tumor regression in all 5 patients, launching new avenues for the nonsurgical approach to treating TSC-associated lesions (Fouladi et al. 2007).

12.5 Ataxia-Telangiectasia

12.5.1 Epidemiology

Ataxia telangiectasia (AT) is an autosomal recessive disorder with an incidence of 1:40,000 to 1:80,000 and equal predilection in both sexes. Patients with AT may present during infancy with ataxia without any cutaneous manifestations, which may become apparent after 2 years of age (Gosink et al. 1999; Lavin 1999).

12.5.2 Molecular Biology and Genetics

The gene for AT has been mapped to the long arm of chromosome 11 (11q23.3). The Ataxia Telangiectasia Mutated (*ATM)* gene is very large with 66 exons spanning 150 kb of the genome, which renders mutation analysis challenging (Bakkenist and Kastan 2003). The *ATM* gene product is a member of the phosphatidylinositol 3-kinase (PI3-kinase) family and is activated by autophosphorylation in response to DNA double strand breaks. It contains a PI3-kinase domain, a putative leucine zipper, and a proline-rich region. The ATM protein detects DNA double strand breaks and activates a number of substrates including p53, chk-2, nibrin, and BRCA1 (Kastan and Lim 2000; Shiloh 2003). ATM plays an important role in cellular responses to DNA damage, cell-cycle control, and maintenance of telomere length.

Over 300 different mutations have been identified in AT patients. Database screening has revealed that most mutations are unique to a given family. Mutations are distributed anywhere in the gene and no hotspots or high frequency mutations have been

reported (Concannon and Gatti 1997; Mitui et al. 2003). Almost 85% of mutations are of the premature truncation type, making the majority null mutations. Missense mutations occur in 10% of the known mutations among AT families (Chun and Gatti 2004).

12.5.3 Diagnostic Criteria & Clinical Features

AT is the most common ataxia in infancy (Kamiya et al. 2001), although the initial manifestations of cerebellar ataxia may not be noted until early walking. AT is a common cause of progressive ataxia in children younger than 10 years of age, second only to tumors of the posterior fossa. Ataxia is generally the presenting symptom of AT. Oculomotor apraxia is a distinguishing feature of the disease, which is often present prior to the cutaneous findings.

Teleangiectasias are a second major clinical manifestation of the disease (Table 12.4). Progressive oculocutaneous telangiectasias represent a key feature of AT. Bulbar conjunctivae telangiectasias first appear between 2 and 8 years of age and subsequently involve ears, eyelids, malar prominences, neck, antecubital and popliteal fossae, as well as dorsum of hands and palate. Initially they appear as bright-red, thick, symmetrical streaks that resemble atypical conjunctivitis and only later become frank telangiectasias. These skin lesions become more prominent with sunlight exposure and age. Premature aging of hair and skin is frequent.

Patients with AT have a high tendency to develop chronic sinopulmonary infections. The immunodeficiency involves both cellular and humoral immunity. Absence of the tonsils, adenoids, lymphoid tissue, and thymus gland is commonly seen in AT. The incidence of cancer in AT is approximately 100-fold higher than in matched populations. These neoplasms consist of Non-Hodgkin's lymphoma, leukemia, and other solid tumors.

Table 12.4. Clinical features for ataxia telangiectasia (Menkes and Maria 2000)

Clinical features
Slowly progressive cerebellar ataxia
Choreoathetosis
Telangiectasia of skin and conjunctiva
Susceptibility to sinobronchopulmonary infections
Cancer (Non-Hodgkin's lymphoma, leukemias, solid tumors)

12.5.4 Natural History and Prognosis

Neurologic deterioration is progressive, and by the end of the first decade of life, children are confined to wheelchairs with myoclonic jerks, drooling, choreoathetosis, oculomotor abnormalities, and dysarthric speech (Paller 1987). Eighty-five percent of AT patients develop choreoathetosis, apraxia of eye movements, and nystagmus. The progressive cerebellar neurodegeneration is the most debilitating feature of AT. Over time patients also develop peripheral neuropathy and eventually spinal muscular atrophy. Intelligence is usually normal in young children but deteriorates with disease progression (Menkes and Maria 2000).

Growth retardation occurs in 72% of patients with AT. Progeric changes have been noted in almost 90% of AT patients with early loss of subcutaneous fat, loss of skin elasticity, and premature graying of hair by adolescence (Paller 1987). AT patients are immunodeficient with compromised humoral immune surveillance and cellular immunity. Specifically, AT patients have IgA deficiencies that predispose them to infectious agents that enter through exposed sites. Consequently, they tend to suffer recurrent bacterial and viral sinopulmonary infections that can be life-threatening (Paller 1987).

Children with AT have an increased incidence of cancer, primarily lymphoid tumors, due to acute sensitivity to ionizing radiation and defective cell-cycle checkpoints (Kamiya et al. 2001). AT patients are 40–100 times more likely to develop leukemias, lymphomas, lymphosarcomas, and Hodgkin's disease, leading to neoplastic development in 30% of patients. Lymphoreticular malignancies predominate in younger patients, whereas epithelial malignancies occur most frequently in adult patients (Paller 1987).

Some penetrance appears in AT heterozygotes leading to intermediate radiosensitivity and increased risk of cancer, particularly breast cancer. ATM heterozygotes have a nine-fold increased risk of developing

breast cancer, characterized by bilateral disease and early age of onset (Lavin et al. 1999). Not surprisingly, death frequently occurs in late childhood or early teenage years. Mean age of death is 14 years (Kamiya et al. 2001) due to malignancy or complications from pulmonary infection and respiratory insufficiency.

12.5.5 Laboratory Studies

Highly elevated serum α-fetoprotein is detected in nearly 95% of AT cases, and this laboratory marker often precedes the appearance of telangiectasias by several years (Menkes and Maria 2000). Patients may display elevated levels of carcinoembryonic antigen (CEA) and low or absent total IgA or IgE levels. Markedly decreased serum IgA (<80 mg/L) and IgE (<3 mg/L) levels are seen in 70–90% of AT patients. Conversely, IgM, IgG1, and IgG3 levels tend to be high (Menkes and Maria 2000). Elevated hepatic transaminases are seen in 40–50% of patients, and glucose intolerance is seen in 50% of patients. An unusual form of adolescent diabetes is observed in which hyperglycemia occurs with rare glycosuria, absent ketosis, insulin hypersecretion, and peripheral insulin resistance.

Chromosomal abnormalities occur 2–18 times more frequently in AT patients than in normal individuals, with chromosomal abnormalities observed in 80% of AT patients. Rearrangements of chromosomes 7 and 14, and especially 14:14 translocations may anticipate the development of lymphoreticular malignancies (Lavin et al. 1999). Analysis of amniotic fluid allows prenatal diagnosis using measurements of α-fetoprotein and high-resolution chromosomal analysis. New ATM protein and enzyme assays are in development, but not yet commercially available.

12.5.6 Imaging Studies

MRI of the brain is normal with a well-formed cerebellum for many years after onset of ataxia. By 10 years of age, volume loss of the cerebellum often becomes apparent. Posterior fossa abnormalities include cerebellar atrophy, particularly of the anterior vermis, atrophy of the dentate and olivary nuclei; spine MRI demonstrates degeneration of the posterior columns. These imaging findings correlate with well-described neuropathologic features of AT. In the cerebellum, there is a reduction in Purkinje cell number and atrophy of dentate nuclei. In addition, there is atrophy of anterior horn cells, demyelination of gracile fasciculi in the spinal cord, and appearance of nucleocytomegalic cells in the anterior pituitary.

12.5.7 Treatment

To date, there is no therapy available to cure or prevent progress of the disease, and interventions are mainly supportive. These efforts include prophylactic therapy for infections. Antibiotics and plasma gamma globulin infusions have been utilized for IgA deficiencies and intercurrent sinopulmonary infections. Thymus gland and bone marrow transplantations have been reported as well. Judicious use of sunscreen is warranted to retard actinic-like skin progeric changes. Radiation therapy and radiomimetic chemotherapeutic agents should be avoided in treating lymphoreticular malignancies. Early pulmonary physiotherapy and physical therapy appropriate for the neurologic dysfunction should be instituted. Many treatments employed for ataxia, including acetylcholine, γ-aminobutryic acid, dopamine, diazepam, chlordiazepoxide, trihexyphenidyl, diphenhydramine, and haloperidol have been ineffective. A patient disabled with an extremely severe involuntary movement disorder responded well to dantrolene, a hydantoin compound. Unfortunately, to date, no specific treatment prevents the neurologic progression of AT (Paller 1987; Lavin et al. 1999). Neoplastic processes that require aggressive treatment with chemotherapy or radiation present a formidable challenge, given the high vulnerability to further oncologic insults in AT patients.

12.6 Von-Hippel Lindau Syndrome

12.6.1 Epidemiology

VHL is an autosomal dominant disorder with an incidence of 1:40,000 (Maher and Kaelin 1997). It exhibits 90% penetrance and equal incidence in males and females. Generally, VHL does not present

during childhood, but more often during the second or third decade of life (Singh et al. 2001).

12.6.2 Molecular Biology and Cytogenetics

The VHL gene maps to chromosome 3p25–p26 and is a putative tumor suppressor gene (Latif et al. 1993). Two VHL gene products have been identified that are translated from mRNAs generated from two alternative start codons. In most functional studies these two proteins are indistinguishable and, therefore, are referred to as one. The VHL protein forms a complex with Elongin BC called the VBC complex. The role of the VBC complex is ubiquination and further proteasomal degradation of target proteins like the hypoxia inducible factor (HIF). In VHL-associated hemangioblastomas, HIF-regulated growth factors like vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF) α, and erythropoietin and their associated receptors are overexpressed (Reifenberger, Reifenberger et al. 1995; Wizigmann-Voos et al. 1995; Chan et al. 1999). It is currently hypothesized that VEGF and PDGF stimulate proliferation of endothelial cells, while TGF and erythropoietin promote tumor growth.

For VHL, disease genotype–phenotype correlation has revealed a strong association of missense mutations with the presentation of pheochromocytoma, whereas null mutations carry a very low risk to develop these tumors (Crossey et al. 1994; Chen et al. 1995).

12.6.3 Diagnostic Criteria and Clinical Features

Although it is classified as a neurocutaneous syndrome, VHL is not associated with any specific cutaneous lesion. VHL is a multisystem disorder with marked phenotypic variability (Table 12.5). The main pathological lesions are capillary hemangioblastomas that are highly vascularized benign tumors composed of pericytes and blood vessels. Patients with VHL are at risk of developing benign and malignant tumors in the CNS, kidneys, retina, adrenal glands, pancreas, and reproductive adnexal organs. Retinal hemangioblastoma is often the first clinical sign and

Table 12.5. Clinical features for Von Hippel Lindau

Clinical features
Cerebellar, retinal, and spinal cord hemangioblastoma
Renal cell carcinoma
Pheochromocytoma
Pancreatic neuroendocrine tumors
Pancreatic and renal cysts
Endolymphatic sac tumors
Polycythemia

leads to diagnosis in 30% of VHL patients (Joerger et al. 2005). Diagnostic features include a positive family history of VHL, identification of one CNS hemangioblastoma, or a single visceral lesion (Richard et al. 2000; Sims 2001). For example, a retinal or cerebellar hemangioblastoma, renal-cell carcinoma, or pheochromocytoma in an at-risk individual would be an adequate criterion. In isolated cases with absent family histories, 2 or more retinal or cerebellar hemangioblastomas or a single hemangioblastoma and a visceral tumor are required for diagnosis. Multiple, frequent retinal angiomas may lead to retinal detachment, hemorrhage, and blindness if left untreated.

CNS hemangioblastomas occur most commonly in the cerebellum (44–72%) and with a much lower incidence in the spinal cord (13–44%) at a mean age of 33 years (Wanebo et al. 2003). These lesions are often multiple, and are generally benign without metastases. Surgical excision results in excellent clinical outcome. Mean age of onset of cerebellar hemangioblastomas in VHL is considerably younger than in sporadic cases (Richard et al. 2000; Sims 2001). Cerebellar hemangioblastomas are found in approximately 75% of patients with VHL. However, only 5–30% of all patients with cerebellar hemangioblastomas are found to have VHL. Many patients with VHL ultimately develop multiple CNS hemangioblastomas and management of brainstem and spinal tumors can be difficult. Thus, CNS involvement remains an important cause of morbidity and mortality in VHL patients.

Fifty to seventy percent of VHL patients develop renal cysts, although renal impairment from cysts is

rare. However, the lifetime risk of clear cell renal-cell carcinoma is greater than 70% and renal-cell carcinoma is a major cause of death in VHL patients. Pheochromocytomas arise in up to 24% of patients with VHL, with a mean age of 27 years at presentation (Joerger et al. 2005). These tumors may be multiple, bilateral, or extra-adrenal. Pancreatic neuroendocrine tumors develop in 5–17% of patients with VHL, with a mean age of 36 years at presentation (Hes et al. 2001a, b).

12.6.4 Natural History and Prognosis

Patients with VHL usually present in adulthood. Initial symptoms are often visual, and related to retinal angiomas with a mean age of onset of 20–40 years. Symptoms from cerebellar hemangioblastomas present later and include headache, disequilibrium, nausea, and vomiting. In a large 10-year retrospective NIH study of 160 consecutive VHL patients, many patients presented with mass effect attributable to a cyst that was far greater in size than the causative tumor (Wanebo et al. 2003). Neither tumors nor cysts spontaneously diminished in size although many untreated tumors remained the same size for several years. The tumors demonstrated a step-wise pattern of growth with enlargement followed by a plateau. Usually the mass effect caused by the cyst was responsible for symptoms.

The median age of death for patients with VHL is 49 years. Fifty-three percent of deaths are due to complications of cerebellar hemangioblastomas, while 32% are due to renal-cell carcinoma (Singh et al. 2001). Pure solid lesions have worse prognoses than mixed (cystic and solid) hemangioblastomas.

12.6.5 Laboratory Studies

Laboratory studies are very nonspecific. Urinary catecholamines, VMA, and HVA, may be elevated in cases of pheochromocytoma. Hemangioblastomas may produce excess erythropoietin resulting in elevated hematocrit values. Commercial genetic testing is now available with sequencing of the VHL gene.

12.6.6 Imaging Studies

With CT head scanning, a low-density cystic mass is often present in the posterior fossa. Isodense mural nodules may enhance intensely with contrast (Fischbein et al. 2000). On MRI, brain cysts may be isointense to cerebrospinal fluid or proteinaceous (hyperintense on T1-weighted sequences) with variable hyper- or hypointensity on T2-weighted sequences (Fig. 12.6). Prominent flow voids are seen in and adjacent to solid portions of the hemangioblastoma. Conventional catheter angiography demonstrates intense tumor blush localized to the posterior fossa. The typical blood supply is from superior cerebellar, anterior inferior cerebellar, or posterior inferior cerebellar arter-

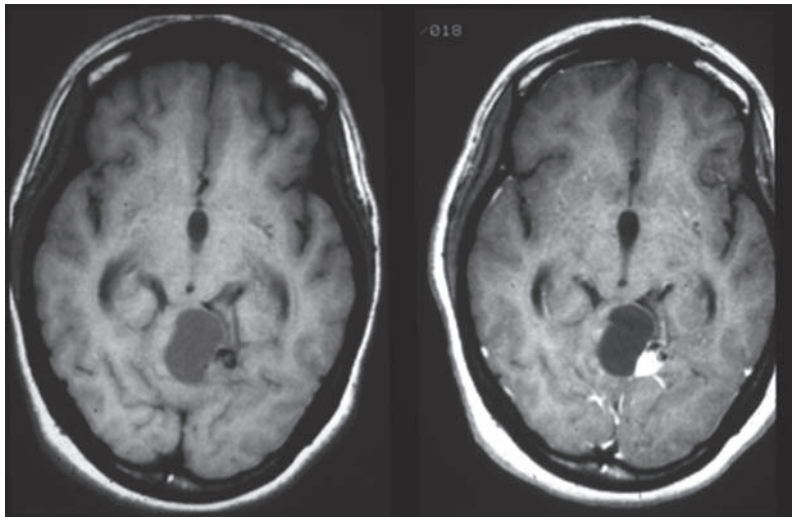

Figure 12.6
VHL syndrome. T1-weighted images, pre- and postcontrast, demonstrating a small enhancing tumor nodule adjacent to a cyst located within the cerebellar vermis. The cyst contents are slightly hyperintense to cerebrospinal fluid

ies, but may also arise from branches of the internal and external carotid arteries. Angiography may assist with operative planning and, if possible, embolization may reduce the tumor vascularity allowing resection with reduced blood loss.

12.6.7 Treatment

To identify retinal angiomas, ophthalmologic examinations are required and, when indicated, laser therapy and cryotherapy are effective (Hes et al. 2001a, b). Surgical removal of symptomatic lesions may also be considered. The NIH group emphasizes that the pattern of growth may be variable (Wanebo et al. 2003). Some tumors remain quiescent for many years, while others grow quickly over several months. As aforementioned, the growth of the cyst is often greater than the tumor itself, and is responsible for the development of symptoms related to mass effect. In their series, asymptomatic patients rarely underwent surgery. Overall, surgical resection of cerebellar, and even brainstem and spinal cord tumors was associated with acceptable morbidity. External beam radiation or stereotactic radiosurgery may be helpful for multiple or inaccessible lesions. Antiangiogenic inhibitors like sunitinib have been studied for the treatment of renal-cell carcinoma. Sunitinib and the VEGF inhibitor, SU5416, inhibit cellular signaling by targeting PDGF and VEGF signaling pathways, which appear to be upregulated in patients with VHL. A phase III trial for renal cell carcinoma showed improved outcome in the sunitinib group versus the interferon-treated group (Motzer et al. 2007). SU5416 has been used for the treatment of retinal hemangioblastomas as well as CNS hemangioblastomas with variable success (Aliello et al. 2002; Madhusudan et al. 2004). Other molecules like vandetanib (VEGF receptor inhibitor) are currently under inverstigation, as is immunotherapy.

Surveillance guidelines recommend screening patients with VHL annually or even bi annually with MRI of the brain and spine. High resolution MRI scans through the temporal bones are recommended to screen for endolymphatic sac tumors. Annual fundoscopic exams are recommended starting at 6 years of age. Abdominal CT scans or ultrasounds should be performed at least once per year starting at 15–18 years of age. To assess for pheochromocytoma, annual plasma and/or urine catecholamines/metanephrines should be checked (Joerger et al. 2005).

12.7 Sturge–Weber Syndrome

12.7.1 Epidemiology

SWS, or encephalofacial angiomatosis, is a rare, sporadic neurocutaneous syndrome. The incidence is currently estimated to be 1:50,000. There is no sexual predilection and no racial bias. Although there are rare familial cases of SWS, there are no convincing data to suggest that it is a heritable condition.

12.7.2 Genetic and Molecular Biology

There are no known molecular biology factors or cytogenetic features of SWS. Recent genetic studies revealed a possible role of fibronectin in the disease process of SWS (Comi et al. 2003). From a pathologic perspective, malformations of embryonic vascular plexi give rise to abnormalities of the skin, leptomeninges, choroids, and cortex. Interference with vascular drainage at 5–8 weeks of gestation affects the face, eye, leptomeninges, and brain. Resultant angiomatosis is accompanied by poor superficial cortical venous drainage with enlarged regional transmedullary veins developing as alternate pathways. It is postulated that inefficient outflow of venous blood causes chronic hypoxia that results in brain tissue loss and dystrophic calcifications. The HIF system has emerged as the key regulatory system of responses to hypoxia. Immunohistochemical analysis demonstrated markedly elevated nuclear HIF-1α and HIF-2α protein levels in SWS vessels, and might lead to the identification of targeted therapies (Comati et al. 2007).

12.7.3 Diagnostic Criteria and Clinical Features

Two essential features of SWS are facial cutaneous nevi (commonly known as “port-wine” stains) and leptomeningeal angiomas (Table 12.6) (Menkes and

Table 12.6. Clinical features for Sturge–Weber syndrome (Bodensteiner and Roach 1999; Menkes and Maria 2000)

Major clinical features	Additional features
Congenital facial vascular nevus	Glaucoma/Bupthalmos
Focal or generalized seizures	Neurologic deterioration
Brain MRI leptomeningeal enhancement after gadolinium administration plus enlarged transmedullary veins and unilateral hypertrophy of the choroid plexus	CT head parieto-occipital calcifications arranged in parallel lines "railroad tracks"

Maria 2000). The other accepted name for port-wine stain is capillary vascular malformation. Skin findings are generally noticed at birth, and seizures may present in infancy. Classic manifestations include an ipsilateral facial port-wine stain, mental retardation, contralateral hemiparesis, contralateral hemiatrophy, and contralateral homonymous hemianopsia. Other features of the syndrome include glaucoma, dental abnormalities, and skeletal lesions. Although the diagnosis of SWS is seldom difficult, challenges remain in predicting functional outcome (Oakes 1992; Maria et al. 1998a, b). The facial nevi are the most obvious of the possible manifestations of SWS, although the ipsilateral leptomeningeal angioma is regarded as the most important component in determining prognosis. Children with widespread vascular lesions often have more seizures and greater intellectual impairment. The SWS clinical triad consists of (1) seizure disorder, (2) mental retardation, and (3) facial angiomas.

Although facial nevi are relatively common malformations, occurring in approximately 3 in 1000 births, only 15% of infants with typical port-wine cutaneous lesions have SWS. In fact, up to 85% of patients with typical upper hemifacial nevi are not associated with leptomeningeal angiomatosis found classically in SWS. Conversely, 13% of patients with cerebral manifestation of SWS do not display facial nevi. Involvement of the eyelid is associated with ipsilateral brain involvement, and usually conforms to the distribution of the first division of the trigeminal nerve. The second and third divisions of the trigeminal nerve can also be involved. There is no correlation between size of facial involvement and CNS malformations (Bodensteiner and Roach 1999). Cutaneous facial nevi are usually present at birth but may become more prominent, thicker, and darker with age.

Seizures often begin in the first year of life as the initial presenting feature in 80% of patients with SWS, and are often medically refractory (Maria et al. 1998a, b). Seizures usually arise focally at first but may secondarily generalize into tonic-clonic seizures. In addition, patients experience focal neurologic deficits that develop acutely in conjunction with flurries of seizures, and also as Todd's paralysis that recovers more readily. Hemiparesis occurs with or without seizures and affected extremities often grow poorly, eventually resulting in hemiatrophy. Visual field defects result from involvement of one or both occipital lobes or optic tracts with leptomeningeal angiomatosis. Hydrocephalus may occur as a result of increased venous pressure from thromboses of deep venous channels or extensive arteriovenous anastomoses.

Mental retardation is common in SWS, with IQs lower than 90 in 70% of patients (Menkes and Maria 2000). There is some controversy in the SWS literature regarding intellectual status. One study reports that all SWS patients without seizures are mentally normal (Sujansky and Conradi 1995). A conflicting study reports that although most infants with SWS have normal neurologic function, nearly all adults with SWS are impaired, suggesting a pervasive deterioration of function regardless of seizures (Maria et al. 1998a, b).

Other signs and symptoms of SWS include headaches, stroke-like episodes, contralateral hemiplegia, hemisensory deficits, and contralateral homonymous hemianopsia. Ocular involvement is common and includes glaucoma, buphthalmos (enlarged ocular globe) in up to 40% of patients. The vascular malformations of the conjunctiva, episclera, choroid, and retina predispose to abnormal intra-globe fluid dynamics.

12.7.4 Natural History and Prognosis

SWS is associated with progressive CNS disease that results in seizures as well as motor, sensory, visual,

and cognitive deficits. Early development of intractable seizures associated with hemiparesis and bilateral involvement are poor prognostic signs for cognitive development and general health. Recent studies showed that early white matter volume loss measured on brain MRI is associated with poor cognitive outcome (Juhasz et al. 2007).

12.7.5 Laboratory Studies

There are neither laboratory tests nor genetic tests available for the diagnosis of SWS.

12.7.6 Imaging Studies

Although facial nevi are the most obvious manifestations of SWS, leptomeningeal angiomas are clearly the most important determinants of ultimate patient prognosis. Leptomeningeal malformations typically involve posterior cerebral hemispheres, especially occipital lobes. Such malformations cause ischemia in adjacent brain resulting in gliosis, demyelination, parallel cortical calcifications, focal cerebral atrophy, and hemiatrophy. Other findings include absent superficial cortical veins adjacent to the malformation and enlarged ipsilateral deep venous system choroid plexi.

Head CT scans reveal gyral or "tram-track" cortical calcifications (absent in very young patients), most commonly over posterior hemispheres. There is often underlying cortical atrophy. Enlargement of the skull, diploic space, subarachnoid space, sinuses, and mastoid air cells occur ipsilateral to port wine stains. Contrast-enhanced scans may reveal diffuse staining of involved cerebral cortex and intense leptomeningeal enhancement if performed prior to the development of cortical calcifications (Fischbein et al. 2000).

Brain MRI scans (Fischbein et al. 2000) demonstrate ipsilateral parenchymal atrophy, compensatory skull thickening, and sinus enlargement. There is marked gadolinium enhancement in areas of leptomeningeal angiomatosis. Enlargement of the ipsilateral choroid plexus occurs secondary to angiomatosis. T2 shortening in the white matter underlies angiomatous malformations, usually seen in infants, and may be due to ischemia. In later life, areas of T2 shortening are usually secondary to calcifications. Enlargement of deep venous structures occurs ipsilateral to meningeal angiomas.

12.7.7 Treatment

Unlike other neurocutaneous syndromes, SWS is not associated with heightened predisposition to CNS tumors. Treatment of facial nevi has been revolutionized by vascular-specific pulsed dye laser therapy. Ophthalmologic consultation is often required for aggressive medical and surgical management of glaucoma. If intractable seizures affect neurologic development and quality of life in young patients, there is general agreement that surgical resection (lobectomy, hemispherectomy) can significantly reduce seizure frequency and improve quality of life (Kossoff et al. 2002). This usually requires removal of the involved cortex and leptomeningeal abnormality. One author provided limited evidence that aspirin therapy at 2–5 mg/kg/day may be associated with two-thirds fewer stroke-like episodes, but confirmatory data is lacking (Maria et al. 1998a, b).

12.8 Conclusions

The neurocutaneous syndromes are among the most common genetic disorders observed in humans. Furthermore, this unique group of patients is at higher risk for the development of CNS neoplasms. The responsible genes have already been identified for most disorders, although the molecular pathophysiology remains unclear in many cases. Please refer to Table 12.7 for up-to-date information. For the clinical oncologist, the challenge is the decision to treat or observe. Generally, this decision is driven by the tempo and severity of the patient's clinical picture, although a clear understanding of the natural history of the disease is essential. Fortunately, most patients do not develop malignant tumors, but this information is tempered by the need for life-long observation and follow-up.

Table 12.7. Internet sites with additional information for the phakomatoses

Neurofibromatosis	www.ctf.org
Tuberous sclerosis	www.tsalliance.org
Ataxia telangiectasia	www.atsociety.org.uk www.atcp.org
Von Hippel Lindau	www.vhl.org
Sturge Weber	www.sturge-weber.com

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Modern Neuroimaging of Pediatric Brain Tumors

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A. James Barkovich

Contents

13.1 Modern Neuroimaging of Pediatric CNS Tumors

Neuroimaging has been an important tool in the diagnosis and surveillance of brain tumors for more than 30 years. Although magnetic resonance (MR) imaging remains the most important imaging tool for assessing CNS neoplasms, new techniques have allowed physiologic features of brain tumors and the surrounding functional brain tissue to be performed noninvasively. In this chapter, these new techniques and their applications are discussed.

13.2 MR Spectroscopy

13.2.1 Principles

Proton MR Spectroscopy (MRS) is a powerful and sensitive technique that can be added to a standard MR study with only a small time penalty (Hunter and Wang 2001). MRS provides information about the activity of specific metabolites that can supplement the information obtained from routine anatomic sequences (Kim et al. 1997; Kimura et al. 2001). MRS may be useful to differentiate tumor from normal tissue, help stratify neoplasms as high- or low-grade, plan biopsies, distinguish between treatment injury and recurrent neoplasm, and separate cystic infection from cystic neoplasm (Yousem et al. 1992; Ott et al. 1993; Poptani et al. 1995; Shimizu et al. 1996; Wang et al. 1996b; Nelson et al. 1997a; Lazareff et al. 1999; Nelson et al. 1999; Norfray et al. 1999; Dowling et al. 2001; Horska et al. 2001; Martin et al. 2001; Vigneron et al. 2001). Routine MR imaging may lead

to incorrect tumor classification in up to 40% of cases (Ott et al. 1993).

MRS displays peaks from functional groups of numerous neurochemicals (Salibi and Brown 1998). Several of these neurochemicals are important in the analysis of patients with brain tumors, including *N*-acetylaspartate (NAA), trimethylamines (choline [Cho] and related compounds), creatine constituents (Cr), lactate (Lac), myoinositol (Myo), and amino acids (AA) (Birken and Oldendorf 1989; Urenjak et al. 1993; Poptani et al. 1995; Tomoi et al. 1997; Dezortova et al. 1999; Norfray et al. 1999; Hunter and Wang 2001).

A normal NAA peak is thought to reflect a normal number of mature, normally functioning neurons (Birken and Oldendorf 1989; Hunter and Wang 2001). NAA is believed to be a key component in an acetyl-group carrier between neuronal mitochondria and cytoplasm. It is vital in the regulation of neuronal protein synthesis and the metabolism of several neurotransmitters (Birken and Oldendorf 1989). NAA is also present in oligodendrocyte precursors, and may be elevated or reduced in processes involving oligodendrocytes and myelin, as well as those involving neurons and axons (Urenjak et al. 1993; Tzika et al. 1997). The NAA concentration is dependent on location (it is 10% lower in the normal cerebellum compared to cerebrum), maturity (increases as the brain develops and neurons mature), and neuronal health (decreased after injury or infiltration by neoplasm) (Usenius et al. 1995; Wang et al. 1996b).

The Cho resonance mainly comprises molecules from cell membranes, such as choline, phosphocholine, and glycerophosphorylcholine (Waldrop et al. 1998). Protons in choline molecules within intact membranes (such as those found in phosphotidylcholine), however, are immobile and do not contribute to MR signal (Waldrop et al. 1998; Norfray et al. 1999; Dowling et al. 2001). Since the Cho peak in the MR spectrum is composed of signal from these compounds during the processes of membrane synthesis and degradation (Waldrop et al. 1998; Norfray et al. 1999; Dowling et al. 2001), elevated Cho is found in neoplasms, active infection, and regions containing inflammatory cells.

The Cr peak comes from methylamine peaks of creatine and phosphocreatine – compounds that provide a high-energy phosphate buffer for adenosine triphosphate synthesis (Norfray et al. 1999). In most disorders, it is not clear what processes produce changes in Cr concentrations. Cr can be depressed in high-grade or metabolically active neoplasm, due to the overwhelming requirements of the proliferating tumor cells (Tzika et al. 1996, 2001). It can also be depleted in regions of necrosis secondary to lack of metabolic needs and cell death (Yousem et al. 1992; Taylor et al. 1996; Tzika et al. 1997, 2001).

Lactate is an end product of anaerobic glycolysis that accumulates when the glycolytic rate exceeds lactate catabolism or overwhelms export by the blood stream (Wang et al. 1995; Tomoi et al. 1997; Norfray et al. 1999). It is a nonspecific marker seen in a variety of conditions such as tumors, necrosis, ischemia, cysts, and treatment injury (Wang et al. 1995).

13.2.2 Technique

Currently, at the University of California, San Francisco (UCSF), we obtain spectra from a large area of the brain ($8 \times 8 \times 8$ cm), and can resolve spectra from volumes of less than 1 cm^3 within that area. These data are acquired in approximately 8 min on a 3 T magnet (Nelson et al. 1997b, 1999; McKnight et al. 2001). Using this technique, a small tumor focus can be identified in a large region of heterogeneous tissue. Moreover, postprocessing allows the voxel to be placed in precisely the same region of interest as in prior studies, allowing increased confidence that the tumor has been sampled in precisely the same location (Nelson et al. 1994). On MR scanners without 3D spectroscopic imaging (3D MRSI), 2D MRSI, commercially available from all major manufacturers, can be extremely useful. Two-dimensional MRSI allows coverage of a large area of tissue with small voxel size and an excellent signal-to-noise ratio (Taylor et al. 1996; Dowling et al. 2001). The only disadvantage is the necessity to acquire separate spectra for each plane sampled.

13.2.3 Application

MRS is useful in diagnosing and assessing brain tumors because tumors usually have elevated Cho

levels and subnormal NAA levels compared to normal brain tissue. These features are also found in other conditions in which membrane turnover is increased and the number of healthy, mature neurons is decreased (e.g., immature brain, some types of dysplastic brain, and inflammation). It is important to know the normal peak ratios in the region of brain being investigated. The concentration of NAA is normally 10% lower in the cerebellum than in cerebral white matter (Usenius et al. 1995; Wang et al. 1995). Cho concentrations in the cerebellum and pons are 70% higher than in other areas (Usenius et al. 1995). Increased Cho in relation to NAA is even more dramatic in neonates (Tzika et al. 1996). Ratios of metabolites can also differ in different regions of the brain, even within different portions of the cerebral cortex (Wang et al. 1995). Therefore, it is critical to correlate MRS with MRI and other tests in order to avoid false positive results suggestive of tumor, when the actual process is another diagnosis (Sutton et al. 1992).

Once the diagnosis of tumor is established, MRS can be of some use in grading astrocytic neoplasms. In general, the farther the metabolite peaks vary from normal, the more likely that the tumor is aggressive (Hunter and Wang 2001). In particular, the Lac peak magnitude tends to be more elevated in more aggressive neoplasms (Girard et al. 1998). It should be noted, however, that juvenile pilocytic astrocytomas, among the most benign of brain tumors, have elevated choline and lactate, along with reduced NAA (Lazareff et al. 1999). In addition, similar grades of tumors of different histologic type may have very different spectra (e.g., a low-grade oligodendroglioma may have a very different spectrum from a low-grade astrocytoma). For these reasons, grading of neoplasms based on MRS has focused on determining peak magnitudes and ratios in tumors of the same histologic type (Poptani et al. 1995; Shimizu et al. 1996; Tzika et al. 1996; Cheng et al. 1998; Horska et al. 2001), and even in these cases it is not entirely reliable (Barker et al. 1993; Tzika et al. 1996, 1997; Chang et al. 1998; Lazareff et al. 1999; Shino et al. 1999; Kimura et al. 2001).

Rarely, tumors have unique spectra that can help narrow the differential diagnosis from what is derived from routine MR imaging alone. For example, meningiomas and central neurocytomas exhibit an alanine peak that is typically not found in other neoplasms. In these two tumor types, it may represent a secondary marker for more aggressive histology (Kugel et al. 1992; Kinoshita and Yokota 1997; Lehnhardt et al. 2001; Krishnamoorthy et al. 2007). An elevated taurine peak has been preferentially discovered in medulloblastomas, which is not the case for astrocytomas within the posterior fossa (Moreno-Torres et al. 2004; Chawla et al. 2007).

MRS can be helpful in selecting the best biopsy site in heterogeneous neoplasms (Dowling et al. 2001; Martin et al. 2001). However, for MRS to be useful in this regard, the voxel size must be small compared to the size of the neoplasm. Spectroscopic data obtained from a given volume of brain represents the average of the metabolic components of the volume. If the voxel is large or the tumor is small, the voxel might contain regions of both high and low grade tumor, normal brain, and necrosis (Tzika et al. 1996). The resultant spectrum reflects the percentage of each component and does not reflect the nature of the tumor. For example, the MRS of a highly aggressive neoplasm with a large component of necrosis or normal brain or low-grade tumor could mimic the spectra of a low-grade neoplasm (Sijens et al. 1995; Venkatesh et al. 2001). Because spectra can also be contaminated by adjacent CSF or by fat from the calvarium or scalp (Sijens et al. 1995; Wang et al. 1996bNorfray et al. 1999; Hunter and Wang 2001), it is imperative to use as small a voxel as possible. However, sampling many different voxels during a single exam necessitates excessively long scan times if each voxel is acquired separately. In order to reduce acquisition time, 3D MRSI can be used to sample a large volume of brain during a single acquisition, with small areas within the volume analyzed during the postprocessing step.

Although MRS can clearly distinguish abnormal from normal brain tissue, it does not always correctly differentiate a neoplasm from other disorders (Sutton et al. 1992; Kim et al. 1997; Wilken et al. 2000), particularly those with a high concentration of inflammatory cells (Krouwer et al. 1998; Venkatesh et al. 2001). There are many examples of inflammatory

disorders, such as demyelinating plaques, tuberculomas, xanthogranulomas, HIV encephalitis, and HSV encephalitis, that have MRS features nearly identical to neoplasms (Krouwer et al. 1998; Butzen et al. 2000; Shukla-Dave et al. 2001; Venkatesh et al. 2001). These other processes should always be considered, particularly when the patient's history or imaging features are not consistent with a CNS tumor.

MRS can be useful in differentiating pyogenic abscess from tumor. Increased glycolysis and fermentation by bacteria produce elevated levels of lactate, acetate, and succinate, while proteolysis by enzymes produces valine, isoleucine, and leucine (Kim et al. 1997; Chang et al. 1998; Gupta et al. 2001). These compounds have protons that precess in the aliphatic region, upfield from NAA. Although elevated lactate and succinate associated with radiation necrosis makes MRS nonspecific in the posttherapy patient (Kim et al. 1997; Yeung et al. 2001), the presence of these peaks seems rather sensitive (92–100%) and specific when MRS is performed at presentation (Kim et al. 1997; Grand et al. 1999; Gupta et al. 2001; Kimura et al. 2001; Shukla-Dave et al. 2001).

Distinguishing posttherapy injury from recurrent or residual neoplasm has been difficult using anatomic imaging techniques, as the enhancement and edema seen with the two conditions can be nearly identical. This distinction is pivotal, as earlier recognition of recurrence can prolong survival or guide future treatment (Shtern 1992). MRS can be a useful technique in making this distinction, as an injured brain produces a different spectrum than a normal brain or tumor (Kamada et al. 1997). Early radiation injury produces elevated Cho from plasma and intracellular membrane disruption, but this usually clears quickly and a normal NAA peak remains (Szigety et al. 1993). A global decrease in peak amplitudes (NAA, Cho, and Cr peaks) is consistent with treatment injury without active neoplasm (Yousem et al. 1992; Ott et al. 1993; Taylor et al. 1996; Tzika et al. 1997; Kimura et al. 2001). Recurrence is suggested by new or persistent elevation of Cho and reduction of NAA (Fig. 13.1) (Sijens et al. 1995; Tzika et al. 1997; Lazareff et al. 1999).

There is no consensus as to how often patients should be evaluated. We believe that the most sensitive method to evaluate treatment efficacy and to screen for early recurrence or residual neoplasm is to perform serial exams, which allows comparison with a known baseline prior to treatment (Nelson et al. 1997a, 1999; Lazareff et al. 1999; Norfray et al. 1999; Vigneron et al. 2001). It is important to remember that, although combining MRS with MR imaging is more sensitive than MR imaging alone, sensitivity is not 100%. A necrotic neoplasm with a paucity of viable tumor cells can have identical spectra to posttreatment necrosis (Taylor et al. 1996); this can only be differentiated when the Cho increases on subsequent exams. Serial follow-up studies are, therefore, essential to detect early growth of residual neoplasm.

MRS is a promising tool for assessing pediatric patients with brain tumors. In the appropriate setting, spectroscopy can improve the delineation of neoplastic brain involvement, increase specificity of diagnosis, and help discriminate post treatment injury from residual neoplasm. Research continues to define the role of MRS in grading neoplasms and possibly predicting treatment response (Negendank et al. 1996; Girard et al. 1998; Waldrop et al. 1998; Lazareff et al. 1999; Lin et al. 1999; Tzika et al. 2001).

13.3 MR Perfusion

13.3.1 Principles

Cerebral perfusion is defined as the delivery of nutrients and oxygen, via the blood, to brain tissue per unit volume. This is typically expressed in units of milliliters per 100 g of parenchyma per minute (Cha et al. 2002). With recent advances in fast imaging techniques and computer technology it is now possible to capture the dynamic changes in cerebral perfusion using MR imaging. Perfusion MR imaging (pMRI) provides information on cerebral hemodynamic parameters that are reflective of tissue perfusion, including relative cerebral blood volume (rCBV), cerebral blood flow (CBF), and mean transit time (MTT).

pMRI has evolved from a research tool into a clinically useful technique due to wider availability of

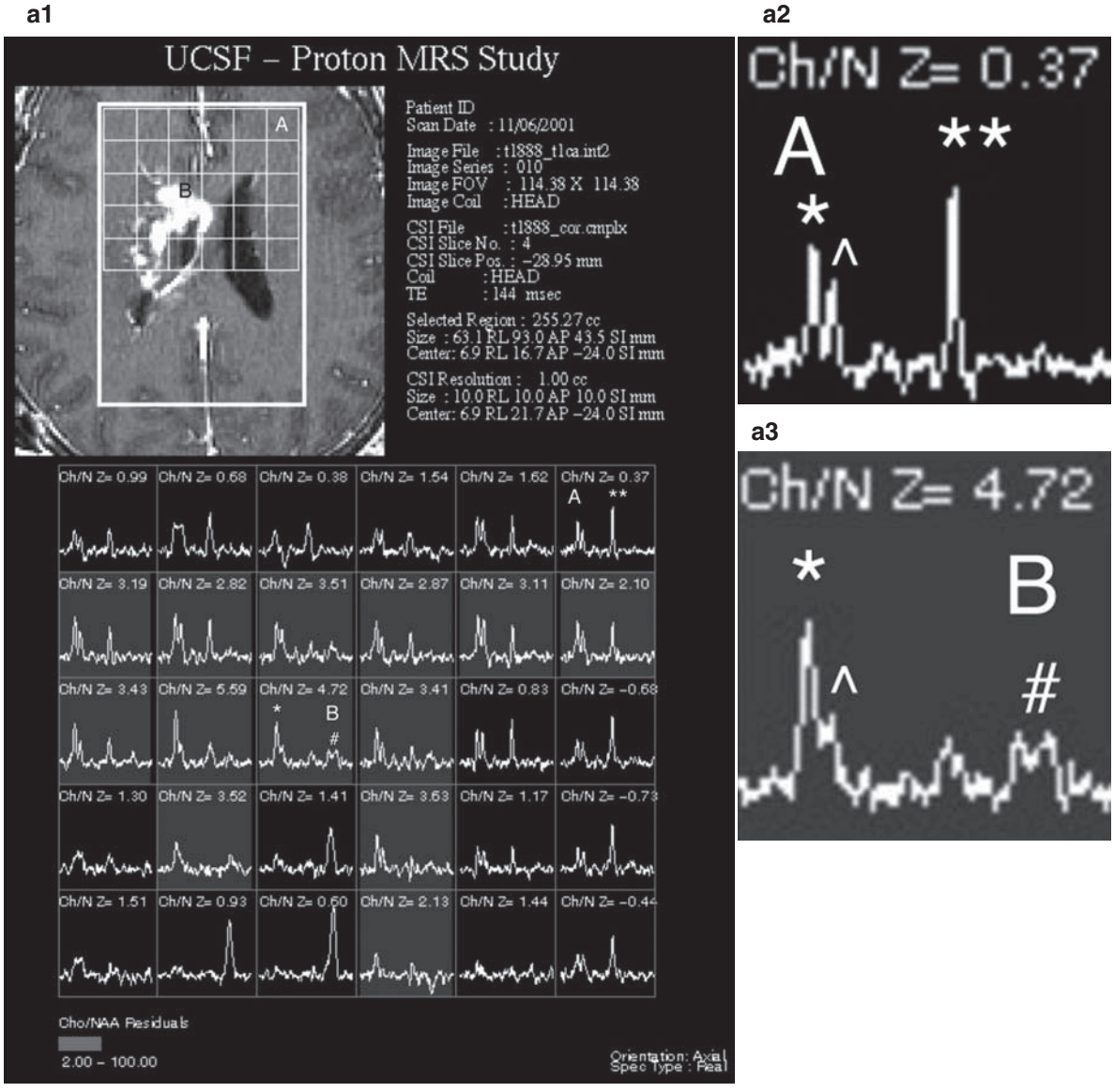

Figure 13.1

High-grade glioma with both improved spectra and anatomic imaging after receiving radiation therapy. (**a1**) Pretreatment 3D chemical shift imaging (CSI) transposed on T1-weighted gadolinium enhanced axial image. Spectrum voxel labeled *A* is within normal left frontal white matter; choline (*), creatine (^), and NAA (**) peaks are normal for age and location. Spectrum voxel labeled *B* is within enhancing neoplasm; the spectrum shows elevated choline and lactate/lipid (#), with decreased NAA in the right genu. (**b1**) Follow-up 3D CSI in the same location as image a. Choline peak (*) has decreased since the prior study, resulting in an improved *Z*-score, yet still has evidence of residual neoplasm. Spectrum voxel labeled *C* shows necrosis; all metabolites are decreased

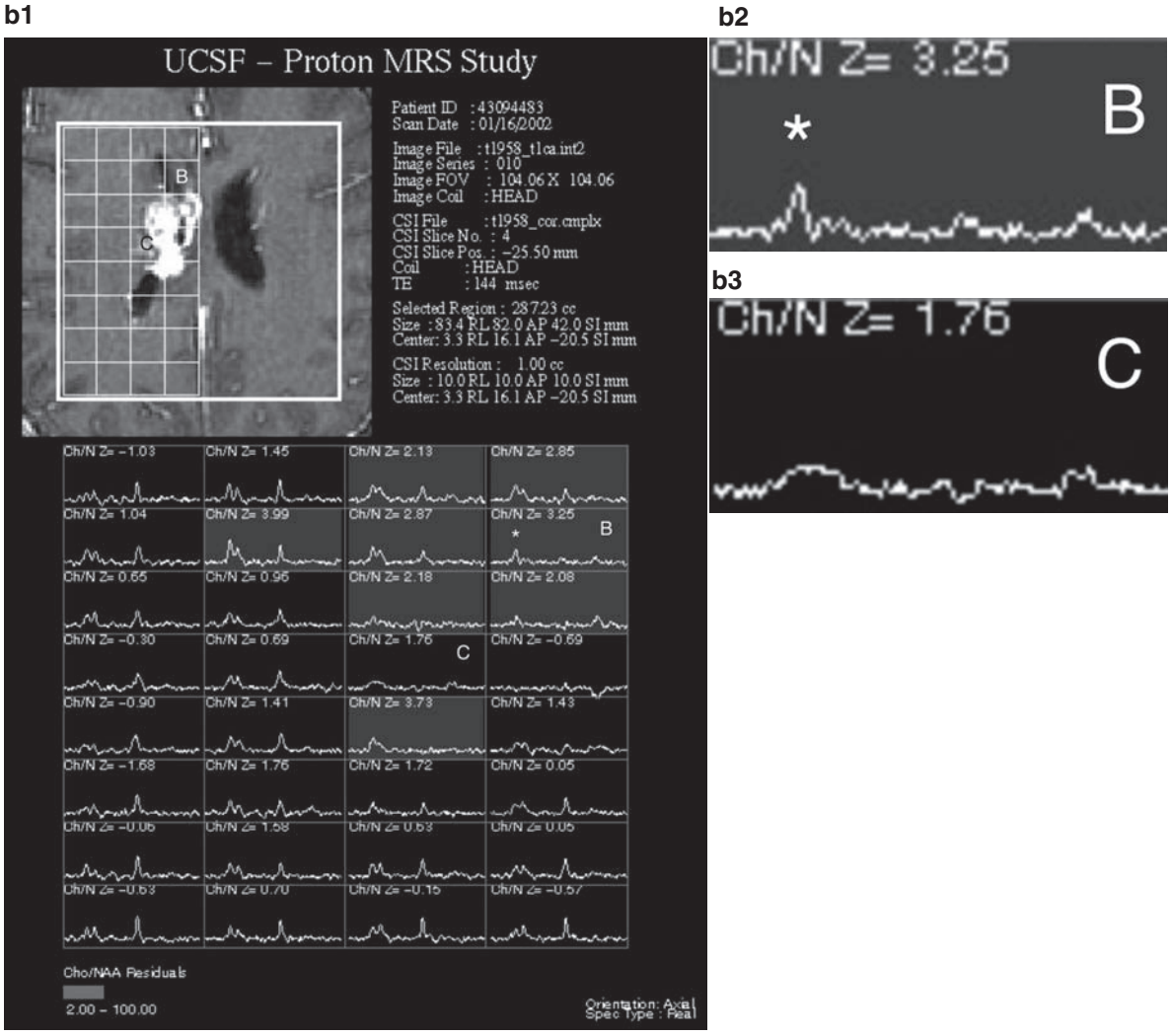

Figure 13.1
(Continued)

high-performance MR gradients that allow faster imaging sequences (e.g., echo planar imaging (EPI)), and improvement in computer image processing algorithms. Quantitative analysis of perfusion parameters can now be derived from a clinically useful volume of brain using MR perfusion. This technique takes us one step closer to evaluating intracranial pathophysiology, in addition to the anatomical information gathered from conventional MR. A brief review of pMRI is presented to better understand the methodology and the basis for clinical application of MR perfusion.

13.3.2 Technique

There are several methods to derive perfusion parameters using MR imaging. pMRI can be performed using either endogenous (arterial water) or exogenous

(gadolinium, deuterium oxide) contrast agents (Cha et al. 2002). Endogenous perfusion imaging (e.g., arterial spin labeling) provides absolute quantification of CBF, but suffers from several pitfalls. These include long imaging time, extreme sensitivity to motion, and low signal-to-noise ratio (Cha et al. 2000b). This section is limited to the discussion of pMRI using exogenous contrast (e.g., gadolinium-DTPA) DSC-pMRI, due to its readily available clinical benefits and ease of use.

MR perfusion (e.g., dynamic susceptibility weighted contrast enhanced perfusion MR imaging, DSC-pMRI) exploits the signal changes (T2* signal loss) during bolus passage of a contrast agent through the cerebral vessels (Strong et al. 1993; Aronen et al. 1994; Siegal et al. 1997; Cha et al. 2000b; Ludemann et al. 2000; Ball and Holland 2001). Using tracer kinetic principles, the signal change is converted to an integral of tissue contrast agent concentration (Rosen et al. 1990; Weisskoff et al. 1994; Peters 1998). These values are then used to generate perfusion maps of various hemodynamic parameters.

To successfully image a large volume of brain during the finite time that contrast is within the cerebral vessels, faster imaging methods are necessary. EPI fulfills this requirement, with a temporal resolution of 100 ms/slice. Several different pulse sequences can be used with EPI (e.g., spin echo, gradient echo). Spin echo images are thought to be more sensitive to signal changes from contrast agent within the intracapillary volume (Weisskoff et al. 1994). Gradient echo images are more sensitive to medium to large vessels, and therefore greater signal drop is seen during the first pass of a contrast agent. Although more prone to susceptibility artifact, gradient echo techniques are more sensitive to small changes in blood volume. Therefore, the gradient echo technique does not require high doses of contrast agent as does spin echo to produce diagnostic images (Hunter and Wang 2001; Yeung et al. 2001; Cha et al. 2002).

13.3.3 Applications

DSC-pMRI, as adjunct imaging to conventional MR imaging, has several potential applications. With the wide availability and application of faster imaging hardware and software, DSC-pMRI can be incorporated into the routine evaluation of intracranial lesions. Clinical roles for DSC-pMRI include grading neoplasms, distinguishing high-grade primary neoplasm from single metastases, directing stereotactic biopsies, and distinguishing therapy-related brain injury from residual or recurrent tumor (Maeda et al. 1993; Knopp et al. 1999; Cha et al. 2002; Law et al. 2002; Tzika et al. 2002). Some advocate that DSC-pMRI may be helpful in adjusting chemotherapy dosing (Cha et al. 2000a).

Preliminary results on grading of gliomas with DSC-pMRI are promising. Although some authors using spin echo sequences have shown no statistical correlation between tumor grade and perfusion imaging, gradient echo-derived blood volumes have been more robust in distinguishing grades of glioma (Rosen et al. 1991; Aronen et al. 1994; Sugahara et al. 1998, 1999; Ludemann et al. 2000; Roberts et al. 2000a; Ball and Holland 2001).

Separating high- from low-grade gliomas by histology relies on the presence of neovascularity and necrosis (Plate and Mennel 1995; Giannini and Scheithauer 1997). DSC-pMRI is a method that can noninvasively assess tumor vascularity and is complementary to histopathology in determining the grade and malignancy potential of a neoplasm (Fig. 13.2) (Gerlowski and Jain 1986).

Histology alone may not accurately predict tumor biology or patient prognosis. DSC-pMRI correlates with the degree of tumor angiogenesis and therefore may be able to predict aggressive biology (Aronen et al. 1994). Hence, the more aggressive the tumor, the larger the rCBV, presumably due to tumor angiogenesis (Knopp et al. 1999; Sugahara et al. 1999). This technique offers a potentially powerful and noninvasive means of assessing tumor biology and serially monitoring changes in the tumor during therapy.

Most published reports using DSC-pMRI for tumor grading have studied adult patients. Sensitivity for this technique may be reduced in children since certain benign tumors, such as pilocytic astrocytoma and choroid plexus papilloma may have increased vascularity; that is, high rCBV (Strong et al. 1993; Plate and Mennel 1995; Giannini and Scheithauer 1997; Keene et al. 1999; Ball and

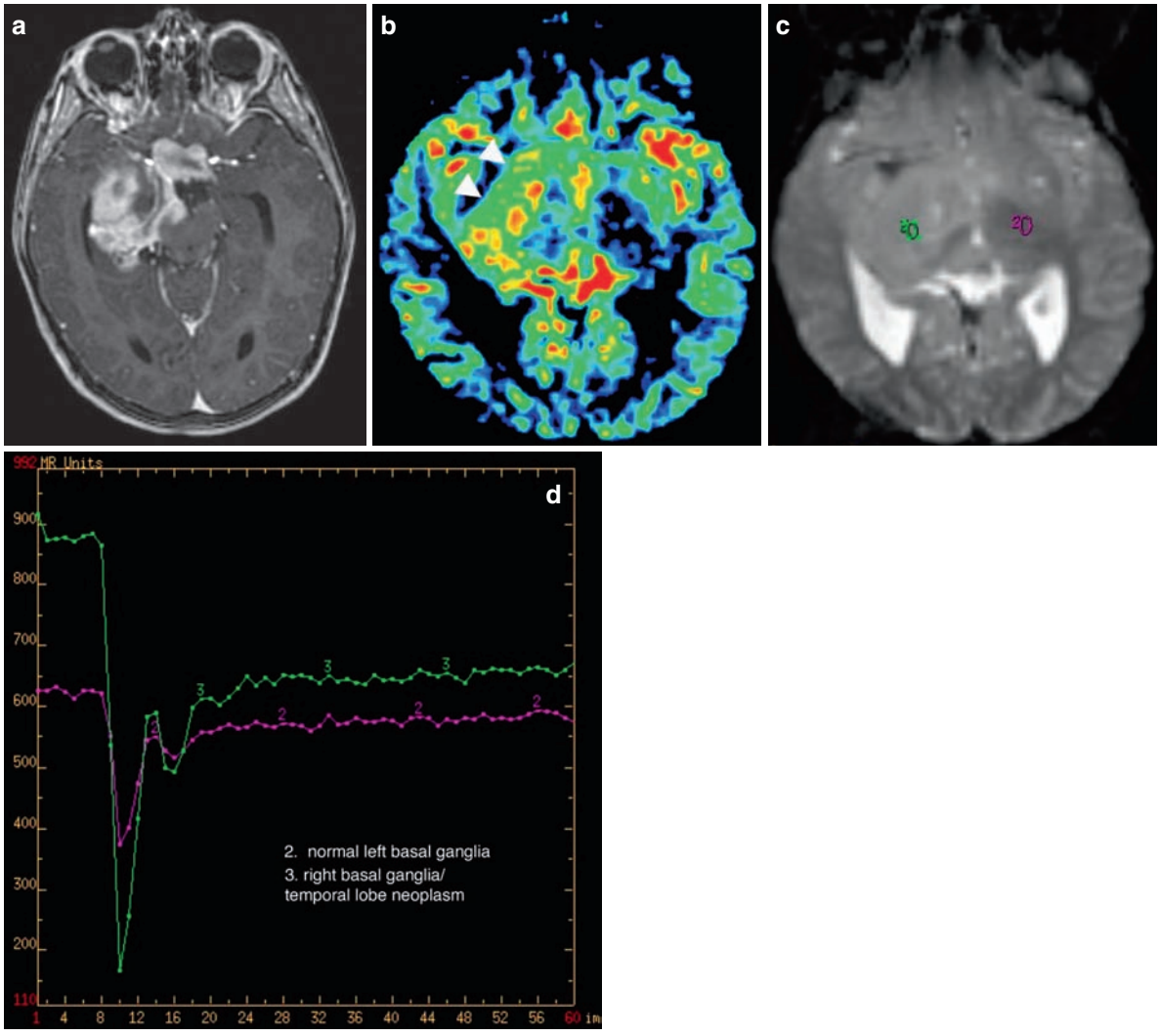

Figure 13.2

Right medial temporal lobe and chiasmatic glioma with pMR imaging characteristics of a vascular, intra-axial neoplasm. (**a**) Axial T1-weighted gadolinium-enhanced image of the infiltrating, enhancing neoplasm. (**b**) Axial color map of the relative cerebral blood volume (CBV) showing increased CBV within the neoplasm (*white arrowheads*) relative to normal vascularity on the contralateral side. (**c**) Axial T2-weighted image shows the regions (ovals) that were sampled to calculate the time-signal curves (*2* normal left basal ganglia, *3* neoplasm). (**d**) Time-signal curve shows an intact blood–brain barrier (BBB) in region *2* (normal recovery of signal after the passage of the contrast bolus), but a partially disrupted BBB in region *3* (slower, incomplete recovery after the bolus due to contrast leaking through the BBB)

Holland 2001). DSC-pMRI should be interpreted cautiously in heterogeneous tumors since rCBV can vary depending on the location chosen to place the region of interest. A region of interest placed in an area of necrosis or nonaggressive portion of the neoplasm could erroneously underestimate rCBV and result in undergrading of tumor. Alternatively, cortically based neoplasms that are contiguous with the brain surface vessels may be falsely given a higher grade due to a high rCBV from a region of interest placed over vessels (Sugahara et al. 2001). Larger studies are needed prior to DSC-pMRI's inclusion as a routine clinical practice for grading tumors in children.

A promising application of perfusion imaging is distinguishing treatment-induced brain injury from residual or recurrent neoplasm (Rosen et al. 1991; Siegal et al. 1997; Sugahara et al. 1999, 2000; Cha et al. 2000a, 2002; Roberts et al. 2000a). With routine MR imaging, both entities can enhance after contrast administration and are indistinguishable until growth on serial imaging favors a diagnosis of neoplasm. DSC-pMRI takes advantage of the pathophysiologic differences in vascularity to separate the entities. Posttreatment brain injury, in part, is believed to be the result of endothelial damage followed by vascular thrombosis and blood–brain barrier (BBB) breakdown. This ultimately leads to hypoperfusion of the affected tissue (Chan et al. 1999). The final common pathway of delayed radiation injury is vascular thrombosis and fibrinoid necrosis, which on DSC-pMRI manifests as a decrease in rCBV when compared to normal tissue (Cha et al. 2000a, 2002). On the other hand, tumor cells require a viable blood supply for growth and spread and, therefore, increased rCBV is seen in recurrent and residual neoplasms (Plate and Mennel 1995; Cha et al. 2000a; Ball and Holland 2001). Preliminary results show that decreased signal on DSC-pMRI correlates well with treatment-induced brain injury (Siegal et al. 1997; Cha et al. 2000a; 2002).

Exceptions still exist in making this important distinction between tumor and therapy-induced brain injury. Normal or even decreased rCBV in the area of residual tumor can occur if neoplastic tissue is mixed with hypovascular necrotic tissue. Treatment-induced injury can lead to aneurysmal dilation of vessels and formation of telangiectasias that can artificially elevate the rCBV, leading to false positive results. Petechial hemorrhage or calcification in an area of residual tumor can produce susceptibility artifact that artificially reduces the rCBV, resulting in a false negative result (Sugahara et al. 2000). Further research is needed prior to standardized clinical use throughout multiple institutions.

DSC-pMRI continues to be investigated for use in guiding stereotactic biopsy of intracranial neoplasms. Usually, CT and MRI-guided biopsies of brain tumors, are directed to areas of conventional contrast enhancement. This approach, however, is prone to sampling error due to the intrinsic limitations of imaging enhancement to detect the most aggressive portion of a tumor (Joyce et al. 1978; Cha et al. 2002). In addition, limited tissue sample size can lead to erroneous grading and inadequate evaluation (Chandrasoma et al. 1989; Cappabianca et al. 1991).

Contrast enhancement on MR images reflects the areas of breakdown within the BBB (Greenwood 1991). This is often in the rim adjacent to a necrotic portion of the neoplasm. Elevated rCBV is considered to represent the areas of vascular hyperplasia in the aggressive, viable neoplasm, and may not always correspond to a contrast enhancing portion (Cha et al. 2002). Using DSC-pMRI in addition to conventional anatomical images could result in reduced false negatives and errors in assessing tumor grade. Although still investigational, DSC-pMRI may be helpful in localizing the most aggressive portion of a neoplasm and serve as a complimentary tool to anatomic imaging (Rosen et al. 1991; Aronen et al. 1994; Knopp et al. 1999).

Future applications for DSC-pMRI under development include mapping dose distributions in neoplasms and following perfusion maps for therapy-outcomes research for new therapeutic agents (Cha et al. 2000a, 2002; Ludemann et al. 2000; Roberts et al. 2000a).

In summary, DSC-pMRI is no longer primarily a research tool, and promises to become an important diagnostic tool complementing conventional anatomical imaging. Clinical use for tumor grading, differentiating between residual neoplasm and treatment-associated injury, and assisting in therapy

dosing and treatment follow-up are on the horizon. Guiding biopsies within heterogeneous tumors by perfusion imaging may reduce sampling errors and improve diagnostic accuracy.

13.3.4 Limitations

DSC-pMRI has several important constraints. Sensitivity to susceptibility artifact prevents its use in brain adjacent to the paranasal sinuses or the skull base (Poussaint et al. 1995; Ball and Holland 2001; Cha et al. 2002). The sequence is very sensitive to patient motion, and SNR is low in comparison to anatomic MR images (Aronen et al. 1994; Siegal et al. 1997; Cha et al. 2002). Only a limited volume of brain can be covered during the time it takes the contrast bolus to pass through the intracranial vasculature. Also, a compact delivery of the bolus may be difficult to attain in a patient who has limited intravenous access (Siegal et al. 1997). Furthermore, care must be taken to recognize false positives that are created by normal structures (e.g., choroid plexus and cortical veins) (Aronen et al. 1994; Sugahara et al. 1998). Additional costs may be substantial, due to the stringent hardware and software requirements to acquire and process the MR data. Access to a physicist familiar with the MR technique is also beneficial for continued support (Cha et al. 2002).

13.4 Nuclear Medicine

13.4.1 Principles

The role of radionuclide CNS imaging continues to evolve. The most commonly used techniques are single photon emission computed tomography (SPECT), which is readily available in most hospitals, and positron emission tomography (PET), which is more expensive, but is becoming more accessible to the majority of sites. Areas of current study include: differentiating lesions with similar imaging appearances (e.g., lymphoma from toxoplasmosis by thallium uptake), differentiating treatment injury from residual neoplasm, grading neoplasms, localizing the most aggressive portion of the tumor prior to therapy, predicting response to therapy, and localizing eloquent cortices prior to surgery (Maria et al. 1998; Ricci et al. 1998).

The most widely practiced application is that of differentiating residual neoplasm from treatment injury. Without special techniques (such as MRSI, see earlier section), this differentiation can be extremely difficult by conventional CT and MRI (Di Chiro et al. 1988; Valk and Dillon 1991; Brunelle 2000). Both entities produce altered vasculature that can result in identical-appearing edema and enhancement. Even biopsy can lead to a false diagnosis. It is difficult to know which area of enhancement represents an aggressive margin of neoplasm or just an area of active necrosis and BBB breakdown (Poussaint et al. 1995). If cognizant of the limitations, radionuclide imaging may be very helpful to select clinical scenarios.

Both SPECT and PET, utilizing several radionuclide imaging agents, have been studied in attempts to distinguish treatment injury from neoplasm. ^{99m}Technetium, ^{201}thallium, ^{18}fluorine and ^{11}carbon agents are the most cited (Di Chiro et al. 1988; Ogawa et al. 1991; Kim et al. 1992; Go et al. 1994; Maria et al. 1994; Shinoura et al. 1997; Dadparvar et al. 2000). ^{201}Thallium SPECT and ^{18}F-fluorodeoxyglucose (FDG) PET are currently the most utilized methods, but additional promising radionuclides are on the horizon (Lorberboym et al. 1997; Maria et al. 1997; Chen and Silverman 2008; Hatakeyama et al. 2008). The remaining discussion is limited to these agents.

13.4.2 Mechanism and Technique

The mechanism of thallium sequestration within tumor cells is unknown. The most accepted theories propose either passive uptake over a potential membrane gradient or high affinity for potassium-activated adenosine triphosphatase (Kaplan et al. 1987; Kim et al. 1992). Alteration of the BBB also contributes (Kim et al. 1992). Whatever the mechanism, thallium seems to be incorporated into neoplastic glial cells considerably more than into nonneoplastic cells. A typical dose for a ^{201}thallium brain scan is 0.03–0.05 mCi/kg, and images are obtained 5–10 min after administering the dose intravenously (O'Tuama et al. 1998).

PET imaging for brain tumors is primarily with ^{18}FDG, a compound that has chemical properties similar to glucose, and is therefore incorporated into astrocytes as an energy source. However, ^{18}FDG cannot be normally metabolized and, therefore, becomes entrapped within cells (Wang et al. 1996a). Increased ^{18}FDG within tumor cells is attributed to the increased rate of glycolysis in rapidly growing neoplasms (Shinoura et al. 1997; De Witte et al. 2000). For pediatric brain scans, 0.14 mCi/kg of ^{18}FDG is given intravenously and images are usually obtained 30 min later (Kincaid et al. 1998; Kaplan et al. 1999).

More recently, ^{18}F-fluorothymidine (^{18}FLT) and ^{11}C-thymidine (TdR) have shown promise as alternatives to ^{18}FDG for the evaluation of brain tumors in adult patients and animal models. These agents may more accurately reflect tumor-cell biology, owing to their interaction with thymidine kinase 1 (TK1), which is preferentially expressed during the S-phase of the cell cycle in proliferating cells. Intracellular phosphorylation of these agents by TK1 results in their retention within tumor cells. In addition, the near absence of proliferating cells in normal brain results in increased conspicuity of tumor from background with these agents. The higher cortical background activity of ^{18}FDG results in a relatively lower sensitivity to distinguish between normal tissue and brain tumor cells (Muzi et al. 2006; Bradbury et al. 2008; Hatakeyama et al. 2008; Ullrich et al. 2008).

13.4.3 Applications and Limitations

The usage of PET and SPECT to distinguish tumor from posttreatment injury has been studied extensively (Fig. 13.3). Both sensitivity and specificity of ^{18}FDG PET are in the range of 80–90% (Di Chiro et al. 1988; Valk and Dillon 1991; Kim et al. 1992; Pujol et al. 1998). At least 80% of pediatric tumors have a high affinity for thallium. It may therefore be useful to distinguish neoplasm from posttreatment granulation tissue (Maria et al. 1998; Brunelle 2000). However, the grade of the neoplasm and histologic type do not always correlate with the amount of thallium uptake (Maria et al. 1994). Pilocytic astrocytoma has a very high metabolic rate and therefore often a high radiotracer uptake, even though it is a relatively benign neoplasm.

The data for PET is calculated from lesions that are at least 5–7 mm in dimension, the lower limits of resolution for this modality. This imposes a limitation on early detection of subtle neoplastic recurrence. Furthermore, the percentage of false negatives is rather high and, as a result, many authors do not consider this method acceptable for making therapeutic decisions (Valk et al. 1988; Ogawa et al. 1991; Kim et al. 1992; Barker et al. 1997). Other PET agents, such as FLT, TdR ^{11}C-methionine, ^{11}C-choline and ^{11}C-tyrosine, have either had limited success in detecting neoplastic recurrence or are under active investigation (Go et al. 1994; Shinoura et al. 1997; Pirotte et al. 2007; Hatakeyama et al. 2008). The 20-min half-life of ^{11}C agents necessitates on-site production, which is an obstacle to widespread use.

Biopsy guidance by PET has been successful in the limited number of patients studied (Go et al. 1994; Massager et al. 2000; Pirotte et al. 2007). In theory, the most aggressive portion of a tumor has the highest glucose uptake and, thus, the highest ^{18}FDG uptake; thus, the PET can assist in localizing the most aggressive portion of a heterogeneous neoplasm for proper staging. However, identification of the most aggressive portion of the tumor has not been reproducible at every institution. This may be due to difficulties in coregistering the PET images to anatomic imaging (e.g., MR imaging) and, perhaps, a result of the difficulty in identifying very small regions of high-grade tumor (Maria et al. 1994; 1998). Furthermore, it can be difficult to differentiate regions of cortex (which has higher ^{18}FDG uptake compared to normal white matter) from regions of tumor recurrence without additional MR imaging.

The thymidine radionuclides do not suffer from this high background activity. Yet, analysis of uptake kinetics for thymidine tracers offers conflicting results as to their utility in assessing tumor proliferation (Muzi et al. 2006; Ullrich et al. 2008). Localizing the most aggressive portion of the tumor with thymidine agents has been most successful with suspected high-grade, untreated gliomas (Muzi et al. 2006).

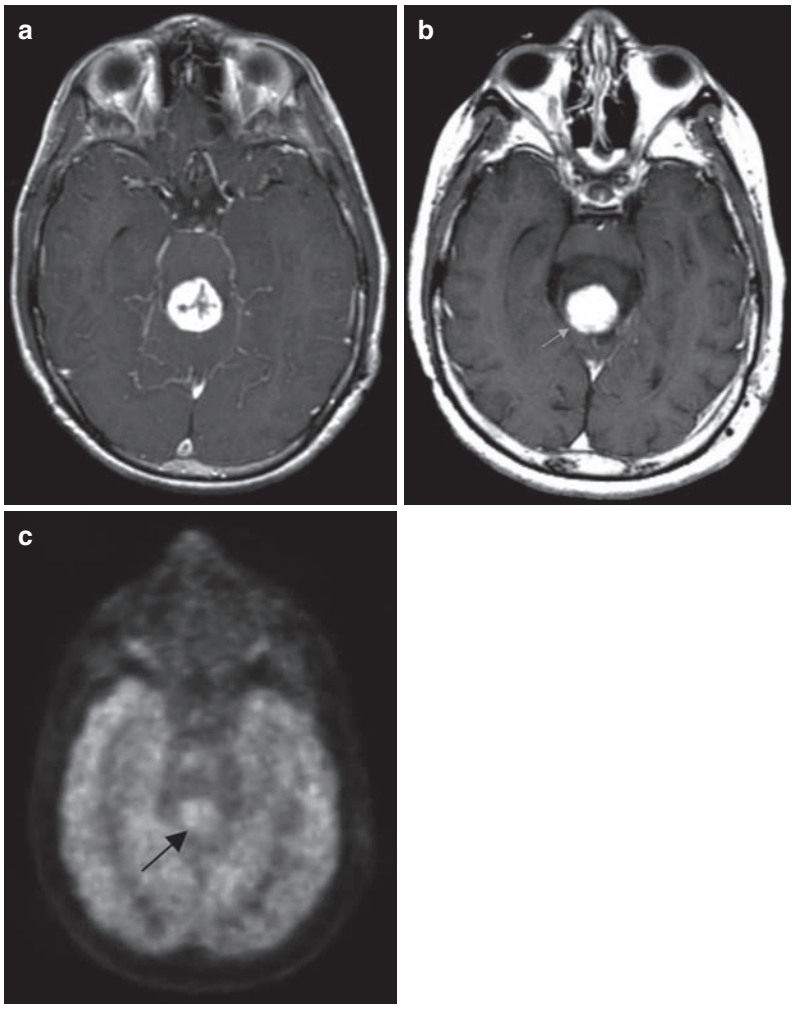

Figure 13.3

PET imaging complimenting anatomic MR imaging in a case of tumor recurrence. (**a**) Axial T1-weighted gadolinium-enhanced image of a tectal glioma at presentation. (**b**) Axial T1-weighted gadolinium-enhanced image of the same tectal glioma after radiation treatment. The enhancing mass may represent posttreatment granulation tissue or residual neoplasm. (**c**) Axial PET image showing increased activity (*black arrow*) within the tectal mass, indicating residual active neoplasm

Accurately predicting tumor grade by imaging is imprecise and remains an elusive goal in practice. Some authors claim that radionuclide imaging is an equivalent, or occasionally better, predictor of survival in patients with a malignant glioma compared with the prediction based on histologic grade (Valk et al. 1988). Others believe that PET is at least adequate to distinguish high- from low-grade brain neoplasms (Valk and Dillon 1991; Black et al. 1994; Kincaid et al. 1998; Provenzale et al. 1999; Pirotte et al. 2007). However, most results indicate that nuclear imaging does not grade brain neoplasms with adequate accuracy to make it useful in clinical practice (O'Tuama et al. 1998; Choi et al. 2000; De Witte et al. 2000; Muzi et al. 2006; Hatakeyama et al. 2008). For example, high-grade neoplasms, often necrotic in part, have low uptake in the necrotic regions so that when averaged with high-uptake regions may appear as low-grade neoplasms when calculating overall uptake. In addition, some low-grade, pediatric neoplasms, such as pilocytic astrocytomas have increased uptake, making them appear to be high-grade neoplasms.

Another potential application of radionuclides is to identify tumors that are sensitive to antiangiogenic

agents (Valk et al. 1988; O'Tuama et al. 1998). Some authors suggest using PET to localize eloquent cortices preoperatively for patients unable to tolerate MR imaging (Kaplan et al. 1999).

In general, radionuclide imaging is infrequently used for pediatric brain neoplasms at UCSF, with conventional MR imaging, MRSI, perfusion imaging, and magnetic source imaging (MSI) being the imaging tools of choice. Each institution should determine the optimal tools for their patients depending upon their equipment and individual strengths.

13.5 BOLD/MSI

13.5.1 Principles

Two techniques used for locating brain activity during specific tasks are blood oxygenation level-dependent (BOLD) imaging and MSI. Many clinical applications of these techniques are under investigation, including evaluating reorganization after injury and deterioration during progressive disease, evaluation of therapies, and cortical mapping prior to neurosurgery (Vezina 1997; Roberts et al. 2000b). These techniques are well-developed in adults, but are less useful in children, as they require a great deal of cooperation by the patient. Some authors have had success in children through the use of multiple training sessions. However, such training requires considerable time, personnel, and space, which are rarely available in most centers. Task-related activations, which require that the patient perform specific tasks, may be difficult or impossible in individuals with deficits such as reading disorders, mental retardation, hearing loss, and paralysis (Breier et al. 1999; Simos et al. 1999; Otsubo and Snead 2001). It is possible to perform some studies on sedated children, but it is not yet clear how much effect the sedation has on the results. Therefore, this section is based mainly on results in adults, in the hope that the difficulties in performing these studies in children will soon be overcome.

13.5.2 Mechanism of BOLD Imaging

In BOLD images, contrast is created by a local increase of oxygenated blood in activated tissue (Stippich et al. 1998; Martin and Marcar 2001). In theory, an activated group of neurons requires increased oxygenation. This increased need is fulfilled by local vasodilation, allowing more oxygenated blood to be transported to the activated cerebral cortex. The increase in blood flow more than compensates for the increased oxygen consumption, resulting in local increase in oxyhemoglobin and decrease in deoxyhemoglobin. As oxyhemoglobin is diamagnetic (does not alter the local magnetic field) and deoxyhemoglobin is paramagnetic (alters the local magnetic field and results in local signal loss), the reduced local concentration of deoxyhemoglobin results in less signal loss and increased local signal intensity (Beisteiner et al. 1995; Boxerman et al. 1995). This local signal alteration can be detected by susceptibility-weighted MR imaging sequences, if multiple acquisitions are performed.

13.5.3 Mechanism of MSI

Neuronal activation results in electrical current, which can be measured with electroencephalography. The electrical current generates magnetic flux, the magnitude of which is in the order of a few picoTeslas, a quantity that is 8 orders of magnitude smaller than that produced from the earth's magnetic field and 12 orders smaller than that produced from MR imaging(Alberstone et al. 2000; Lev and Grant 2000). When performed in a room shielded from external magnetic fields, superconducting quantum interference devices (SQUIDs) (Stippich et al. 1998; Ganslandt et al. 1999) can be used to measure and localize these minute neuromagnetic signals using small receivers placed on the scalp (Alberstone et al. 2000; Papanicolaou et al. 2001). This technique is known as magnetoencephalography (MEG). MEG signal is generated from intracellular electron flux, not local vascular changes (as seen with fMRI) (Roberts and Rowley 1997), distinguishing it from EEG, which detects extracellular currents and is therefore less precise than MEG (Alberstone et al. 2000). Superimposition of MEG data on colocalized MR images is referred to as MSI (Stippich et al. 1998).

13.5.4 Applications of BOLD and MSI

The most widely used clinical application of BOLD imaging and MSI is the localization of eloquent function in the brain for preoperative planning (Fig. 13.4) (Roberts and Rowley 1997; Disbrow et al. 1999). Both BOLD and MSI can accurately localize the primary motor cortex (Roberts and Rowley 1997; Pujol et al. 1998). Sensitivity varies from 82 to 100%, and often depends on whether the primary motor cortex is merely displaced, or partially destroyed by the pathologic process. Both techniques can also be used for localizing the language centers prior to surgical resection of neoplasm or of the temporal lobe for epilepsy (Simos et al. 1999). BOLD may have the additional benefit over MEG of simultaneously localizing multiple areas involved in complex brain function (Roberts et al. 2000b).

The definitive test used to localize motor cortex is intraoperative cortical surface recording (Suzuki and Yasui 1992). For identification of language centers in either the right or left cerebral hemispheres, the Wada test (intracarotid amytal test) has been the standard test for many years, but BOLD techniques have similar sensitivities and are less invasive.

BOLD imaging has two major advantages in comparison to intraoperative surface recording: (1) localization is obtained preoperatively, allowing prospective surgical planning; and (2) the study can be performed at the same time as the preoperative MR imaging instead of lengthening operating room time for an additional procedure. Both techniques suffer when anatomic landmarks are distorted by the tumor, as the surgeon may encounter inadequate surgical exposure of the primary motor cortex, and the navigation based on the MR image may be changed by opening of the calvarium (Cedzich et al. 1996). Anesthetic agents may also influence the sensitivity of both the intraoperative and BOLD techniques (Cedzich et al. 1996), although older children and teens can generally undergo BOLD analysis without the need for sedation. In adults, overall sensitivity of intraoperatively localized eloquent function is roughly 91–94% (estimated by postoperative deficits), which

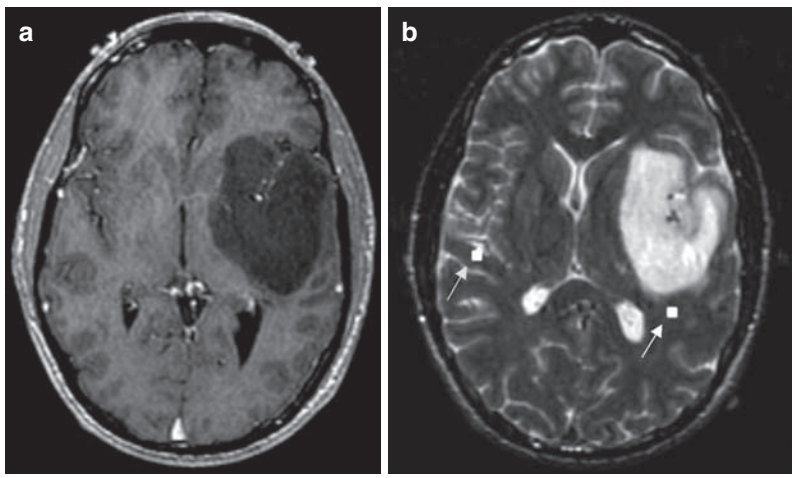

Figure 13.4

Magnetic source imaging for preoperative surgical planning in a patient who presented with grand mal seizure and aura, but without speech or motor deficits. (**a**) Axial T1-weighted gadolinium-enhanced image showing a nonenhancing left temporal lobe/basal ganglia low-grade glioma. (**b**) Axial T2-weighted image showing white squares (arrows) that correspond to areas of auditory stimulation with a 1,000 Hz frequency tone. The auditory cortex on the left side is displaced, but not invaded, by the neoplasm

is similar to functional imaging (Ganslandt et al. 1999; Simos et al. 1999; Szymanski et al. 2001).

The Wada test requires an invasive catheter angiogram and sedation, both with inherent risks. Hemispheric dominance can be established in the majority of cases, but more specific cortical mapping is not possible (Simos et al. 1999). MSI and BOLD are both as sensitive and provide additional information that guides surgical approach and extent of resection (Pujol et al. 1998; Dillon and Roberts 1999; Ganslandt et al. 1999; Alberstone et al. 2000). MSI localizes eloquent regions of cerebral cortex, such as the primary motor cortex, within 3–4 mm in comparison to intraoperative electrocortical stimulation (Breier et al. 1999; Wheless et al. 1999; Szymanski et al. 2001).

13.5.5 Limitations

Several pitfalls must be kept in mind when implementing these new techniques. Limitations of BOLD imaging include poor temporal resolution that can never be better than the time that is required to produce a hemodynamic response to activated neurons, roughly 2–5 seconds (Roberts and Rowley 1997; Lev and Grant 2000; Martin and Marcar 2001). The spatial resolution is dependent on the anatomic proximity of vessels to activated brain; high-signal contribution by sulcal veins has a marked negative effect on resolution (Roberts and Rowley 1997; Dillon and Roberts 1999; Holodny et al. 1999). Infiltration by neoplasm and edema can further distort the anatomic relationship, and possibly alter the autoregulation of local vessels (Pujol et al. 1998; Dillon and Roberts 1999; Holodny et al. 1999). Motion artifact, larger caliber vessels, and inflow effects can further distort localization (Beisteiner et al. 1995; Boxerman et al. 1995; Pujol et al. 1998; Holodny et al. 1999; Field et al. 2000). Despite these shortcomings, BOLD generally localizes activated groups of neurons within 1–2 cm of their anatomic location.

MSI is hindered by susceptibility artifact from orthodontia and other ferromagnetic metals that cause overwhelming artifacts (Breier et al. 1999); BOLD imaging is also affected by such artifacts, but not as severely. The precision of labeling eloquent cortex by MEG is very good, but not perfect. Point localization is reduced by the inaccuracies of transposing data from MEG to MRI, by roughly 4 mm of dispersal (Szymanski et al. 2001). Overall error in localization is thought to be approximately one centimeter (Beisteiner et al. 1995). This is superior to other accepted techniques, including BOLD. The largest drawback of MSI is the cost and lack of availability of the necessary equipment; whereas BOLD can be performed on a clinical magnet with software upgrade, MSI requires an expensive neuromagnetometer in addition to a clinical magnet.

In summary, functional imaging has some potential for use in pediatric brain tumor patients, but a number of problems need to be overcome before these techniques will be used routinely.

13.6 Diffusion Imaging

13.6.1 Principles

Diffusion-weighted imaging (DWI) is a technique that relies on the fact that the motion of water molecules causes decreased signal on specially acquired MR images (Mitchell 1999). Also available are special types of DWI, known as diffusion tensor imaging (DTI) and high angular resolution diffusion imaging (HARDI), which allow both the net direction and the magnitude of water motion in a voxel to be determined. These techniques have applications in the assessment of brain tumors.

13.6.2 Technique

All diffusion techniques allow the calculation of net water motion in a volume of tissue. The mean diffusivity (MD) represents the average motion of all free water molecules in a voxel during the period of the MR data acquisition (Inglis et al. 1999; Poupon et al. 2000; Filippi et al. 2001).

DTI and HARDI are based upon mathematical probability functions that calculate the precise net motion characteristics of the water protons in the voxel; in other words, they give the probability that any molecule is moving in any direction at any velocity during the time of the imaging. If all the water

protons are equally free to move in all directions, the motion is said to be isotropic. If water protons move predominantly in one direction more than others (due to restricted movement in some directions or accentuated movement in others), the motion is said to be anisotropic. In the normal brain significant anisotropy is seen in the white matter. Water motion is greatest along the long axis of the axon fascicle, parallel to the axons and the axoplasmic flow. Motion along the short axis is perpendicular to the axons in the fascicle, hypothesized to be primarily impeded by the cell membrane and hydrophobic myelin sheath. The characteristics of the motion can be displayed either as images or mathematically (Pierpaoli et al. 1996; Melhem et al. 2000; Filippi et al. 2001; Gauvain et al. 2001).

Fractional anisotropy (FA) and MD are measurements derived from the diffusion tensor that have been independently studied with brain tumor imaging. FA quantifies the magnitude of diffusion directionality and is hypothesized to reflect the degree of alignment of cellular structures within fiber tracts as well as their structural integrity. MD (also called average diffusivity or apparent diffusion coefficient) is a measure of mean molecular motion that is hypothesized to be affected by cellular size and integrity. These measurements are commonly displayed as quantitative color maps overlying the brain images using commercially available software.

13.6.3 Applications

Few applications of diffusion imaging have been implemented for the routine analysis of pediatric brain tumors. DWI is less sensitive than routine sequences for assessing the extent of tumor involvement (Stadnik et al. 2001). Distinguishing between high- and low-grade primary tumors using MD values has too much overlap to be clinically useful (Lam et al. 2002). One area in which diffusivity measurements have been found to be helpful is in distinguishing between ring-enhancing tumors and pyogenic abscesses. In general, cystic tumors have increased water motion compared with surrounding brain, but pyogenic abscesses have reduced water motion secondary to protein content from bacteria and inflammatory cells (Fig. 13.5) (Gauvain et al. 2001).

Diffusion characteristics can also be helpful to distinguish between cystic and solid tumors. For example, differentiation between an arachnoid and an epidermoid cyst may be difficult by conventional MR sequences or CT. CSF freely moves in an arachnoid cyst and therefore is isointense to the CSF space on DWI. An epidermoid cyst, however, is gelatinous and therefore has diffusion characteristics similar to brain tissue (Gauvain et al. 2001).

A current area of research for the use of DWI in brain tumor patients is delineating postoperative injury (Tanner et al. 2000; Smith et al. 2005). Acutely injured tissue generally has reduced diffusion for several days to weeks after the surgery. Nodular and fingerlike areas of reduced diffusion around the surgical cavity in the first few days after tumor resection likely represent tissue injury in the region of the resection (Fig. 13.6). Such areas will generally show marked enhancement from 2 weeks to 6 months after surgery, and ultimately evolve to become astrogliosis or encephalomalacia. Mistaking this area of enhancement for recurrent tumor on the early postoperative scans could lead to unnecessary treatments that could adversely affect the patient (Smith et al. 2005). Therefore, analysis of the DWI on the early postoperative MRI scans is recommended to help determine whether new enhancement on later postoperative imaging is the result of perioperative injury versus recurrent tumor.

DTI can be used to identify specific white matter tracts within the brain, a technique referred to in the literature as tractography. Tractography is helpful in localizing large bundle white matter tracts, such as the corticospinal tracts, based on anatomic characteristics (Fig. 13.7). Knowledge of the location of these tracts, which can be shifted by mass effect from the tumor, can reduce postoperative morbidity and allows for more aggressive tumor resection, which has been shown to improve long-term survival (Keles et al. 2006; Smith et al. 2008).

Obtaining DWI in the spine is difficult due to artifact created by the bony spinal column. Moreover, the small size of the spinal cord creates problems in resolution. For these reasons, clinical applications of DWI for spinal cord tumors are infrequent. Nevertheless, this remains an area of active research.

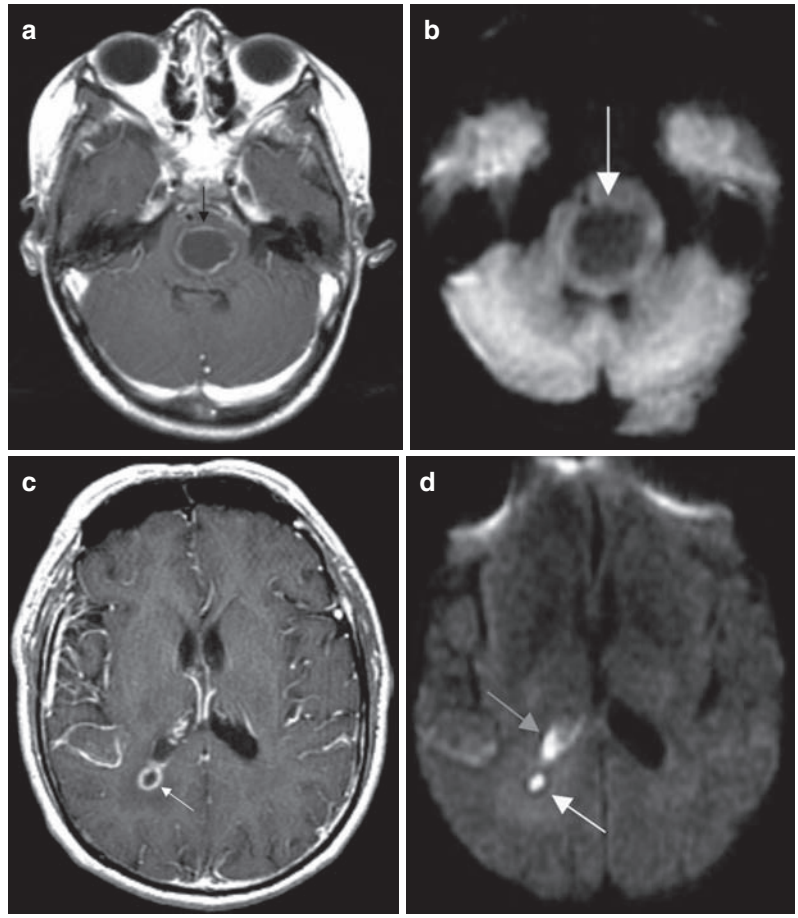

Figure 13.5
Diffusion-weighted images used to help distinguish abscess from necrotic glioma. (**a**) Axial T1-weighted gadolinium-enhanced image showing a rim-enhancing, centrally hypointense brainstem lesion (*black arrow*). (**b**) Axial diffusion-weighted image at the same level showing increased diffusion within the central portion of the lesion (*white arrow*) consistent with a necrotic glioma. (**c**) Different patient. Axial T1-weighted gadolinium-enhanced image showing a deep right parietal ring-enhancing lesion (*white arrow*). (**d**) Axial diffusion-weighted image at the same level showing reduced diffusion within this lesion (*white arrow*) and adjacent ventricle (*gray arrow*) confirming that this was an abscess and not a neoplasm

One last potential application is possibly detecting loss of anisotropy in tumors; a few studies suggest that DTI may be able to distinguish between high- and low-grade neoplasms (Gauvain et al. 2001). In addition, reduced diffusion (measured on the MD map) within medulloblastomas and ependymomas is a sensitive feature to distinguish these cellular tumors from less cellular astrocytomas found in the posterior fossa (Rumboldt et al. 2006; Schneider et al. 2007). In summary, diffusion-weighted sequences have several promising applications in pediatric brain tumor imaging that are under active investigation and will have an expanded role in the future.

13.7 Magnetization Transfer

13.7.1 Principles

Magnetization transfer is a technique that allows imaging of molecules that interact with macromolecules in the brain (predominantly the components of myelin) separately from free, unbound water molecules. This technique gives us indirect information about the macromolecules that the water has interacted with. Although it is a useful technique in the assessment of patients with disorders of myelin, particularly multiple sclerosis, few applications to brain tumor imaging have been discovered.

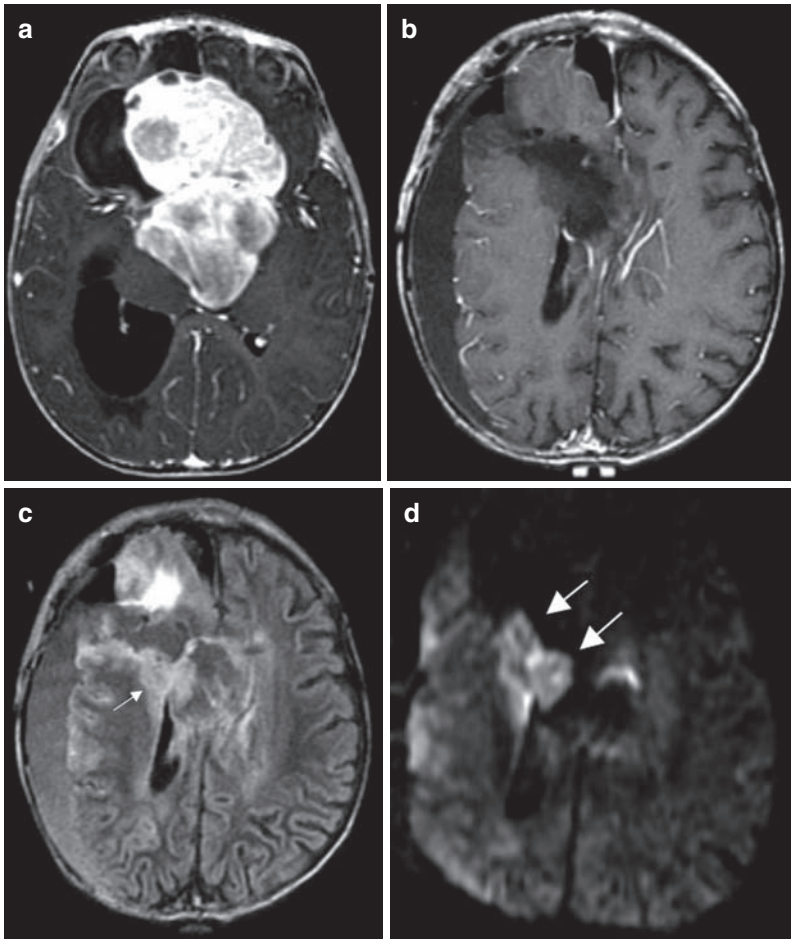

Figure 13.6

Large chiasmatic and hypothalamic astrocytoma treated with partial surgical resection showing imaging evidence of postoperative ischemia. (**a**) Axial T1-weighted gadolinium-enhanced image shows the enhancing tumor preoperatively. (**b**) Axial T1-weighted gadolinium-enhanced image shows the postoperative resection cavity without evidence of residual enhancement. (**c**) Axial fluid attenuation inversion recovery (FLAIR) image of the resection cavity with thick posterolateral rim of high signal (*white arrow*) that may represent interstitial edema and/or injury. (**d**) Axial diffusion-weighted image at the same level shows high intensity (*arrows*), confirming that the area of increased signal on the FLAIR image was not edema, but postoperative ischemia

13.7.2 Technique

Magnetization transfer images can be obtained by acquiring two sets of gradient echo scans with gradient spoilers. Data is best acquired using a repetition time of 300 ms, echo time of 7 ms, *theta* (flip angle) of 20°, 3-mm partition thickness, 12-cm field of view, and 3D Fourier transform reconstruction techniques. The amount of magnetization transfer in e different regions of the brain, which reflects the amount of water-binding macromolecules, can be calculated from region-of-interest measurements (MTR = (Mo–Ms)/Mo, where MTR is the magnetization transfer ratio, M_o is the magnitude of signal without saturation by an off frequency radiofrequency pulse and M_s is the magnitude of tissue signal with the saturation pulse on) (Graham and Henkelman 1997). Alternatively, magnetization transfer images can be produced when the off-resonance radiofrequency (RF) pulse is applied during the imaging sequence. Application of this pulse negates the contribution of bound water protons to the overall MR image. As the binding of the macromolecules causes T1 shortening (by slowing the rotation and translation of the water molecules), the high signal of cerebral white matter is reduced on T1-weighted images.

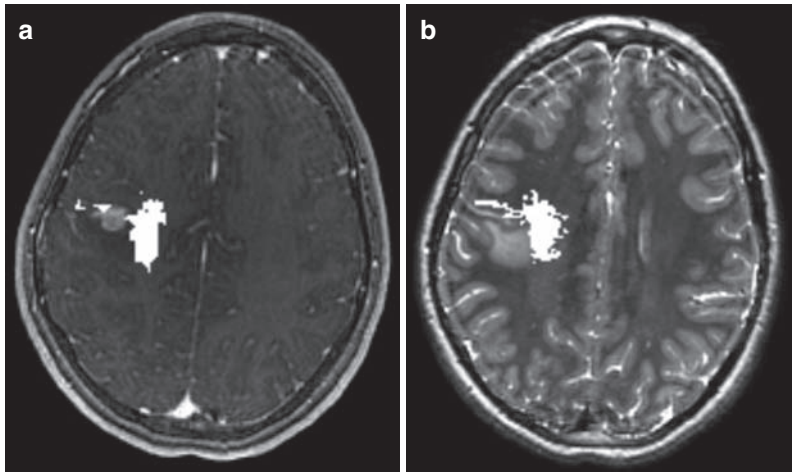

Figure 13.7

Small ganglioglioma within the postcentral gyrus presenting with left-arm seizures. (**a**) Axial 3D Spoiled Gradient Recalled (SPGR) gadolinium-enhanced image shows the corticospinal tracts medial to the enhancing tumor by diffusion tensor imaging (DTI) fiber tracking. The fiber tracts are overlaid on the anatomic images. (**b**) Axial T2-weighted image at the same level showing a similar relationship

13.7.3 Applications

The major application of magnetization transfer imaging for brain tumors is to increase lesion conspicuity; by reducing the hyperintensity of white matter on T1-weighted images, enhancement becomes more conspicuous. The literature is mixed concerning the effect of magnetization transfer imaging on lesion conspicuity after administration of low-dose gadolinium (Knauth et al. 1996; Han et al. 1998; Haba et al. 2001). It is generally accepted that lesion conspicuity after administration of a low gadolinium dose with magnetization transfer is as good as high-dose imaging without magnetization transfer in the evaluation of extra-axial neoplasms (Han et al. 1998; Haba et al. 2001). Higher sensitivity in defining the involvement of intra-axial neoplasms by magnetization transfer, in comparison to routine MR imaging, has been proposed, yet remains unproven (Grossman et al. 1994).

Other authors have explored the possibility that magnetization transfer may distinguish cystic neoplasms from cystic infection. A potential role has been proposed in separating nonpyogenic abscesses (such as tuberculomas) from neoplasms (Pui 2000; Gupta et al. 2001). If proved in subsequent studies, this application would fill a void where MRS is deficient. At present, bacterial abscesses are better evaluated by MRS (Kim et al. 1997; Grand et al. 1999).

13.8 Improving Image Sensitivity to Analyze Small Tumors

Subtle or small neoplasms of the cortex (ganglioglioma, DNET), internal auditory canal (schwannoma in neurofibromatosis), and spinal cord (astrocytoma, ependymoma) can be missed on traditional MR sequences. There are primarily two methods to increase sensitivity to detect and characterize these neoplasms when they are small: higher resolution images obtained with a high-field-strength magnet (4+ T) or imaging with a routine strength magnet and using special coils and software (Moyher et al. 1997). In the past, use of phased array surface coils

and image intensity correction algorithms increased the signal-to-noise ratio for superficial lesions beyond traditional imaging sequences. Newer multichannel coils, using parallel imaging, are now commercially available as an alternative to surface coils and provide similar sensitivity.

13.9 Conclusions

Neuroradiologic evaluation of tumors has grown to include many more techniques than anatomic imaging. Metabolic assessment, assessment of perfusion, and assessment of the function of surrounding brain can now be performed along with anatomic imaging in a single visit to the MR suite. These techniques provide useful tools to assess the character of pediatric brain tumors and their responses to therapy.

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Current Surgical Management

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Contents

14.1 Introduction

For the majority of brain tumors in children, the extent of resection is the most important factor predicting long-term outcome. This has led many neurosurgeons to be as aggressive as possible during the initial surgical procedure in an effort to achieve gross total resection (GTR;(Pollack 1999)). It should be recognized that GTR is not the primary goal for tumors, where sensitivity to adjuvant therapy is high (e.g., germinoma), or where there is clear extension into eloquent regions (e.g., brainstem and thalamic glioma). Fortunately, these latter groups represent a minority of pediatric brain tumors (Pollack 1994).

The majority of pediatric tumors are primary glial neoplasms arising within the cerebellar or cerebral hemispheres. Factors affecting the extent of resection are: relation to functionally important structures, degree of infiltration, and the presence or absence of tumor dissemination at time of presentation. Although the portions of infiltrative supratentorial tumors that extend into eloquent locations (primary motor, speech cortex, basal ganglia, or major white matter tracts such as the internal capsule) are likely to defy GTR, an argument can be offered for extending resection sufficiently to allow a change to occur in the natural history of the disease (Keles et al. 2001). Earlier, the definition of eloquent cortex relied mainly on variable anatomical maps, and resective procedures were limited by the inability to predict functional anatomy in specific patients. In the posterior fossa, GTR is limited either by involvement of the brainstem or the cranial nerves. Monitoring of virtually all cranial nerves is now possible, which greatly

facilitates safe dissection of the tumor from normal structures. Infiltration into the brainstem by malignant tumors is not amenable to surgical resection.

Progress in various technologies has allowed maps to be created for individual patients that define the actual boundaries of eloquent cortex. These advances consist of neuronavigation, coupled with high-resolution anatomic imaging noninvasive functional imaging, and adaptation of brain and spinal cord mapping techniques to the pediatric population.

14.2 Technical Adjuncts for Resection of Brain Tumors

14.2.1 Ultrasound

Despite recent technological advances centered around three-dimensional navigation based on preoperative magnetic resonance imaging (MRI), a well-established and time-tested intraoperative tool is the ultrasound (Gooding et al. 1983). Intraoperative ultrasound remains a safe, nonradiative method used to determine depth, tissue consistency (solid, fluid-filled, complex, etc.), and relationship to adjacent anatomic structures. Doppler ultrasonography, in particular, is useful for determining proximity to vascular structures. Ultrasound avoids the pitfalls of initial misregistration and tissue shift during the course of tumor resection. It does not rely on static, preoperative imaging, but instead provides real-time updates regarding extent of resection (Fig. 14.1). Ultrasound lacks the image resolution of MRI, but it compensates for this shortcoming with low cost, reliability, ease of use, and shortening of operative time.

14.2.2 Neuronavigation

Conventional MRI provides the necessary detail to assess the anatomic relationships of most intracranial tumors. Several manufacturers supply systems that use a preoperative MRI scan as the basis for an intraoperative three-dimensional guidance system. In their various configurations, these are all considered neuronavigation systems. Standard MRI may be complemented by more specialized MR techniques (see Chap. 13) such as MR spectroscopy (MRS), diffusion tensor imaging (DTI), and functional MRI (fMRI), in addition to other tools such as magnetoencephalography (MEG) and conventional catheter angiography. These special MR sequences can be merged with conventional anatomic images, and then used in the operating room during surgery.

Neuronavigation has impacted brain-tumor surgery in three major ways. First, surgical routes can be simulated and planned preoperatively, allowing

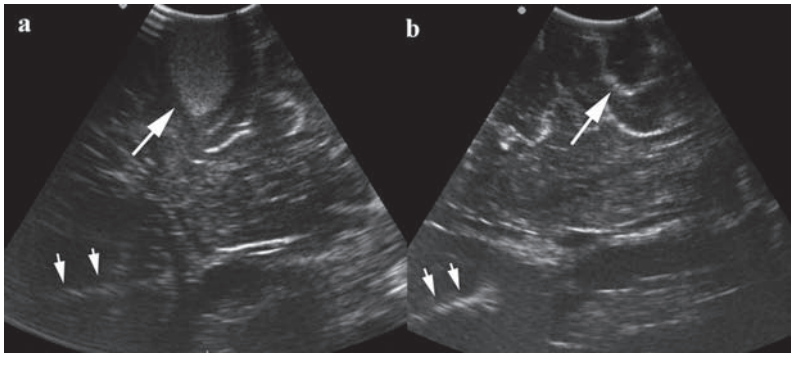

Figure 14.1

Intraoperative ultrasound images of a 4-year-old boy with a low-grade glioma of the left frontal lobe. Preresection (**a**) and postresection (**b**) coronal plane images demonstrate the distinct echogenicity of neoplastic tissue (*large arrow*) from the surrounding brain. The midline falx cerebri is seen as an anatomic reference point (*small arrows*)

maximum accuracy of craniotomy placements and cortical incisions. As a result, mistakes in trajectory and depth during tumor resection are prevented. Second, the shortest and safest route through brain tissue that avoids important neural and vascular structures can be determined well before the procedure. This reduces the risk of postoperative neurologic deficits, and improves assessment of risk preoperatively. Third, the use of neuronavigation improves the extent of tumor resection by providing "feedback" to augment the surgeon's perception of anatomic placement. Despite all these advantages, the major limitation of preoperative registered imaging data is obvious: intraoperative shifts of tissue cannot update a static set of data obtained prior to tumor resection.

The original intraoperative navigation systems used metal stereotactic frames rigidly attached to the calvarium. These were referred to as "frame-based" stereotactic devices. Target guidance relied upon anatomic coordinates as defined in anatomic atlases. Coordinates and targets could be refined modestly by imaging studies such as plain films and air ventriculograms. The inherent inaccuracy of this system is obvious, in that patient-specific data is not used to guide the actual procedure. A critical advance occurred when computed tomography or MRI scans were used in conjunction with frame-based systems (e.g., Leksell, Brown-Roberts-Wells [BRW], Cosman-Roberts-Wells [CRW)]) to select targets and mathematically compute trajectories. These systems use guidance arcs that move directly over the surgical field and obstruct the surgeon if a large craniotomy is to be performed. These systems are, however, highly accurate and continue to be used widely in situations where target selection is critical such as Gamma Knife radiosurgery and functional procedures such as pallidotomy (both of which utilize refinements of the Leksell frame, Elekta AB, Stockholm).

Advances in technology with sufficient computational power to allow manipulation and calculation of three-dimensional image sets represented a major innovation in the field. This led to the creation of systems known as "frameless stereotaxy" that recreated a three-dimensional volume space by using fiducials placed on the patient's head and registered to a preoperative imaging study. This allows "real-time" intraoperative guidance, and the facility to visualize the target in multiple planes (Fig. 14.2). A variety of tools, including surgical instruments, can also be registered and used as pointers that provide continuous updated information on a computer monitor as the tumor resection is performed. In children, the requirement for a preoperative MRI scan can limit the use of neuronavigation if general anesthesia is required for the imaging study. Nonetheless, many centers routinely use neuronavigation in all pediatric brain-tumor cases. Earlier, keeping scalp fiducials in place was a major problem, which was solved by the use of surface registration of facial landmarks (Gleason et al. 1994).

Intraoperative MRI (iMRI), the next step in image-directed surgery, allows continual updating of preoperative image sets and adjustment of navigational parameters. This technique has been used to augment posterior fossa procedures (Lam et al. 2001; Chen et al. 2007). Some reports indicate that the use of intraoperative imaging improves the extent of resection, although it is unclear whether it results in improved outcomes (Fahlbusch et al. 2000; Schneider et al. 2001). An intermediate step is the use of intraoperative-ultrasound-assisted navigation as a means to update imaging data (Regelsberger et al. 2000). Integration with functional information obtained from MRS, DTI, and fMRI allows intraoperative "guideposts" for the surgeon, delineating regions amenable to resection and regions representing eloquent cortex or functional tracts (Nimsky et al. 2006).

14.2.3 Functional Imaging

Several imaging technologies have been adapted to create functional maps of the brain: fMRI, diffusion weighted imaging (DWI), positron emission tomography (PET), and MEG. Differences that occur in blood flow between the active and inactive cortical areas are exploited by fMRI. These differences are magnified by instructing the patient to perform repetitive tasks, which may be as simple as repeatedly moving the fingers. Local increases in blood flow are then detected by specific MRI sequences. Patient cooperation is, of course, required.

DTI exploits the differences in the diffusion of water molecules depending on the local

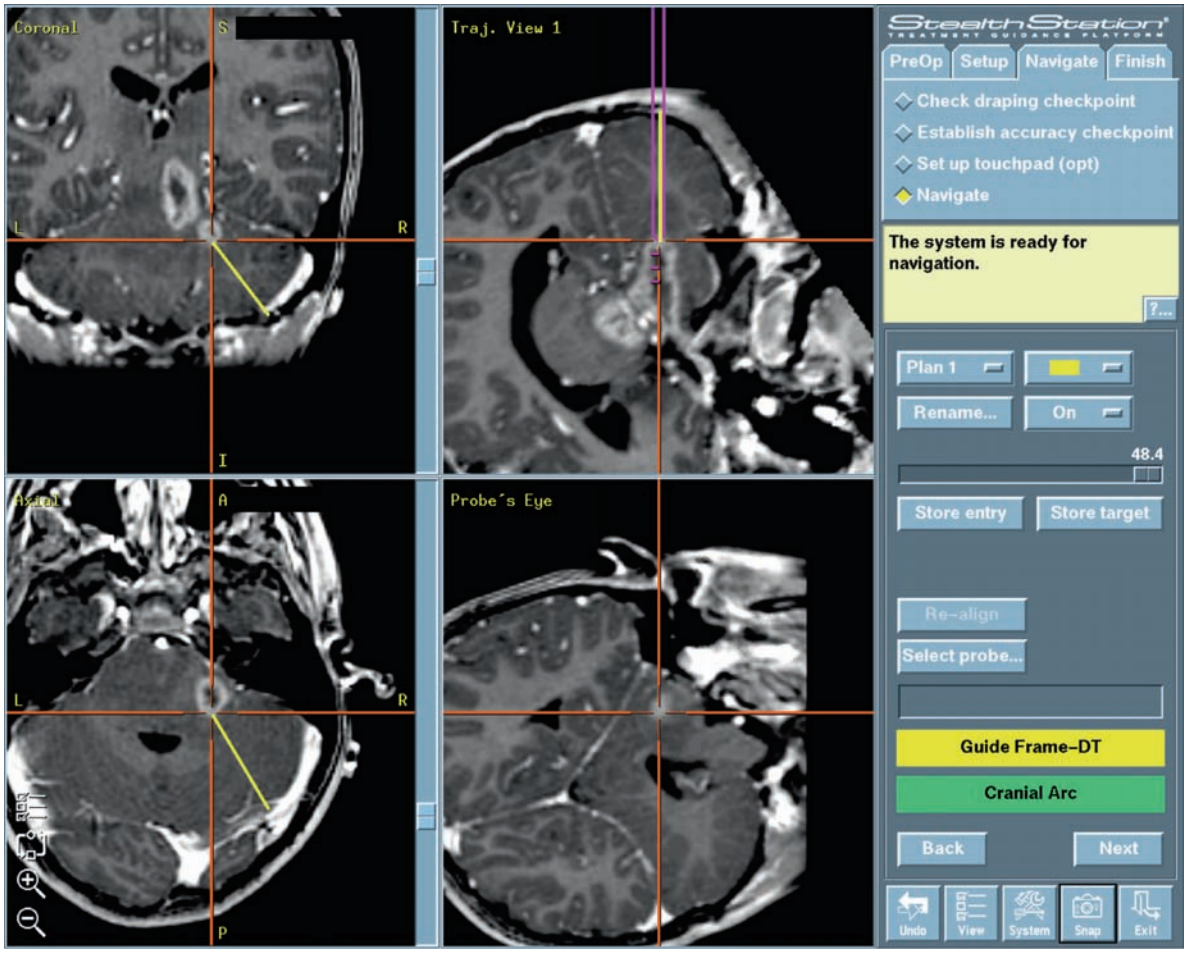

Figure 14.2

A screen capture image from a brainstem biopsy procedure. The biopsy trajectory is shown in three planes and the tip of the biopsy needle can be tracked in real time as it enters the brain ("Probes Eye" view, *bottom right*). StealthStation is a trademark of Medtronic Corporation (Minneapolis, MN)

environment of those molecules (e.g., water molecules within axons vs. those in the interstitial space) (Pierpaoli et al. 1996). This information can then be extracted to create maps demonstrating the location and direction of white-matter pathways. Large white-matter pathways are particularly well- identified using these techniques (see Chap. 13, Fig. 13.7).

Preoperative use of PET was originally presented by LeBlanc and Meyer (1990) and Leblanc et al. (1992). PET relies on metabolic differences within active cortex to isolate functional areas. More recently, a variety of radiolabeled compounds such as [^{18}F] fluorodeoxyglucose (FDG), [^{11}C] L-methionine, and [^{15}O] H_2O were used by Kaplan et al. to create functional maps prior to brain tumor resection in a pediatric

population (Kaplan et al. 1999). Coregistering [^{15}O] H_2O PET images with MRI allowed accurate determination of eloquent cortex prior to tumor resection. PET has also been used to select targets for biopsy within brainstem tumors (Pirotte et al. 2007).

MEG relies on the ability to detect single dipole magnetic fields created by the pooled activity of groups of neurons to define potential areas of seizure activity (Chuang et al. 1995; Otsubo et al. 2001). Further refinement of these techniques, known as magnetic source imaging (MSI), allows the identification of functional areas of cortex and deep brain regions (Fig. 14.3). This information is especially valuable when correlated with tumor localization (Schiffbauer et al. 2001). Delineation of entire functional pathways using a combination of techniques may be possible in the near future.

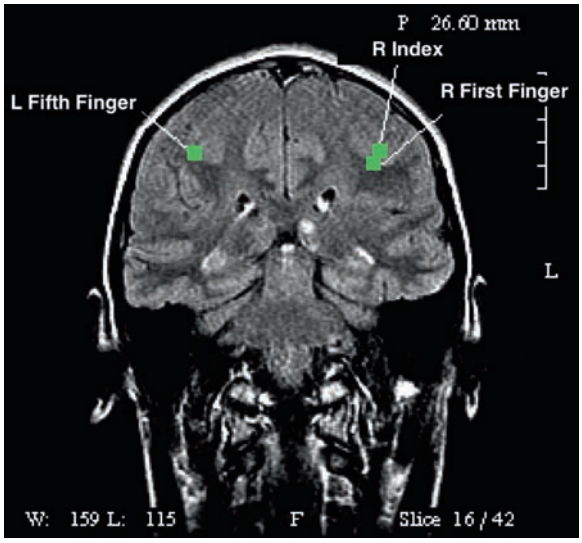

Figure 14.3

Magnetic source imaging (MSI) of a 15-year-old boy with an infiltrative anterior insular mass (not visible in this image). *Green squares* demonstrate sensory cortex representing left fifth finger, right index finger, and right first finger. These functional maps were integrated into the neuronavigation system prior to tumor resection

14.2.4 Cortical Mapping for Supratentorial Tumors

The gold standard for functional mapping of the human brain remains direct electrical stimulation of the cortex and observation of its effect upon patient-directed actions during open craniotomy (Berger and Ojemann 1992). Although pioneered in the early part of the twentieth century, continual refinements are improving the sensitivity and accuracy of these techniques. For the most part, the vast majority of mapping cases are restricted to either motor or speech mapping. The major limitations of cortical mapping in children are the relative immaturity of the central nervous (CNS) system in very young children, and the inability of children to cooperate in the execution of repetitive language tasks during speech-mapping procedures.

Motor mapping as described by Penfield remains the most robust electrical technique that can be practiced in the operating room (Penfield and Boldrey 1937). Patients remain under general anesthesia and direct systematic electrical stimulation of the precentral area permits the accurate mapping of primary motor cortex. Areas of cortex responsible for specific muscle groups (e.g., face, arm, hand, leg) can be reliably identified. A bipolar electrode with 5-mm spacing is used to deliver stimuli at 60 Hz with duration of 1 ms (biphasic square wave pulse). In children less than five years of age, the cortex is generally less excitable by direct stimulation and motor cortex may not be clearly identified. An alternative method to detect the location of the central sulcus is by detecting a phase-reversal potential as one records over the motor and sensory cortex. Using subdural grids, mainly for the treatment of patients with epilepsy, Chitoku et al. were able to define the motor cortex in all children studied, using a variety of stimulation thresholds (Chitoku et al. 2001). Younger children responded to stimuli in the range of 8–12 mA, while older children responded to stimuli in the range of 4–6 mA.

For language mapping, a basic surgical decision point is whether a child can tolerate an "awake craniotomy" (usually above 10–12 years of age). Language mapping is entirely dependent upon patient cooperation and,

therefore, is the most difficult technique to accomplish in young children. During an awake craniotomy, a handheld stimulator is used to directly inactivate the cortex, while the patient names objects presented visually. Stimulation of Broca's area, which is often adjacent to the primary motor cortex, usually leads to speech arrest although significant variability exists between individuals of different ages (Haglund et al. 1994; Ojemann et al. 2003). Current techniques of speech mapping allow accurate intraoperative localization of speech function with minimal long-term impacts upon speech function following tumor resection (Sanai et al. 2008).

In children unable to tolerate an awake craniotomy, and for whom functional localization is crucial to the success of the procedure, placement of subdural grids allows bedside cortical mapping. This requires two procedures for the patient, a substantial degree of patient cooperation, and close communication between child neurologists, psychologists, and nursing staff. Generally, this technique can be performed in children above the age of 4 years, although it is most reliable in older children. The first procedure involves a craniotomy encompassing the area of resection and placement of an implantable subdural grid containing multiple electrical contacts. The contacts on the grid are then stimulated sequentially, while the patient is led through specific language tasks such as naming, counting, and repeating. As with awake craniotomy, speech arrest during stimulation is the clue for identifying active cortex. Language paradigms have to be tailored according to the age of the patient and level of comprehension. The procedure is time-consuming and laborious, often requiring sessions over 2 or 3 days. In the patient shown in Fig. 14.4, an infiltrative tumor was noted in the left frontoparietal region. Although the patient was but 5 years old, he tolerated placement of subdural grids for several days and bedside mapping revealed the locations of the language and motor cortex allowing an extensive resection of the tumor.

14.2.5 Mapping of Seizure Foci

If seizures are particularly intractable or appear to be the dominant symptom associated with a brain tumor, the actual ictal focus may need to be identified. For most types of epilepsy associated with a definite lesion, resection of the lesion will result in seizure control in the majority of cases (Mosewich et al. 2000). In some cases, the presence of a tumor is only detected after pathologic examination of the resected tissue. In a series of surgical treatment for epilepsy, approximately 25% of temporal lobe resections revealed a neoplasm, the majority of which were dysembryoblastic neuroepithelial tumors (DNET, see Chap. 8) (Hennessy et al. 2001).

Scalp electroencephalography is an essential first step in localization of seizure foci. This may be complemented by MEG or invasive monitoring with subdural grids and strip electrodes. Insertion of a subdural grid electrode array provides ictal and interictal information. Strip electrodes are used for recordings from mesiobasal structures. In addition, recording along the hippocampus can be performed following the removal of lateral temporal cortex and entry into the temporal horn of the lateral ventricle. Strip electrodes may also be used for the orbitofrontal cortex or under the bone flap, if the cortical exposure is not adequate. The recording may either be done for short time periods intraoperatively (5–20 min) prior to resection, or for prolonged periods postoperatively in the ward in specialized monitoring units. Intravenous infusion of methohexital (Brevital 0.5–1 mg/kg) may be used to chemically induce ictal discharges if epileptiform activity is sparse. Following tumor removal, electrocorticography is always performed in patients with identifiable preresection seizure foci. Infrequent spike activity is not pursued, especially when it involves functional cortex. Resected seizure foci are identified with respect to their geographic orientation to the tumor nidus, and should be submitted separately for histopathologic analysis.

14.3 Posterior Fossa Tumors

14.3.1 Surgical Principles

Posterior fossa tumors are among the most commonly encountered tumors in children, and are located in the midline within the vermis, cerebellar hemisphere, and/or brainstem. Standard approaches

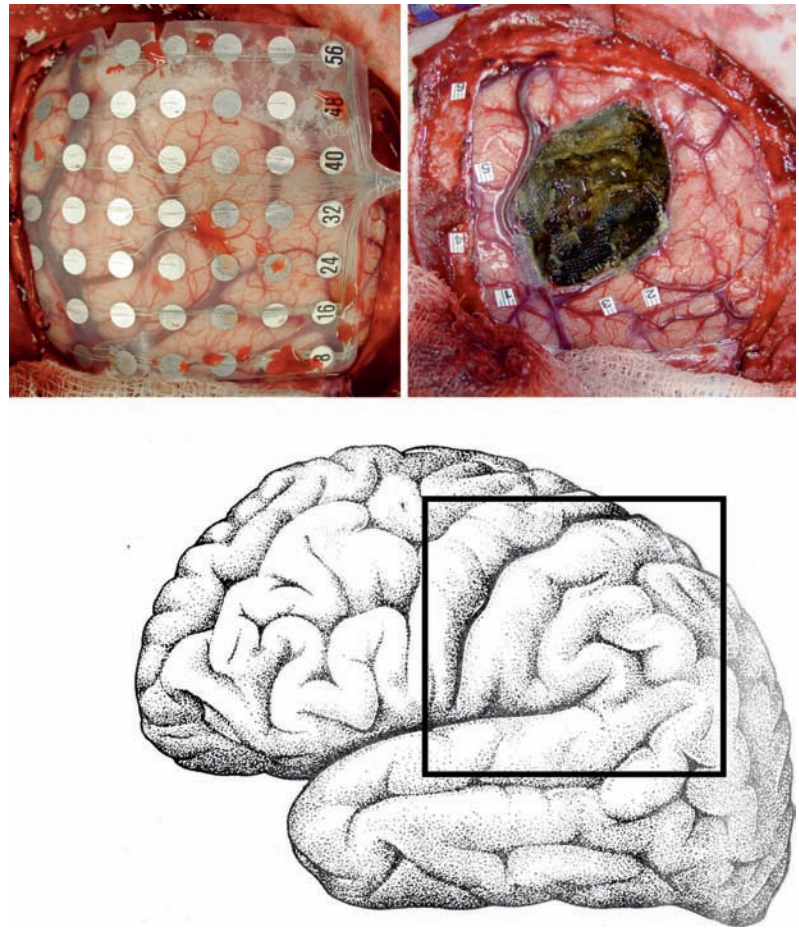

Figure 14.4

An implanted subdural grid used to map speech and motor cortex in a 5-year-old boy with an infiltrative tumor of the left hemisphere. A 64-contact subdural grid was implanted over the area of the tumor (*left image*). Speech cortex was localized to numbers *2* and *3* during two sessions in the telemetry unit, and motor cortex to numbers *1, 4, 5*, and *6* (*right image*). The location of the tumor was correlated with intraoperative neuronavigation and an extensive resection was performed

to the posterior fossa are well developed and are described in various sources in the literature. Surgical planning is often modified by the pathology of the tumor. The three main pathologic types that occur in this location are astrocytoma, medulloblastoma, and ependymoma. Cerebellar astrocytomas are usually eccentric in location, associated with a cyst, and often cause obstructive hydrocephalus. Medulloblastomas are characteristically midline tumors occupying the vermis and in some cases extending into the cerebellar hemisphere. Ependymomas of the posterior fossa can extend into the fourth ventricle and also may extend into the cerebellopontine angle closely associated with the cranial nerves. Both ependymoma and medulloblastoma can invade the brainstem.

For midline tumors, the standard approach is to position patients prone, with the head flexed forward. A vertical incision allows access to most of the posterior fossa. If the tumor extends anterior to the cerebellum or brainstem, the tumor must be approached from a more lateral position; often with the head turned to allow a posterolateral trajectory. In the past, most surgeons would remove the overlying bone without replacement (craniectomy), but now, most surgeons attempt to replace the bone flap at the conclusion of the procedure (craniotomy). There is some evidence that this reduces the risk of cerebrospinal fluid (CSF) leakage and pseudomeningocele formation (Gnanalingham et al. 2002). Dural opening is followed by definition of the boundary

between the tumor and the normal cerebellum. The character of the interface between tumor and brain can vary across tumor types. In general, the interface is better defined with ependymomas as compared to medulloblastomas. Cerebellar astrocytomas have a clear margin between the tumor and the adjacent brain. The large size of most pediatric tumors and the need to avoid unnecessary brain retraction results in many tumors being resected piecemeal using either standard tools (cautery and suction) or ultrasonic aspirators that use a rapidly vibrating metal tip to disintegrate tissues. Removal of the central portion of the tumor then allows reflection of the deeper tumor tissue into the operative field and subsequent removal. For deep tumors, and those related to important structures, the use of frameless stereotaxy (neuronavigation) has revolutionized intraoperative guidance and structure localization.

Finally, additional safety can be obtained by monitoring various cranial nerves such as the facial, oculomotor, and hypoglossal nerves (Grabb et al. 1997; Sekiya et al. 2000). Tumors either infiltrating the floor of the fourth ventricle or along the anterior portion of the brainstem involve cranial nerves. These nerves are sensitive to manipulation, and can be difficult to identify when tumors surround them. Gradual dissection through tumor tissue requires careful identification of important structures.

14.3.2 Complications

Surgical resection of posterior fossa tumors may lead to both nonneurologic and neurologic complications (Table 14.1). Fortunately, the majority of these adverse effects are either transient or treatable, making the overall morbidity quite low. The tendency of posterior fossa tumors to occupy a midline position creates a stereotypical pattern of symptoms following surgery.

Table 14.1. Complications following surgery for cerebellar astrocytoma

Complication	Percent
Pseudomeningocele	12–24
Wound infection	2–5
Aseptic meningitis	4.5
Septic meningitis	6
Persistent hydrocephalus	10
Hematoma	
Epidural	3
Subdural	3
Operative site	1.5
Transient CN palsy	4.5
Hemiplegia	1.5
Transient mutism	1.5
Permanent neurological deficit	15

14.3.2.1 Injury to Local Structures

Symptoms include long-tract signs of weakness and sensory loss, mutism, and cranial neuropathies (Cochrane et al. 1994). Ataxia and dysmetria are usually due to retraction injury or swelling of the cerebellum and improve after several weeks and months. Injury to the vermis can cause disabling truncal ataxia, which may improve, but can be permanent, particularly if large areas of the vermis have been involved. Impaired initiation of chewing, voiding, and eye opening may present after injury to areas of the cerebellum responsible for repetitive motor movement memory. Restiform body injury may result in permanent ipsilateral limb ataxia (Rosenfeld 2000b). Patients with these deficits commonly have tumors involving the floor of the fourth ventricle, the brainstem, or cerebellar peduncles. Sometimes, removal of a hemispheric tumor creates enough intracranial shifts to affect cranial nerve VI and cause transient diplopia. Approximately one-half of those with new deficits experience complete recovery of function (Pollack et al. 1995; Ersahin 1998).

14.3.2.2 Cerebellar Mutism

Cerebellar mutism is a well-recognized complication of surgical removal of large midline posterior

fossa tumors in children. Patients demonstrate transient mutism with unimpaired consciousness, intact comprehension, and no detectable cranial nerve or motor deficits. The majority of cases will awake from surgery with intact speech function, but then develop mutism within 24–94 h (Pollack et al. 1995). In the largest series to date, the incidence was 8.5% for all posterior fossa tumors and 12% for vermian tumors, but did vary with histology (Catsman-Berrevoets et al. 1999). Patients with malignant tumors involving the brainstem, fourth ventricle, or vermis experienced mutism more often (20–24%) than those with less invasive tumors (1%) (Ersahin et al. 1996; Doxey et al. 1999).

Recovery from complete mutism begins with profoundly dysarthric and abnormal speech, usually with isolated words and phrases, progressively improving to full sentences. Most patients recover fluent speech within four months of surgery with an average duration of mutism lasting six weeks (Aguiar et al. 1995; Pollack et al. 1995; Ersahin et al. 1996). Up to 20% of patients may have permanent dysarthria following recovery from mutism. A small case-controlled radiological review identified bilateral edema in the brachium pontis as the only factor significantly associated with mutism (Pollack et al. 1995).

14.3.2.3 Cognitive Consequences

Cerebellar lesions or injury result mainly in deficits of motor control and coordination. It is becoming clear, however, that in addition to these deficits, alterations in higher cognitive function and affect also occur (Cantelmi et al. 2008). Neuropsychological changes at 2-year follow-up in a cohort of patients having had posterior fossa surgery included visual–spatial dysfunction in 37%, expressive language problems in 37%, verbal memory decline in 33%, and difficulty with affect control in 15–56% (Levisohn et al. 2000). Irritability, impulsiveness, and disinhibition were the most common changes in affect and increased in parallel with greater involvement of the vermis. These neuropsychological consequences are often temporary, but longer-term follow-up studies indicate that neurologic and neuropsychological changes persist more frequently with injury to the dentate nuclei and inferior vermis during resection (Puget et al. 2009). School performance and IQ are also affected by cerebellar surgery, but studies are confounded by the inability to separate the emotional and psychological effects of childhood illness and stress from the surgical procedure. The majority of patients (~60%) with benign or more indolent tumors such as cerebellar astrocytoma or histologically benign ependymoma will have normal IQ after surgery. This is in contrast to patients with medulloblastoma of whom only 10% will have IQ > 90 after treatment (Hoppe-Hirsch et al. 1995). Overall, the rate of IQ decline is determined by multiple factors such as age at time of treatment, presence or absence of hydrocephalus, use of radiotherapy, and the volume of brain that received radiation (Mulhern et al. 2004).

14.3.2.4 Hydrocephalus

Hydrocephalus is the result of a mismatch between CSF production and absorption leading to an accumulation of CSF, with characteristic symptoms and ventricular enlargement. In the setting of a posterior fossa tumor, hydrocephalus is defined as "obstructive" because the ventricular CSF pathways are blocked by a mass lesion. Children can have hydrocephalus at presentation, or it can develop acutely in the postoperative period, usually in the setting of cerebellar swelling or a hematoma accumulating in the resection cavity. Acute symptomatic hydrocephalus, either pre- or postoperative, should be treated by immediate placement of an external ventricular drain. In most patients, complete removal of the mass lesion results in resolution of the hydrocephalus. Most surgeons attempt to "wean" a patient from the external drain following tumor resection. Following GTR, this is usually successful, although the need for placement of a permanent CSF shunt is increased in younger children (<3 years of age) (Kumar et al. 1996).

Hydrocephalus can occur in a subacute manner following tumor resection even when GTR is achieved. These patients will usually have "communicating" hydrocephalus, as demonstrated by enlargement of the entire ventricular system. This term is probably a misnomer since the presumed site of obstruction is the arachnoid villi, where CSF is normally absorbed

back into the venous system. The presumed etiology of this type of hydrocephalus is from localized inflammation secondary to subarachnoid blood or high CSF protein leading to loss of function of the arachnoid villi. Children should be observed carefully in the first few weeks following tumor resection for symptoms suggestive of hydrocephalus.

Asymptomatic ventricular enlargement resulting from a temporary alteration of CSF dynamics requires no immediate intervention, and the patient can be followed by clinical examination and serial CT scans. Placement of a shunt is indicated if symptoms develop, a persistent pseudomeningocele is present, and/or CSF leak occurs from the wound. The rate of CSF shunting following posterior fossa surgery ranges from 10 to 26% of patients (Imielinski et al. 1998; Steinbok and Mutat 1999) to as high as 42% (Gjerris et al. 1998). In the latter study of 497 patients with a posterior fossa tumor, 68 (14%) were shunted prior to tumor resection, 94 (19%) after tumor resection, and 43 (9%) were treated by placement of shunt alone.

Endoscopic third ventriculostomy (ETV), or fenestration of the floor of the third ventricle to bypass the posterior fossa obstruction, is another alternative to placement of a permanent shunt. A recent report suggests that ETV is successful in avoiding the placement of a permanent ventriculoperitoneal shunt in the majority of patients (Tamburrini et al. 2008). The risk of extra-neural metastasis from shunting in children with cerebellar astrocytomas is virtually nonexistent (Berger et al. 1991).

14.3.2.5 Pseudomeningocele

Pseudomeningocele, the formation of a CSF collection outside the confines of the subarachnoid space, has been reported in 12–24% of patients postoperatively (Abdollahzadeh et al. 1994). It occurs 1–2 weeks after the initial surgery, and presents as fluctuant, occasionally tense mass under the incision. A pseudomeningocele predisposes surgical incisions to infection and dehiscence, which can then lead to more serious complications, including meningitis. The formation of a pseudomeningocele may indicate the presence of untreated hydrocephalus, a CSF fistula, or a wound infection. Most pseudomeningoceles resolve within days to weeks without intervention. Wound breakdown and hydrocephalus are indications for CSF diversion/shunting and antibiotic treatment if meningitis or other infection is suspected. Percutaneous aspiration for cell count and culture is usually not recommended as risk of infection rises with skin puncture, although it may provide temporary relief of pain from skin tension, or prevent wound dehiscence.

14.3.2.6 Other

Wound infection and breakdown are rare (2–5%). Risk factors include poor nutritional state, formation of a CSF pseudomeningocele, poor surgical closure, wound hematoma, and premature removal of sutures. Meningitis occurs in 3–8% of patients (Abdollahzadeh et al. 1994). Aseptic meningitis is a well-described postoperative finding after posterior fossa surgery in children. Patients complain of increasing headache 4–7 days following surgery, accompanied by fever, nuchal rigidity, and CSF pleocytosis (Rosenfeld 2000a). Organisms are not isolated and symptoms seem to correspond with steroid taper. No treatment is necessary, though bacterial meningitis must be excluded. The risk of bacterial meningitis is higher in patients with pseudomeningocele and shunts. Cervical spine instability requiring structural support is exceedingly rare, but can occur when a laminectomy extends below C1.

14.4 The Role of Second-look Surgery

"Second-look" surgery refers to a planned second procedure to resect residual tumor prior to observation of radiographic progression. It may also be applied to situations where tissue is obtained for pathologic diagnosis in patients previously treated by adjuvant therapy. The primary procedure may have been either a biopsy or an attempt at debulking. The general utility of performing second procedures remains unclear, and few reports directly refer to its use for brain tumors. It may lead to improved rates of GTR for a subset of patients (Khan et al. 2001),

but it has not been formally examined in a randomized clinical trial. Second-look surgery must be distinguished from procedures to remove "residual" disease, which can be defined as macroscopically visible tumor remaining after what was believed to be a GTR. In clear instances of residual disease remaining after the primary resection, the patient should be returned to the operating room for removal of the residual tumor.

Residual disease may be expected, if GTR would lead to unacceptable morbidity. This is usually in the context of infiltration of eloquent areas and unresectable tissues (brainstem, cranial nerves, and vascular invasion). Interval adjuvant therapy may reduce the size of the tumor, vascularity, or may define the tumor/brain interface, ultimately facilitating the second surgical procedure (Foreman et al. 1997). A second procedure following chemotherapy has been advocated most forcefully in the treatment of intracranial germ cell tumors. Most of these tumors arise in the pineal region closely approximated to the deep cerebral veins and the brainstem. Subtotal resection is common, and adjunctive therapy is frequently used. Excluding pure germinomas, which are sensitive to either radiation or chemotherapy, malignant nongerminomatous germ cell tumors (NGGCT) pose particularly difficult management problems. Most authors recommend tissue biopsy for marker-negative tumors with pathologic diagnosis guiding further treatment. Based upon favorable responses to chemotherapy, Weiner and Finlay advocate a second-look surgery for any residual mass remaining after aggressive chemotherapy treatment (Weiner and Finlay 1999). In another analysis of malignant germ cell tumors, neoadjuvant therapy followed by surgical resection for residual disease revealed that the majority had mature teratomas (Friedman et al. 2001). Outcomes following surgery were good in 5 of the 6 patients operated on.

14.5 Conclusions

For most supra- and infratentorial brain tumors, GTR is associated with improved outcome. Cortical mapping, neuronavigation, and functional imaging can, and should be utilized in children to increase the chances of a complete resection. Staged and second-look surgery may also facilitate the resection of tumors located in eloquent cortex or difficult to reach sites.

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Chemotherapy

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Contents

15.1 Introduction

The numerous chemotherapy treatment protocols for pediatric brain tumors reflect the extreme heterogeneity of these neoplasms. In the setting of average-risk medulloblastoma and germinoma, which have high cure rates with radiation treatment alone, chemotherapy is used to reduce radiation doses, yet maintain high cure rates. For infants with malignant brain tumors, who are particularly vulnerable to radiation-related morbidity, chemotherapy has been used to delay radiation treatment. Similarly, in the setting of unresectable, low-grade astrocytoma, chemotherapy can provide prolonged disease stabilization, perhaps allowing for delay of radiation.

While many clinical trials evaluating chemotherapy for the treatment of central nervous system (CNS) tumors are exploratory, two randomized controlled trials have shown a survival benefit from the addition of chemotherapy to radiation therapy in comparison to radiation therapy alone in children with brain tumors. Sposto et al. reporting for the Children's Cancer Group, described a randomization of patients with newly diagnosed high-grade glioma between two treatment arms: postoperative radiation treatment alone versus treatment with postoperative radiation followed by chemotherapy (Sposto et al. 1989). The chemotherapy group had 46% 5-year event-free survival (EFS), while the radiation-only group had 18% 5-year EFS. More recently, a large-scale, multiinstitutional European trial reported improved 5-year EFS with the addition of chemotherapy to radiation therapy for average-risk medulloblastoma (74% for radiation with chemotherapy vs. 59% for radiation alone) (Taylor et al. 2003).

While most chemotherapeutic agents are initially tested in single-agent clinical trials to determine the effectiveness against a particular tumor type, combination chemotherapy regimens are in widespread use. The goal of combination therapy is to maximize therapeutic effectiveness by overcoming drug resistance, which exists in a high proportion of tumors. An optimally designed combination regimen combines agents with high-response rates in single-agent trials, noncross-resistant mechanisms of action in tumor-cell subpopulations, and nonoverlapping toxicity profiles.

This chapter reviews important conventional chemotherapeutic agents in brain tumor management, the use of combination chemotherapy for infants with brain tumors, high-dose myeloablative chemotherapy, and new classes of therapeutic agents. Disease-specific chemotherapy regimens are discussed separately in earlier chapters.

15.2 General Principles of Chemotherapy

For most solid tumors such as CNS neoplasms, chemotherapy is considered most effective when used as an adjuvant to local control measures, specifically surgery and radiation. Chemotherapy is most likely to contribute to long-term disease control when residual disease is minimal; this has been demonstrated in both medulloblastoma and high-grade glioma, where improved prognosis is clearly associated with gross total or near total resection followed by radiation (Sposto et al. 1989; Packer et al. 1994). While adjuvant chemotherapy is important for preventing distant metastases in extracranial solid tumors (Ortega et al. 1975; Link et al. 1986; Eilber et al. 1987), the role of chemotherapy in preventing CNS dissemination or extraneural metastasis is unclear. Neoadjuvant chemotherapy can also be used for a patient who may have unresectable or difficult-to- resect disease at diagnosis, with the hope of eliciting a tumor response that would allow improved, posttreatment resection (Rosen 1986; Trimble et al. 1993). While this strategy is used in the management of extracranial pediatric solid tumors, its utility in CNS tumors is uncertain. This rationale is being investigated in ongoing clinical trials for infant embryonal tumors and ependymoma.

The blood–brain barrier (BBB) is an anatomic feature of the CNS consisting of specialized capillary endothelial cells that lack fenestrations and pinocytic vesicles, and express specialized transport proteins. The ability of a compound to cross the BBB is restricted by molecular weight, as well as lipid solubility and pH. Small, lipid-soluble molecules at physiologic pH readily cross the BBB (Rall and Zubrod 1962), although the properties of most chemotherapeutic compounds prevent movement across the BBB. Despite this fact, the objective response of some CNS tumors to chemotherapy alone suggests that systemically administered agents are still able to reach brain tumor cells. This observation, as well as the ability of CNS tumors to enhance with gadolinium on MRI (requiring the gadolinium to cross the BBB), suggests that the BBB is physiologically disrupted in the tumor environment, and that concentrations of systemically administered drugs are likely to be higher in tumors than in normal brain (Stewart 1994). Nevertheless, concerns about the role of the BBB in contributing to chemotherapy resistance have resulted in the development of various treatment strategies to overcome it, which are summarized later in this chapter.

15.3 Specific Chemotherapeutic Agents

15.3.1 Platinums

Cisplatin and carboplatin are non-cell-cycle-specific alkylating agents. The cytotoxic (free or unbound) fraction of drug acts to form a platinum-DNA adduct that produces inter- and intrastrand cross-links by alkylating the N7 position of guanine (Zwelling and Kohn 1979). When used as a single agent, cisplatin has been shown to produce disease responses in medulloblastoma, germinoma, ependymoma, and astrocytoma (Sexauer et al. 1985; Walker and Allen 1988; Bertolone et al. 1989). Used adjuvantly with CCNU and vincristine, cisplatin has been shown to improve disease-free survival in medulloblastoma (Packer et al. 1991, 1994). The toxic side effects of cisplatin are substantial, including hearing loss, nephrotoxicity, myelosuppression,

nausea and vomiting, and peripheral neuropathy (Hartmann and Lipp 2003).

Carboplatin, an analog of cisplatin, has similar efficacy, but a somewhat different toxicity profile. While less ototoxic and nephrotoxic than cisplatin, carboplatin is more myelosuppressive. Carboplatin also has less associated peripheral neuropathy and is less emetogenic than cisplatin (Duffull and Robinson 1997). Significantly, a considerable number of patients (estimated as high as 30–40%) develop a hypersensitivity reaction to carboplatin in some treatment regimens using weekly dosing. This is characterized mostly by skin rash and urticaria, but occasionally can be life-threatening (Lafay-Cousin et al. 2008). Single-agent treatment results in moderate tumor responses in recurrent childhood brain tumors (Walker and Allen 1988; Gaynon et al. 1990). In combination with vincristine, carboplatin has been shown to be an active agent against pediatric low-grade astrocytoma (Packer et al. 1997; Mahoney et al. 2000), and plays a role in the combination chemotherapy of infant brain tumors as well. A strategy using carboplatin in conjunction with a BBB-disrupting agent is discussed later in this chapter.

Oxaliplatin is the latest addition to the platinum family of chemotherapeutics. It is less myelosuppressive than carboplatin, and appears to cause little ototoxicity or nephrotoxicity in adult clinical trials. A single-agent Phase II clinical trial by the Pediatric Brain Tumor Consortium showed that oxaliplatin was well-tolerated, but that it had little activity in children with recurrent medulloblastoma, primitive neuroectodermal tumor (PNET), and atypical teratoid rhabdoid tumor (AT/RT) (Fouladi et al. 2006). It remains to be seen if there is a role for oxaliplatin for newly diagnosed brain tumors in children.

15.3.2 Nitrosoureas

CCNU (lomustine) and BCNU (carmustine), the most commonly used nitrosoureas, are no-cell-cycle-specific alkylators. Both are prodrugs that spontaneously decompose into two active metabolites: an isocyanate group and a chloroethyldiazohydroxide; the chloroethyldiazohydroxide alkylates DNA, resulting in cross-linking followed by cellular instability. Nitrosoureas are small, lipophilic molecules that penetrate the BBB easily, and are among the few systemically administered agents found in moderate to high concentrations in the brain (reviewed in Middleton and Margison 2003). Nitrosourea-based combination therapy resulted in a modest impact on survival in pediatric patients with high-grade astrocytoma in some trials (Sposto et al. 1989; Finlay et al. 1995; Levin et al. 2000). A retrospective analysis suggests that MGMT overexpression predicts poor outcome for patients treated with alkylator-based therapy (Pollack et al. 2006). A single-agent Phase II trial of high-dose BCNU for pediatric high-grade glioma showed only modest tumor response with substantial toxicity (Bouffet et al. 1997). CCNU, in combination with vincristine, is clearly beneficial in the adjuvant, post-radiation treatment of medulloblastoma, and in one study, was the rationale for reducing the neuroaxis radiation dose from 36 to 23.4 Gy, resulting in good disease-free survival in average-risk medulloblastoma patients (Packer et al. 1994). Nitrosourea-based therapy has also been shown to produce disease responses and prolonged stable disease in pediatric low-grade astrocytoma, when used in combination with procarbazine, 6-thioguanine, and vincristine (Prados et al. 1997). The major toxicities of nitrosoureas include nausea, myelosuppression and, less commonly, pulmonary fibrosis and nephrotoxicity. The myelosuppression is typically delayed, seen approximately 3–5 weeks following administration of the dose, and is frequently cumulative (Balis et al. 2002).

15.3.3 Cyclophosphamide and Ifosfamide

These parenterally administered, prodrug members of the nitrogen mustard family of drugs are thought to have the same mechanism of activity as most classic alkylators: by forming covalent bonds with nucleophilic groups, resulting in cross-linking between DNA strands or intrastrand linking, thus impairing DNA replication (Pratt et al. 1994). These agents have produced responses and stable disease in both primary and recurrent pediatric brain tumors, including medulloblastoma, PNET, high-grade astrocytoma, and germcell tumors. These agents are also

an important part of combination chemotherapy for infants with malignant brain tumors (Friedman et al. 1986; Longee et al. 1990; Packer et al. 1999; Zeltzer et al. 1999). Toxicities are substantial, including nausea, myelosuppression, hemorrhagic cystitis, and in the case of ifosfamide, nephrotoxicity (Balis et al. 2002) and encephalopathy (Nicolao and Giometto 2003). Impaired fertility has been reported in patients treated with these agents (Byrne et al. 1987). Secondary leukemia has recently been described in a cohort of infants with malignant brain tumors treated with high cumulative doses of cyclophosphamide and etoposide (Duffner et al. 1998; Smith et al. 1999).

Recently, the Pediatric Brain Tumor Consortium has completed a Phase I clinical trial in children younger than 3 years of age using mafosfamide, a pre-activated cyclophosphamide-derivative that is administered intrathecally through an Ommaya reservoir. This study demonstrated that mafosfamide can be given safely to young children in combination with intensive systemic chemotherapy (Blaney et al. 2005).

15.3.4 Temozolomide

Temozolomide is a rapidly absorbed, oral prodrug that undergoes spontaneous hydrolysis to form its active metabolite, 3-methyl-(triazen-1-yl)-imidazole-4-carboxamide (MTIC). Its mechanism of action is via the methylation of DNA, largely at the O^6 position of guanine (Newlands et al. 1997). While adult patients with glioblastoma multiforme have been shown to have some survival advantage when treated at diagnosis with radiation and temozolomide (Stupp et al. 2002), the role of this agent in pediatric brain tumors has not yet been established. Responses to temozolomide have been reported in pediatric patients with recurrent high-grade astrocytoma, and small series of patients with ependymoma, PNET, and germcell tumor (Pollack et al. 1999). Two recent reports have shown promising response rates in patients with low-grade glioma treated with temozolomide as a first-line agent (Kuo et al. 2003) or as salvage therapy (Khaw et al. 2007). This early promise of temozolomide is undergoing further investigation in ongoing Phase I trials to evaluate safety and toxicity of temozolomide in combination with other agents, including radiation, CCNU, thalidomide, and epidermal growth factor receptor (EGFR) inhibitors. Temozolomide is well-tolerated, although its reported toxicities include nausea, constipation, and myelosuppression (Nicholson et al. 1998; Friedman et al. 2000).

15.3.5 Etoposide

Etoposide is a semisynthetic derivative of a plant extract, podophyllotoxin. Etoposide interacts with DNA topoisomerase II, causing single- and double-stranded breaks and a cell-cycle arrest in G_2 and mitosis (Hande 1998). Despite its highly lipophilic properties, it does not cross the BBB easily due to its large size (Newton et al. 1999). Etoposide can be administered orally or parenterally. It is active against many pediatric brain tumors, including medulloblastoma, PNET, ependymoma, and germ cell tumor (Allen et al. 1985; Bouffet and Foreman 1999; Kobrinsky et al. 1999; Chamberlain 2001). It has been used in combination with cisplatin, carboplatin, ifosfamide, and cyclophosphamide with acceptable toxicity in the treatment of childhood brain tumors (Busca et al. 1997; Guruangan et al. 1998; White et al. 1998; Duffner et al. 1999; Kortmann et al. 2000). Daily oral etoposide has produced modest responses and prolonged stable disease in patients with recurrent PNET and high-grade astrocytoma (Ashley et al. 1996; Fulton et al. 1996; Chamberlain and Kormanik 1997; Needle et al. 1997).

Toxicities of etoposide include nausea and myelosuppression, as well as diarrhea and mucositis, when administered in high doses (Mathew et al. 1994; Taylor et al. 2003). High cumulative doses have been associated with an increased risk of secondary leukemia in infants with malignant brain tumors, as well as other childhood cancers (Duffner et al. 1998; Smith et al. 1999).

15.3.6 Vincristine

Vincristine is a plant alkaloid that binds tubulin and induces metaphase arrest in a cell cycle-specific fashion (Jordan 2002). It has limited CNS penetration,

and has not been rigorously evaluated as a single agent in pediatric brain tumors (Kellie et al. 2002). Nevertheless, it has shown activity in multiagent regimens, and is widely used in combination treatment regimens for medulloblastoma, PNET, low-grade astrocytoma, and infant brain tumors (Packer et al. 1994, 1997; Duffner et al. 1999). Its toxicities include constipation, peripheral neuropathy, and syndrome of inappropriate diuretic hormone (SIADH) (Balis et al. 2002).

15.3.7 Vinblastine

Vinblastine is a Vinca plant alkaloid that has a similar mechanism of action to vincristine. It has shown efficacy against a variety of childhood tumors including non-Hodgkins lymphoma and histiocytosis. Vinblastine is well-tolerated and myelosuppression is the main toxicity (Balis et al. 2002). Two recent reports demonstrated that single-agent, weekly vinblastine has efficacy in children with recurrent or refractory low-grade glioma (Bouffet et al. 2002; Lafay-Cousin et al. 2005). Because of the poor CNS penetration of vinblastine, and the low mitotic rate observed in low-grade gliomas, the authors speculated that vinblastine may be acting as an antiangiogenic agent in this setting. Vinblastine has been shown to have antiangiogenic effects *in vivo* at nontoxic doses (Vacca et al. 1999).

15.3.8 Methotrexate

Methotrexate is an antimetabolite that exerts its antitumor activity by binding and inhibiting dihydrofolate reductase (DHFR), a key enzyme in intracellular folate homeostasis. This depletion of folate results in impaired purine and thymidylate biosynthesis and resultant cytotoxicity during the S-phase of the cell cycle (Balis et al. 2002). Methotrexate was one of the first antineoplastic agents developed, and is an important part of combination chemotherapy regimens for osteosarcoma and acute lymphocytic leukemia. At high doses (>1 g/m^2), systemic methotrexate can penetrate the CNS and has shown efficacy as part of combination chemotherapy protocols for embryonal tumors (Chi et al. 2004). Methotrexate can also be given intrathecally.

High-dose methotrexate therapy is administered via a prolonged infusion and can have significant toxicity including mucositis, myelosuppression, and renal failure. Leukovorin, a folate analog, is given to patients following methotrexate infusion and preferentially rescues normal cells, thus minimizing side effects. Significantly, methotrexate therapy has been associated with leukoencephalopathy, particularly in combination with radiation therapy, and when given intrathecally (Vezmar et al. 2003). The potential toxicity of methorexate therapy in children with brain tumors has made it a controversial agent, and prospective studies addressing its utility are ongoing.

15.4 Combination Chemotherapy for Infant Brain Tumors

Combination chemotherapy is in widespread use for almost all types of childhood CNS tumors. Specific regimens targeted at individual tumor types are discussed in the earlier disease-specific chapters (Chaps. 1–12). Infants and very young children, however, are especially susceptible to complications of CNS irradiation, including neurocognitive decline, neuroendocrine deficits, and hearing loss (Miettinen et al. 1997; Siffert and Allen 2000; Mulhern et al. 2001; Packer 2002; Spoudeas et al. 2003). In order to delay radiation treatment, chemotherapy has been investigated for infants and for very young patients with primary malignant brain tumors as the primary adjuvant therapy following surgery. Because malignant brain tumors in infants are rare, most infant studies include a broad range of diagnoses, often including both embryonal (e.g., medulloblastoma, PNET) and astrocytic tumors, as well as ependymoma. The largest clinical trial for infants, "Baby POG 1," conducted by the Pediatric Oncology Group (POG 8633) reported on 198 patients less than 36 months of age. The patients in this study were treated with 1 (patients 25–36 months of age) or 2 (patients 0–24 months of age) years of preradiation chemotherapy, followed by radiation therapy. Chemotherapy consisted of multiple cycles of a 4-drug (cisplatin, etoposide, vincristine,

and cyclophosphamide) regimen prior to radiation (Duffner et al. 1993, 1999). The overall 5-year survival for all patients was 32%; survival for those who had gross total resection (GTR) was 62% compared with 31% for patients with subtotal resection. Most of the treatment failures occurred in the first 6 months of therapy. These figures were similar when patients with medulloblastoma and ependymoma were examined independently. Significantly, the cumulative incidence of second malignancies in this cohort was 11.3% (Duffner et al. 1993, 1998, 1999).

In another trial that demonstrated the feasibility of preradiation chemotherapy in infants, investigators attempted to achieve further gains by increasing the dose intensity of chemotherapy (Mason et al. 1998a). They used a truncated course of induction chemotherapy including vincristine, cyclophosphamide, etoposide, and cisplatin, followed by high-dose treatment with carboplatin, thiotepa, and etoposide with subsequent autologous stem-cell rescue. Radiation therapy was reserved for patients with residual disease at the time of consolidation or for those with progressive disease. Sixty-two patients under the age of 6 were enrolled; the 3-year progression-free survival was 25% (Mason et al. 1998b). Degree of resection was again found to be an important prognostic feature; 3-year overall survival for children with GTR was 59%, in comparison to 30% for children who had only subtotal resection or biopsy. The proportion of patients undergoing GTR was similar between the two studies (34 and 35%, respectively). The high-dose chemotherapy-based regimen had substantial toxicity with a mortality rate of 8% attributed to toxicity.

The Australian and New Zealand Children's Cancer Study Group reported on a chemotherapy-alone protocol for patients less than 36 months old using a combination of vincristine, etoposide, and cyclophosphamide for 64 weeks without radiation therapy. Forty patients were enrolled; progression-free survival was reported at 11% (White et al. 1998). Geyer et al. reported on the CCG 921 experience in infants with PNET and malignant ependymoma who were enrolled in a randomized trial of two chemotherapy regimens ("8 drugs in one" vs. prednisone, vincristine, and lomustine), with radiation treatment at investigator discretion. Ninety-six patients were treated (only 13 were irradiated); after 3 years of follow-up, progression-free survival was 23% (Geyer et al. 1994). Similar results were obtained in a large French Society of Pediatric Oncology Group Study of medulloblastoma in which children younger than 5 years of age were eligible for 7 cycles of multiagent chemotherapy consisting of carboplatin, procarbazine, etoposide, cisplatin, cyclophosphamide, and vincristine. Patients with progression of disease or relapse received salvage high-dose chemotherapy followed by local or craniospinal radiotherapy. With this approach, 5-year progression-free survival was 29, 6, and 13% for patients with R0M0 (no residual disease, no metastases), R1M0 (radiologic residual disease, no metastases), and RXM+ (metastases), respectively. A number of patients initially treated on this study were salvaged by high-dose chemotherapy and local radiation, and a 5-year overall survival was 73, 41, and 13%, for patients with R0M0, R1M0, and RXM+, respectively (Grill et al. 2005). More recently, Rutkowski et al. reported on 43 infants with medulloblastoma who received adjuvant combination chemotherapy consisting of three cycles of intravenous chemotherapy (cyclophosphamide, vincristine, methotrexate, carboplatin, and etoposide) and intraventricular methotrexate. These patients avoided radiation therapy and had a 5-year progression-free survival of 83 and 50% for patients with GTR and partial resection, respectively. Although there were no toxic deaths associated with this regimen, 19 out of 23 patients for whom data was available were found to have leukoencephalopathy on T2-weighted magnetic resonance images. In addition, the mean IQ of treated patients was found to be significantly lower than healthy controls within the same age group, but higher than that of patients in a previous trial who had received radiotherapy (Rutkowski et al. 2005). While this study appears promising, validation is required, as the majority of patients treated with chemotherapy alone in larger-scale cooperative group studies thus far develop recurrent disease. Additionally, this study raises concerns regarding cognitive effects of chemotherapy.

While these preliminary results have shown the dose-intensive approach to be feasible, albeit with increased toxicity over the standard schedule,

the survival benefit is unknown. There is no clear standard chemotherapy approach for infants with malignant brain tumors. One strategy currently under investigation includes combination chemo-radiotherapy protocols. Incorporation of intrathecal mafosfamide and conformal radiation is currently under investigation by the Pediatric Brain Tumor Consortium. An alternative strategy under investigation is high-dose therapy with hematopoietic stem-cell rescue.

15.5 High-Dose Chemotherapy with Hematopoietic Stem-Cell Rescue

15.5.1 Rationale

Many CNS tumors fail to respond to standard-dose chemotherapy or fail to demonstrate a sustained response. Potential reasons for this failure include inherent or acquired drug resistance and poor CNS penetration of drug. High-dose, myeloablative chemotherapy with autologous stem-cell rescue is a strategy designed to maximize dose intensity and to achieve high systemic drug concentrations, which will improve drug penetration into the CNS. The initial transplant chemotherapy regimens were nitrosourea based; however, dose-limiting neurotoxicity prevented adequate dose escalation (Burger et al. 1981; Hochberg et al. 1981; Bashir et al. 1988). Contemporary regimens use alkylating agents such as thiotepa, carboplatin, melphalan, or busulfan, often in combinations with a topoisomerase inhibitor such as etoposide (Mahoney et al. 1996; Busca et al. 1997; Guruangan et al. 1998; Papadopoulos et al. 1998; Dunkel and Finlay 2002).

The two-patient groups targeted for high-dose therapy are those with recurrent disease following standard therapy (either chemotherapy or radiation), and infants with malignant brain tumors. High-dose therapy is of particular interest for infants as they typically have a poor prognosis and are especially susceptible to late effects of radiation. Multiple investigators have established the feasibility of this approach, and the initial results have been modestly encouraging.

15.5.2 Medulloblastoma

High-dose therapy for recurrent medulloblastoma has been used in a number of studies over the last two decades. Table 15.1 summarizes results of studies that utilized high-dose chemotherapy and autologous stem-cell rescue in children with recurrent medulloblastoma. Progression-free survival varied from 0 to 61.5%. Although direct comparison is not possible due to different inclusion criteria, conditioning regimens, and pretransplant treatments, it appears that several factors may be related to improved outcomes following high-dose chemotherapy. Those factors include: first-line therapy, as children who did not receive upfront craniospinal irradiation had better outcomes after transplant; localized relapse/progression and minimal residual disease at the time of high-dose chemotherapy; and additional use of radiation following transplant (Graham et al. 1997; Ridola et al. 2007; Shih et al. 2008). The conditioning regimen with busulfan and thiotepa, which showed good results in young children with localized relapse, deserves further evaluation (Ridola et al. 2007).

High-dose chemotherapy with peripheral stem-cell rescue showed more promising results in young patients with newly diagnosed medulloblastoma, including metastatic disease, than in patients with recurrent disease.

Mason et al. evaluated high-dose chemotherapy with autologous stem-cell rescue in 13 children less than 6 years of age with newly diagnosed medulloblastoma (Head Start I protocol). Patients received five cycles of induction chemotherapy with vincristine, etoposide, cisplatin, and cyclophosphamide, 3 weeks apart, followed by consolidation chemotherapy with a single myeloablative cycle of thiotepa, carboplatin, and etoposide. Irradiation was used only for residual tumor at consolidation or for progressive disease. Two-year overall survival was 62% (95% CI 35–89%) with a 2-year progression-free survival of 38% (95% CI 11–65%) (Mason et al. 1998b). In the follow-up study known as Head Start II, 21 children (<10 years of age) with newly diagnosed, high-risk disseminated medulloblastoma underwent induction with high-dose intravenous methotrexate in addition to the four drugs used in Head Start I protocol. Consolidation was

Table 15.1. Studies of high-dose chemotherapy and autologous stem-cell rescue in children with recurrent medulloblastoma

Study	Number of patients, age at transplant	Pre transplant status	Conditioning	Post transplant therapies	Outcome
Kalifa et al. 1992	6 Age 8 months to16 years	All patients had residual disease	Busulfan, thiotepa	Local XRT in 2 patients	2/6 with EFS at 24 months
Mahoney et al. 1996	8 Age 2.5–15 years	95% of patients had residual disease	Cyclophosphamide, melphalan	N/A	0 Patients with EFS
Finlay et al. 1996	9 Median age 8 years (8 months to 36 years)	4 patients had bulky disease at transplant	Thiotepa, etoposide	N/A	0 Patients with EFS
Graham et al. 1997	19 Age 12 months to 27 years	10/19 NED at transplant	Melphalan, cyclophosphamide in 16 patients	N/A	3/19 with EFS at >24 months post-transplant
Dunkel et al. 1998	23 Median age 13 years (2–14 years)	N/A	Carboplatin, thiotepa, etoposide	N/A	7/23 with EFS at 54 months post-transplant
Guruangan et al. 1998	5 Median age 2.9 years (0.7–5.9 years)	3 NED; 2 patients with minimal residual disease Did not receive pre-transplant XRT	Carboplatin, thiotepa, etoposide	Reduced-dose craniospinal XRT and local boost	3/5 with EFS at 10–30 months post-transplant
Fagioli et al. 2004	8 Median age 11 years	2/8 NED	Thiotepa, etoposide	No XRT post-transplant given	2/8 with EFS at 7 and 16 months post-transplant
Sung et al. 2007	7 Age 3–17 years	3/7 NED	3 single transplant patients, 4 double transplant patients[a]	No XRT posttransplant	3/7 with EFS at 9–52 months post-transplant
Ridola et al. 2007	39 patients with localized relapse Median age 3 years (1–7 years)	9/39 NED	Busulfan, thiotepa	9 patients had second surgery posttransplant, all had posterior fossa XRT	5-year EFS=61.5%
Shih et al. 2008	12 Median age 6.7 years (1.1–18.8 years)	3/12 NED	Different conditioning regimens	5/12 patients received radiation as part of salvage therapy	3/12 EFS 20–56 months post-transplant

[a] First transplant used cyclophosphamide and melphalan conditioning, second transplant used either carboplatin, thiotepa and etoposide or busulfan and melphalan conditioning regimen XRT, radiation therapy NED, no evidence of disease

the same as in the Head Start I study. The 3-year EFS of those high-risk patients was 49% (95% CI = 27–72%) and overall survival was 60% (95% CI = 36–84%) (Chi et al. 2004).

Strother et al. used full-dose craniospinal radiation (36 Gy) and posterior fossa boost, followed by four cycles of intensive chemotherapy with cisplatin, cyclophosphamide, and vincristine and stem-cell rescue in 53 patients older than 3 years with newly diagnosed average- and high-risk medulloblastoma or supratentorial PNET. The 2-year progression-free survival rate was 93% in the average-risk group and 74% in the high-risk group (Strother et al. 2001). A similar approach was used by St. Jude's Children's Research Hospital; however, they used risk-adapted craniospinal radiotherapy (23.4 Gy for average-risk disease and 36–39.6 Gy for high-risk disease) in children older than 3 years with newly diagnosed medulloblastoma, followed by four cycles of intensive chemotherapy with cisplatin, cyclophosphamide, and vincristine. Autologous stem-cell infusion was used in order to maintain dose intensity in patients who received previous craniospinal radiation. The 5-year overall survival was 85% (95% CI = 75–94%) in the average-risk group and 70% (95% CI = 54–84%) in the high-risk group. Five-year EFS was 83% (95% CI = 73–93%) and 70% (95% CI = 55–85%), respectively (Gajjar et al. 2006).

15.5.3 Gliomas

High-dose chemotherapy with autologous stem-cell rescue has been studied in patients with recurrent as well as newly diagnosed high-grade gliomas. Two clinical trials using high-dose therapy following radiation for patients with diffuse pontine glioma showed no impact on survival, in comparison to historical controls (Dunkel et al. 1998; Bouffet et al. 2000). Heideman et al. treated 11 patients with newly diagnosed and recurrent high-grade astrocytoma with thiotepa and cyclophosphamide following surgery or biopsy. Radiation was given to patients who showed response or stable disease following high-dose chemotherapy. Although one complete response and two partial responses were observed, median progression-free survival remained disappointingly low at 9 months (Heideman et al. 1993). The Children's Cancer Group reported on 18 patients with recurrent malignant astrocytoma/glioblastoma multiforme treated with thiotepa and etoposide and autologous stem-cell rescue, 5 of whom had progression-free survival ranging from 39 to 59 months (Finlay et al. 1996). A follow-up Phase II pilot study conducted by the Children's Cancer Group added carmustine to thiotepa and etoposide, followed by radiation therapy for newly diagnosed glioblastoma multiforme. Although 2-year progression-free survival was promising at 46%, accrual was closed early because of unacceptable pulmonary and neurologic toxicities (Grovas et al. 1999).

Papadakis et al. published a large series of children with newly diagnosed malignant gliomas, who were treated with high-dose carmustine, thiotepa, and etoposide and autologous bone-marrow rescue. This treatment was given following surgery and local radiation. Out of 29 patients with gliomas, 4 died from toxicity and 3 (10%) were alive without evidence of disease or with stable disease at 64–86 months posttransplant (Papadakis et al. 2000). High-dose chemotherapy was used also in patients with newly diagnosed high-grade gliomas. Massimino et al. treated 21 pediatric patients with a combination of induction chemotherapy with cisplatin, etoposide, cyclophosphamide, and high-dose methotrexate, followed by high-dose thiotepa with stem-cell rescue. The myeloablative cycle was given a second time if patients had residual disease after the first round. After high-dose chemotherapy, patients received radiation and 27 weeks of maintenance therapy with vincristine and lomustine. With this approach, at a median follow-up of 57 months, progression-free survival was 46%, and overall survival was 43% (Massimino et al. 2005). Several other studies have included newly diagnosed patients with high-grade gliomas, such as Head Start I and II and Children's Cancer Group Study 99703, and used three rounds of induction chemotherapy followed by three rounds of consolidation. However, data from these studies are not available at the current time.

Although high-dose chemotherapy may be promising in high-grade glial tumors, due to the inconsistency of results from studies published so far, use

of high-dose chemotherapy with autologous stem-cell rescue should be considered experimental for patients with glial tumors, and used in the context of clinical research.

15.5.4 Other Tumor Types

High-dose chemotherapy is not superior to standard chemotherapy in patients with recurrent or newly diagnosed ependymoma as confirmed in Children's Oncology Study and Head Start I and II studies (Mason et al. 1998b; Zacharoulis et al. 2007).

In a study of recurrent, noncerebellar PNETs, which included pineoblastoma ($n=8$), Broniscer et al. describe 17 patients (age 0.9–31.4 years) who were treated with high-dose chemotherapy of carboplatin and etoposide and autologous stem-cell rescue. Eleven percent of patients died of toxicity. EFS was 29% (surviving patients were followed for 40–123 months) (Broniscer et al. 2004). Sung et al. described 7 patients with supratentorial PNET (3 newly diagnosed and 4 with recurrent tumors) who were treated with a double-transplant approach using cyclophosphamide and melphalan for the first transplant and carboplatin, thiotepa, and etoposide for the second transplant. Two out of 3 patients with newly diagnosed PNET, and 1 out of 4 with recurrent disease remained disease-free (14–31 months follow-up) (Sung et al. 2007). A number of smaller studies that included up to 6 patients with recurrent supratentorial PNET indicated salvage rates of approximately 25% with high-dose chemotherapy. However, reported length of follow-up was frequently short (Kalifa et al. 1992; Mahoney et al. 1996; Busca et al. 1997; Graham et al. 1997; Fleischhack et al. 1998; Mikaeloff et al. 1998).

High-dose chemotherapy used in the first-line treatment of pineoblastoma showed quite promising results. Gururangan et al. reported on 12 patients with newly diagnosed pineoblastoma (age 0.3–43.7 years), who were treated with surgery, radiation (given to all but 2 patients), and high-dose chemotherapy with cyclophosphamide, melphalan, and busulfan. Four-year progression-free survival was 69% (Gururangan et al. 2003).

Forty-three children with newly diagnosed supratentorial PNET were treated on the Head Start I and II studies using five rounds of induction followed by high-dose consolidation therapy with etoposide, carboplatin, and thiotepa. Five-year EFS was 39% and overall survival was 49%. Nonpineal supratentorial PNET (sPNET) patients fared significantly better than patients with pineal sPNETs. Twelve of twenty survivors never received radiation therapy (Fangusaro et al. 2008). Finally, children less than 3 years of age with sPNET were included in the CCG 99703 study, which used three rounds of induction therapy followed by three rounds of consolidation with carboplatin and thiotepa. The results of this study are not published yet.

Similar to its use in medulloblastoma, high-dose chemotherapy has efficacy in patients with supratentorial PNET. In the studies published so far, outcomes were best when high-dose chemotherapy was used as a first-line therapy and in combination with radiation.

AT/RT is another embryonal malignant brain tumor that is typically sensitive to chemotherapy. Due to its poor prognosis in children <3 years of age, this tumor is often included in infant brain studies and treated with upfront high-dose chemotherapy. However, larger series describing outcomes with high-dose chemotherapy and autologous stem-cell rescue are lacking.

Studies of high-dose chemotherapy in CNS germcell tumors are rare as this tumor responds well to standard chemotherapy and radiation therapy. However, if tumor recurs following both modalities, high-dose chemotherapy can be effective. A group of Japanese investigators reported a small series of 6 patients with intracranial nongerminomatous germcell tumors treated with myeloablative chemotherapy alone, all of whom survived without tumor recurrence at follow-up of 1–7 years (Tada et al. 1999). Another study described 21 patients with CNS germ-cell tumors that progressed following initial chemotherapy and radiation. These patients were treated with a thiotepa-based conditioning regimen. The response was very good in patients with germinoma as 7/9 patients survived disease-free with a median follow-up of 48 months. However, in the nongerminomatous germcell tumor category, only 33% patients survived without disease progression (Modak et al. 2004).

Although the toxicity of stem-cell transplant has significantly decreased over the last 10 years, some studies of transplant in children with brain tumors still report significant treatment-related mortality (11–19%) (Sung et al. 2007; Dhall et al. 2008). Over the last 20 years, high-dose chemotherapy has been established as an important modality for treating recurrent, chemosensitive brain tumors as well as first-line treatment for malignant brain tumors in young children. Further studies should address the late effects of this therapy as well as combinations of high-dose chemotherapy and localized irradiation or reduced dose craniospinal irradiation.

15.6 New Strategies

15.6.1 Radiation Sensitizers

Numerous investigational chemotherapy treatment strategies are designed to maximize the known benefit of radiation therapy in CNS tumors. Multiple potentiating effects of platinum agents on radiation have been described. Hypoxic cells (typically radiation resistant) are more sensitive to radiation following exposure to platinum agents in vitro (Skov and MacPhail 1991). Platinum agents may also have a role in preventing the development of radiation-resistant clones by inhibiting "potentially lethal damage recovery," a mechanism by which tumor cells are able to repair what would otherwise be lethal or sublethal DNA damage following radiation exposure (Wilkins et al. 1993). Clinical trials evaluating toxicity and response to combination chemo–radiotherapy with carboplatinum are currently underway for newly diagnosed high-risk PNET and for brainstem glioma through the Children's Oncology Group.

Gadolinium-texaphyrin is a metallo-porphyrin-like compound, currently being tested as a radiation sensitizer in brainstem glioma by the Children's Oncology Group. Gadolinium-texaphyrin is preferentially taken up by tumor cells, and has been shown to produce radiosensitization in vitro by prolonging the half-life of cytotoxic radicals formed following exposure to ionizing radiation (Young et al. 1996). An ongoing Children's Oncology Group trial administers gadolinium-texaphyrin simultaneously with radiation to patients with diffuse pontine glioma.

Tyrosine kinase receptor inhibitors, specifically of the EGFR, and farnesyl transferase inhibitors designed to inhibit signal transduction in the Ras pathway also have promising preclinical data to suggest radiosensitizing properties. Phase I clinical trials are underway through the Pediatric Brain Tumor Consortium to further investigate the safety and tolerability of these agents in combination with radiation.

15.6.2 Targeting Drug Resistance

Many brain tumors are resistant to conventional chemotherapeutic agents. Investigators have identified mechanisms of drug resistance amenable to pharmacologic treatment that would render tumor cells more sensitive to chemotherapy.

15.6.2.1 P-glycoprotein Pump

The P-glycoprotein pump (PGP) is the protein product of the multidrug resistance gene (*MDR-1*), which is amplified in many resistant and refractory tumors, including glioblastoma, medulloblastoma, and ependymoma (Chou et al. 1995, 1996; von Bossanyi et al. 1997; Decleves et al. 2002). The PGP serves as an efflux pump, allowing the cell to transport specific toxins, including chemotherapeutic agents (Sikic et al. 1997). In mice, capillary endothelial cells composing the BBB have high concentrations of PGP (Schinkel et al. 1994). Cyclosporine A is a potent inhibitor of PGP and effectively sensitizes high-PGP-expressing cells *in vitro* (Sikic et al. 1997). Clinical trials using cyclosporine A in combination with chemotherapy, largely in the setting of adult myeloid leukemia, have shown high toxicity with unclear therapeutic benefit (Chauncey 2001). A Phase I clinical trial in pediatric CNS tumors consisted of intravenous cyclosporine A in combination with oral etoposide, intravenous vincristine, and radiation therapy for patients with intrinsic pontine glioma. The trial was halted early due to excessive neurotoxicity, and there was no survival advantage for the few evaluable patients (Greenberg et al. 2005).

15.6.2.2 Alkylguanine-DNA-Alkyltransferase

Alkylguanine-DNA-alkyltransferase (AGT) is a DNA-repair enzyme that plays an important role in tumor resistance to alkylnitrosoureas and temozolomide. AGT reverses DNA methylation and chloroethylation (induced by chemotherapy) at the O^6 position of guanine, thus rescuing the cell from lethal injury. Many brain tumors have high levels of AGT, and these high levels are associated with poor survival in clinical trials in adults with malignant glioma (Wiestler et al. 1984; Pegg 1990; Pegg and Byers 1992; Hongeng et al. 1997). A recent trial in adult patients with malignant glioma showed that patients with methylated AGT gene promoters (and thus decreased AGT expression) had a better response to chemotherapy with the alkylating agent temozolomide (Hegi et al. 2005). Experiments in brain-tumor cell lines as well as tumor xenografts have shown that depletion of AGT with O^6-benzylguanine (acting as an alternate substrate for AGT) increases tumor-cell sensitivity to chemotherapy (Jaeckle et al. 1998). A Phase I clinical trial in malignant glioma of O^6-benzylguanine administered preoperatively as a single agent showed reduced levels of AGT in the resected tumor, suggesting that combination treatment with O^6-benzylguanine and nitrosourea or temozolomide would increase tumor-cell sensitivity (Friedman et al. 1998). A Phase I clinical trial of temozolomide in combination with O^6-benzylguanine for recurrent or refractory pediatric brain tumors was recently completed through the Pediatric Brain Tumor Consortium. This study demonstrated that this regimen was well-tolerated and also established modest activity, with 3 patients with recurrent glioma having partial responses (Broniscer et al. 2007).

15.6.3 Molecular Targets and Signal Transduction Inhibition

The enormous expansion in knowledge of the detailed molecular basis of neoplastic transformation has led to the development of a new class of agents designed to inhibit specific intracellular biochemical pathways. The majority of these agents function by inhibiting receptor tyrosine kinases, a class of cellular proteins that bind a specific ligand through their extracellular domains. Activation of the intracellular tyrosine kinase catalytic domain of the receptor after ligand binding subsequently triggers a cascade of biochemical signals. This ligand-dependent tyrosine kinase activation mediates a host of cellular properties, including proliferation, survival, and differentiation. In normal cellular homeostasis, these functions are tightly regulated. In oncogenesis, unregulated, ligand-independent kinase phosphorylation and subsequent receptor activation is a common event and is likely a key mechanism in maintaining the malignant phenotype. Receptor tyrosine kinases known to be important in CNS tumors include the EGFR, the platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptor (VEGFR). An important downstream effector of many of these receptors is mTOR (mammalian target of rapamycin), a key regulator of cell growth and survival. Small-molecule and monoclonal-antibody inhibitors of these proteins are discussed in greater detail in Chap. 16.

15.6.4 Angiogenesis Inhibitors

The role of angiogenesis in supporting tumor-cell proliferation and survival has been extensively investigated since the hypothesis of "angiogenesis dependency" of tumors was first proposed by Judah Folkmann (Folkman 1971; Balis et al. 2002). The angiogenesis hypothesis proposes that tumor-induced proliferation of blood vessels is necessary to support ongoing proliferation and survival. This deceptively straightforward statement must be tempered by the fact that tumor-cell induced angiogenesis appears to have multiple mechanisms, some of which are redundant. Tumor cells produce proangiogenic cytokines, including acidic and basic fibroblastic growth factor (aFGF, bFGF), angiogenin, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and interleukin 8 (IL-8). Additionally, tumor cells produce matrix metalloproteinases (MMP), which can induce breakdown in extracellular matrix, again allowing for release of proangiogenic peptides. Finally, tumor cells recruit

inflammatory cells that subsequently produce proangiogenic cytokines (Bicknell and Harris 1996; Pluda 1997; Paku 1998).

A number of therapeutic agents have been shown to inhibit neovascularization *in vitro* and *in vivo*. Thalidomide, initially developed as a sedative and subsequently found to be a potent teratogen in humans, has antiangiogenic properties (D'Amato et al. 1994). It has been shown to inhibit bFGF-induced corneal vascularization in animals (Kenyon et al. 1997). In a single-agent clinical trial of recurrent gliomas, objective response rates (partial response and stable disease) of up to 45% were reported (Fine et al. 2000). Lenalidomide is an analog of thalidomide that has shown considerable efficacy in multiple myeloma and myelodysplasia. A recent Phase I trial in adults with recurrent CNS tumors showed limited activity and was associated with an increased risk of thromboembolic disease (Fine et al. 2007). Enzastaurin is an oral serine/threonine kinase inhibitor that targets Protein Kinase C-β (PKCβ), a key signaling intermediary downstream of VEGFR [reviewed in (Ma and Rosen 2007)]. In addition, enzastaurin targets the phosphatidylinositol-3-kinase/AKT pathway, which is an important survival pathway in malignant gliomas. Enzastaurin has shown single-agent efficacy in preclinical models of glioblastoma (Graff et al. 2005) and currently in clinical trials in adults with glioblastoma, as well as children with recurrent brain tumors.

The role of cyclooxygenase inhibitors as an antiangiogenic treatment strategy is also under investigation. Cyclooxygenase 2 (COX-2) induces vascular proliferation following trauma or stimulation with growth factor, and is highly expressed in some human tumors, including high-grade glioma (Joki et al. 2000). Treatment of glioma cell cultures with a specific COX-2 inhibitor was found to produce diminished proliferation and invasion and increased apoptosis (Joki et al. 2000). Celecoxib is a specific inhibitor of COX-2, with a highly favorable toxicity profile. While celecoxib is not currently under investigation in large-scale pediatric clinical trials, its ease of use and low toxicity make it an interesting agent to pursue in combination with other agents.

The largest class of antiangiogenic agents under development is small-molecule tyrosine kinase inhibitors, which block VEGF-mediated signaling (Glade-Bender et al. 2003). Matrix metalloproteinase inhibitors and integrin antagonists are also under investigation [reviewed in (Drevs et al. 2002)]. The most successful strategy in adults thus far has combined a monoclonal antibody against VEGF (bevacizumab) with the cytotoxic chemotherapeutic agent irinotecan. Thirty-five patients with recurrent glioblastoma multiforme were treated with this regimen and were reported to have a 6-month progression-free survival of 46%, with 20 of the 35 patients demonstrating at least a partial response (Vredenburgh et al. 2007). This regimen was found to have moderate toxicity, with CNS hemorrhage, in particular, being a concern. A pediatric trial is currently underway through the Pediatric Brain Tumor Consortium.

Finally, the use of conventional cytotoxic agents given in low-dose, metronomic regimens is being piloted. These regimens are based on the principle that while endothelial cell proliferation appears to be sensitive to chronic but low-dose exposure, it has ample recovery time during the recovery phase of dose-intensive therapy schedules. Growing evidence from pilot clinical trials supports this hypothesis (Einhorn 1991; Ashley et al. 1996; Kushner et al. 1999; Klement et al. 2000). A recent report from Kieran et al. described the use of metronomic chemotherapy with daily oral thalidomide and celecoxib, in addition to alternating cycles of daily oral etoposide and oral cyclophosphamide in the treatment of 20 children with recurrent or progressive cancer. The regimen was well-tolerated and prolonged progression-free survival in a number of children with CNS malignancies (Kieran et al. 2005). Larger studies investigating therapies directed against angiogenesis for pediatric brain tumors are ongoing.

15.6.5 Overcoming the Blood–Brain Barrier

The BBB is composed of tight endothelial cell junctions that exclude most large molecules, and is freely permeable only to small molecules that are highly lipophilic. This barrier limits the ability of many systemically administered chemotherapeutic agents to penetrate the CNS. Radiographic evidence based on heterogeneous uptake of gadolinium on magnetic resonance imaging suggests, however, that the BBB is

only partially intact in many patients with CNS tumors. Further support of tumor degradation of the BBB lies in the responsiveness of tumors to large, water-soluble molecules such as the platinum agents. Nevertheless, resistance of CNS tumors to therapy may partially lay in the infiltrative, nonenhancing portions of tumor that presumably have an intact BBB, and thus are able to escape cytotoxicity of systemically administered agents. This is supported by the propensity of many tumors to recur locally, at the infiltrating edge of the tumor. A number of strategies are under investigation with the intent to disrupt or bypass the BBB.

15.6.5.1 Blood–Brain Barrier Disruption

Mannitol was one of the first agents used to attempt disruption of the BBB. Increased osmotic pressure transiently opens the BBB, allowing entry of molecules, otherwise unable to penetrate the CNS (Neuwelt et al. 1983). Increased disease response has been reported following BBB disruption, largely in adult patients with non-AIDS CNS lymphoma (Neuwelt et al. 1981). The Children's Cancer Group reported on the only pediatric experience with this strategy, using mannitol in combination with etoposide for recurrent or refractory CNS tumors. They were unable to document a clear benefit (Kobrinsky et al. 1999).

RMP-7 is a bradykinin analog, which, on binding to specific B_2 bradykinin receptors on the surface of endothelial cells, transiently increases permeability of the BBB. While increased concentration of carboplatin when administered with this agent has been documented in animals (Dean et al. 1999), a randomized, placebo-controlled, Phase II trial in adults with malignant glioma showed no survival benefit from the addition of RMP-7 to carboplatin alone (Prados et al. 2003). A Phase II pediatric trial was conducted by the Children's Oncology Group for patients with recurrent or refractory brain tumors (Warren et al. 2006), and did not show any activity in children with brainstem gliomas or high-grade gliomas.

15.6.5.2 Intra-Arterial Delivery

Intra-arterial delivery of chemotherapy, often delivered in conjunction with mannitol, may improve delivery of drug and minimize systemic toxicity, possibly allowing for the use of lower doses delivered directly to the tumor. A number of studies have investigated the use in intra-arterial carmustine, cisplatin, and carboplatin. While modest responses have been reported, neurologic toxicities are substantial, including irreversible encephalopathy and vision loss (Bashir et al. 1988; Mahaley et al. 1989; Newton et al. 1989).

15.6.5.3 Intratumoral Drug Delivery

A variety of novel techniques to deliver drug directly to the tumor or resection cavity are under investigation. The use of carmustine-impregnated "wafers" in adults with malignant glioma has been reported. This strategy allows for the passive diffusion of high concentrations of carmustine from wafers surgically implanted in the resection cavity to surrounding tumor cells, with minimal systemic exposure. Modest improvements in survival have been shown with this intervention (Brem et al. 1995; Valtonen et al. 1997), and a Phase I trial of carmustine wafers in combination with O^6-benzylguanine has recently begun accruing patients in the Pediatric Brain Tumor Consortium.

Passive diffusion, however, is limited by minimal ability of the drug to penetrate beyond the margin of the tumor resection cavity. Convection enhanced delivery (CED) is a novel delivery strategy that overcomes this barrier, and allows for delivery of larger molecules. CED requires the surgical placement of catheters intra- or peritumorally, through which a therapeutic agent is infused under positive pressure (Bobo et al. 1994). This allows for a substantially larger area of the brain to be treated. This approach has been largely used to deliver biologic cytotoxins targeted to high-grade glioma cells. The first such agent to be reported was a conjugate of transferrin (the receptor for which is highly expressed in GBM) with truncated diphtheria toxin. The infusions were relatively tolerated, and the treatment produced 9 objective responses in 15 evaluable patients (Laske et al. 1997). Another agent for CED is IL13-PE38QQR, a conjugate molecule of IL13 and inactivated *Pseudomonas* exotoxin, capitalizing on the

high expression of IL13 receptor in malignant glioma with minimal expression in normal brain (Debinski et al. 1999). Direct intratumoral infusion in glioblastoma xenografts produces complete regression of tumor. A Phase I study in adult patients with recurrent glioblastoma multiforme demonstrated that this approach, although technically challenging, was well-tolerated (Kunwar et al. 2007).

15.6.6 Differentiation of Neoplastic Cells

Agents that induce differentiation of tumor cells, thereby suppressing neoplastic proliferation, may have a role in the management of brain tumors. Experiments in cell culture using both retinoic acid and phenylacetate show both differentiation and inhibition of proliferation of astrocytoma-derived and medulloblastoma-derived cell lines (Mukherjee and Das 1990; Rodts and Black 1994). Treatment of adult patients with malignant glioma with single-agent 13-*cis*-retinoic acid showed a modest partial response plus a stable disease rate of 46%, with tolerable toxicity (Yung et al. 1996). A recent Phase II study investigated the combination of temozolomide with 13-*cis*-retinoic acid for recurrent malignant glioma in adults. A slight improvement in 6-month progression-free survival was observed over historical controls, suggesting that the combination is active in recurrent malignant glioma (Jaeckle et al. 2003). Another recent Phase II trial used 13-*cis*-retinoic acid as maintenance therapy for adult patients with high-grade glioma after first-line multimodal therapy (Wismeth et al. 2004). This approach was well-tolerated, and resulted in a median survival of 74 weeks. In a randomized trial adding retinoic acid to combination therapy for high-risk neuroblastoma, patients treated with retinoic acid had better outcomes (Matthay et al. 1999). Based on these findings, its favorable toxicity, and ease of administration, retinoic acid is a feasible agent to be used in future combination-regimen clinical trials for medulloblastoma and high-grade glioma in children. Phenylacetate and its analog, phenylbutyrate have also entered clinical trials. Chang et al. published results of a Phase II trial showing a 75% failure rate after 2 months in adult patients with recurrent malignant glioma, and a median survival of 8 months, suggesting no improvement from treatment over historical controls (Chang et al. 1999). Toxicities were mild, but the future impact of this agent is uncertain.

15.6.7 Gene Therapy

The goal of gene therapy is to transfer genetic material into a tumor cell to achieve a targeted therapeutic effect with minimal toxicity to surrounding normal cells. The genetic material is typically transferred using a modified viral vector. A number of genetic events can be introduced to achieve this goal. "Suicide gene" therapy involves the introduction of a gene that encodes for a protein that will make the tumor cell more vulnerable to toxicity from a specific drug. The herpes simplex virus thymidine kinase (HSV-tk) ganciclovir (GCV) model has been used in clinical trials (Culver et al. 1992). The *HSV-tk* gene encodes an enzyme whose substrate range is greater than that of its host. Its function is to phosphorylate purine pentosides and a wide variety of nucleoside analogs. Initial gene therapy directed against brain tumors used retrovirally delivered *HSV-tk*. Cells transfected with the *HSV-tk* gene become susceptible to treatment by GCV. Phosphorylation of GCV by HSV-tk produces a nucleotide-like precursor that blocks replication, thereby causing death of those cells expressing HSV-tk. Cells not transfected by *HSV-tk* are unaffected by GCV. This strategy has been used for both adult and pediatric recurrent gliomas, with minimal success (Viola and Martuza 1996). Poor efficiency of transfection of virus into tumor cells appears to be one of the major barriers. Packer et al. demonstrated the feasibility of this approach in a Phase I clinical trial using this strategy for children with recurrent, supratentorial tumors. Twelve children with recurrent malignant glioma, ependymoma, or PNET were treated with local injections into a resection cavity. While four episodes of transient neurologic deterioration were described, no irreversible toxicity was noted (Packer et al. 2000).

A number of other gene-therapy strategies are in development. Neural stem cells (NSCs) demonstrate remarkable mobility throughout the brain, and have a marked tropism toward medulloblastoma and

high-grade glioma tissue when injected into experimental tumor models. Kim et al. engineered human NSCs to express the prodrug activating enzyme cytosine deaminase. These cells were then injected into mice carrying medulloblastoma xenografts, and this dramatically sensitized tumors to therapy with 5-fluorocytosine (Kim et al. 2006). Another strategy exploits the function of tumor-suppressor genes in brain tumors. A number of tumor-suppressor genes have been characterized in human malignancies, and many are important in gliomagenesis as well as in CNS embryonal tumors (von Deimling et al. 1995; Cogen and McDonald 1996). Tumor-suppressor genes encode proteins that inhibit cell growth; absent or nonfunctional proteins result in loss of inhibition and unchecked tumor growth. Among the important tumor-suppressor genes in CNS tumors are *p53* and *PTEN*. Both genes have been found to be mutated or deleted in a large number of adult high-grade glioma specimens (Koga et al. 1994; Li et al. 1997, 1998; Rasheed et al. 1997). Replacement of *p53* function by transfecting tumor-cell lines that have mutated or deleted *p53* reverses the malignant phenotype in cell culture and animal experiments, suggesting that tumor-suppressor gene replacement is a feasible gene-therapy strategy (Hsiao et al. 1997; Kokunai et al. 1997). Results of a recently published Phase I trial using an adenoviral vector to introduce *p53* into tumor cavities of patients with recurrent glioma support this strategy, although the strategy was found to be limited by inadequate volume of transduced cells (Lang et al. 2003). Similar experiments have been done with tumor cells containing mutations in *PTEN*, another important gene in adult glioma, again showing reversal of the malignant phenotype (Cheney et al. 1998; Tamura et al. 1998). One of the many challenges impeding the progress of tumor-suppressor gene replacement therapy is the heterogeneous nature of many gliomas, in which only a subset of tumor cells carry the tumor-suppressor gene mutation, while other tumor cells may have different genetic changes supporting their malignant behavior.

Antisense gene therapy is designed to block the expression of prooncogenic proteins. A molecule with a gene encoding a nucleotide sequence complementary to the target tumor gene is introduced into the tumor cell with a viral vector; the transcript of the transfected gene binds to the target gene mRNA and impedes protein translation (Yung 1994; Alama et al. 1997). Preclinical studies of this strategy in animal models of non-CNS tumors have targeted the K-*ras* oncogene with mixed success (Aoki et al. 1997; Wickstrom 2001). Poor stability of antisense oligonucleotides is one of the larger problems with this technique.

Gene therapy remains an exciting prospect for future development. The ability to target and disrupt not only genes that modulate tumor proliferation and survival, but also tumor angiogenesis and invasion require further investigation. Vector design also requires substantial further development to overcome such challenges as poor transfection efficiency and risk of pathogenic infection. Significantly, the improved characterization of the genetics of childhood brain tumors is critical, as specific gene therapy targets move closer to clinical trials.

15.6.8 Immunotherapy

The goal of immunologically directed antitumor therapy is to eradicate tumor cells either by stimulating host immunologic antitumor reactions, or by blocking tumor-related local immunosuppression. Immunotherapy can be broadly divided into four categories: cytokine-based therapy, serotherapy, adoptive transfer (of activated lymphocytes), and active immunotherapy (i.e., tumor vaccines) (Parney et al. 2000). Cytokine-based therapy is the systemic administration of immunomodulatory cytokines. A number of cytokines have shown antitumor activity in preclinical studies, including IL-2, IL-4, IFN-α, and TNF-α (Merchant et al. 1990; Lapena et al. 1991; Iwasaki et al. 1993; Kondo et al. 1994). Systemic administration of IL-2 at high doses did show antitumor effect in clinical trials, but was associated with substantial toxicity, including cerebral edema (Rosenberg et al. 1987; Merchant et al. 1990). Clinical trials of other immunostimulatory cytokines have been disappointing, with minimal to no antitumor effect seen (reviewed in Parney et al. 2000).

Serotherapy uses antitumor antibodies, systemically or locally administered. Tenascin and gp240 are glioma antigens for which monoclonal antibodies have been developed and tested in clinical trials. Phase I/II clinical trials of I^{131}-radiolabeled antibodies directed against tenascin and gp240 have shown promising early results with objective response rates up to 50% and modest prolongation of survival in adult patients (Riva et al. 1997; Bigner et al. 1998). EGFRvIII-directed monoclonal antibody therapy shows promise in preclinical studies (Mishima et al. 2001; Ohman et al. 2002; Mamot et al. 2003). Nimotuzumab is a monoclonal antibody directed against EGFR and has shown promising results in children and adults with brain tumors. A recent Phase II trial documented a partial response or stable disease (PR/SD) rate of 45% in children with intrinsic pontine glioma, and a Phase III trial is underway (Bode et al. 2007).

Adoptive transfer therapy, in which ex vivo-activated lymphocytes are administered intratumorally, has been disappointing in clinical trials (Barba et al. 1989; Lillehei et al. 1991; Sankhla et al. 1996). Autologous tumor vaccines, one of the earliest forms of immunotherapy, have not shown a clear benefit in clinical trials (Bloom et al. 1973; Mahaley et al. 1983). A promising new approach involves the use of tumor-derived heat shock protein/protein complexes (HSPPC's) as a tumor vaccine. Heat shock proteins act as molecular chaperones inside cells and have been found to bind a unique "fingerprint" of peptides that are tumor-specific. These HSPCC's have been found to be antigenic in human trials with a variety of tumors and function by eliciting T cell-mediated cytotoxicity. A Phase I/II trial is currently underway for adults with recurrent malignant glioma.

Gene-therapy techniques have been incorporated into tumor vaccine development. Here, immunostimulatory genes are transferred to target cells to enhance antitumor immune function. Animal studies have shown successful vaccination with GM-CSF (a proinflammatory cytokine) transduced melanoma cells, resulting in resistance to repeat tumor challenge (Sampson et al. 1996; Yu et al. 1997). An antisense strategy to block glioma-derived local immunosuppressant cytokines has also successfully produced an antitumor effect in animal models. Dendritic cell therapy involves the collection of these antigen-presenting cells followed by an ex vivo pulse with autologous tumor lysate. These cells are then administered intradermally or intratumorally and stimulate host cytotoxic T-cells to attack the tumor. A recent trial using dendritic-cell therapy in adult patients with recurrent malignant glioma (Yamanaka et al. 2005) showed a PR/SD rate of 58% and resulted in a significant increase in overall survival. Many other immunotherapeutic strategies are under investigation, including local or intratumoral infusion of proinflammatory cytokines. Although relatively few immunotherapies have entered pediatric clinical trials, ongoing research in this field carries future promise.

15.7 Conclusions

While prognosis for malignant brain tumors in children has improved somewhat in the past several decades, 5-year survival for all tumors except low-grade astrocytoma remains suboptimal at 60%. The incorporation of chemotherapy into pediatric brain tumor management has allowed for advances in survival and reduction of morbidity, and is now the standard of care for many childhood brain tumors. Critical to the further improvement of prognosis and long-term outcome is the continued effort of multiinstitutional, cooperative group clinical trials. The largest clinical trials group conducting pediatric brain-tumor trials is the National Cancer Institute (NCI)-sponsored Children's Oncology Group. The Children's Oncology Group includes the majority of pediatric cancer treatment centers in the United States, and incorporates programs in Canada, Europe, and Australia. Research activities include clinical trials for the majority of newly diagnosed and recurrent brain tumors, as well as studies of new agents. The Pediatric Brain Tumor Consortium is a smaller, NCI-sponsored consortium with a mission to expedite the development of new agents' high-risk pediatric brain tumors by bringing novel agents and translational research to the pediatric brain tumor community in a multiinstitutional setting. Information on the

Children's Oncology Group and the Pediatric Brain Tumor Consortium can be found on the World Wide Web at http://www.childrensoncologygroup.org and http://www.pbtc.org.

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Advances in Radiation Therapy

Sean M. McBride • Daphne A. Haas-Kogan

Contents

16.1 Introduction

Despite the known effects of ionizing radiation on the nervous system, most children with brain tumors have to undergo radiation therapy at some point during their treatment. As advances in neurosurgery, chemotherapy, and radiotherapy enter clinical practice, multimodality therapy has become the norm. For any tumor, the incorporation of radiation therapy into such treatment must consider the timing, dose, and treatment volume of radiation, the most appropriate radiation modality, short- and long-term toxicities, both for radiation alone and for radiation in conjunction with chemotherapy, and, finally, the integration of novel antineoplastic agents with radiation.

16.2 Radiobiology

The biologic effects of ionizing radiation primarily result from the formation of double-strand breaks in cellular DNA (Hall 2000). Although most radiation-induced single-strand DNA breaks are efficiently repaired, double-strand breaks cause irreparable damage, resulting in mitotic cell death. Photon radiation (X-ray or gamma ray) can cause damage by direct interaction with the DNA molecule, or indirectly by the formation of free radicals that then interact chemically with DNA leading to double-strand breaks. Charged particles such as helium, carbon, or neon predominantly cause damage by direct interactions. High-energy neutrons, although not charged, also interact with the nucleus of an atom, resulting in the creation of densely ionizing recoil protons, alpha particles, and

nuclear fragments. Linear energy transfer (LET) measures the average energy deposited in the tissue per unit distance traveled by a particle or photon. While conventional radiation is sparsely ionizing (low LET), therapies using fast neutrons and heavy particles are more densely ionizing (high LET) (Hall 2000).

Tissue oxygenation influences the response of tumors and normal tissues to ionizing radiation (Brown and Giaccia 1994; Brown 1999). Poorly oxygenated tissues are 2–3 times more resistant to radiation than normally oxygenated tissues. Oxygen is thought to mediate indirect damage, combining with free radicals to make DNA damage irreversible. The effect of tissue oxygenation is measured by the oxygen enhancement ratio (OER). This is the ratio of doses under hypoxic versus aerated conditions required to produce a given level of cell kill. As LET increases, the magnitude of the OER decreases (Hall 2000). Because tissue hypoxia promotes radiation resistance, investigators are actively pursuing strategies designed to increase intratumoral oxygen levels. Recent studies have used angiogenesis inhibitors with radiation in an attempt to normalize tumor vasculature, thereby enhancing oxygen delivery and radiation sensitivity (Dings et al. 2007).

Radiation causes complex cascades of intracellular molecular events, affecting cell-cycle checkpoints, apoptosis, DNA damage response, and DNA repair. It also dramatically alters the tumor microenvironment. These effects offer many potential approaches to both enhance radiation damage to tumor cells and protect normal tissues. These techniques are discussed further in this chapter.

16.3 Three-Dimensional Conformal Radiation Therapy

While radiation therapy plays a key role in the treatment of pediatric brain tumors, delivery of adequate therapy must always be balanced against potential treatment-related toxicity. As radiation therapy has evolved, treatment modalities have emerged that allow for more precise planning and delivery (Suit 2002). Advances in imaging technologies, including magnetic resonance imaging (MRI) and computed tomography (CT), have allowed better identification of both tumor and surrounding critical structures.

The development of 3D conformal radiation therapy (3DCRT), and more recently, intensity modulated radiation therapy (IMRT), has allowed clinicians to decrease doses delivered to critical structures, while maintaining or increasing doses delivered to the tumor (Weil 2001). While the concept of conformal therapy is not new, dramatic improvements in the power and availability of computers have allowed more complex treatment planning systems. The advent of other technical advances such as multileaf collimation (MLC), digitally reconstructed radiographs (DRRs), and electronic portal imaging have contributed to the integration of conformal radiation delivery. The planning process for 3DCRT is significantly more complex than for conventional radiation therapy and requires multiple well-coordinated steps.

16.3.1 Immobilization and Imaging

The initial step of the planning process is to place the patient in a reproducible position that optimizes treatment of the entire tumor volume while sparing surrounding critical structures. This position may be different for each patient and depends on the specific location, shape, and size of the tumor, and areas at risk for suspected microscopic disease. A variety of customizable immobilization devices are available, including thermoplastic facemasks, alpha cradles, and vacuum bags. It is important to note that as the planned course of radiation therapy becomes increasingly conformal, the importance of reliable and reproducible immobilization becomes critical. Once the patient has been optimally and reproducibly positioned, localization marks are placed on the skin. With the patient in the treatment position, CT images of the area of interest are obtained. These data are then transferred to the planning system, at which point the clinician can define target volumes as well as critical structures. While some well-defined structures can be contoured automatically, most structures must be defined manually. A pretreatment CT scan is generally used for treatment planning, although other modalities such as MRI can be coregistered with the CT data.

16.3.2 Target Definition and Planning

The CT images are analyzed jointly by radiation oncologists, diagnostic radiologists, and occasionally by other treating physicians such as medical oncologists and surgeons. The treatment volume is dictated by the natural history of the tumor. Gross tumor volume (GTV) is defined by physical exam and imaging studies and encompasses the macroscopic extent of the tumor. Clinical target volume (CTV) contains both the GTV and areas at risk for microscopic spread of disease. The planning target volume (PTV) is defined as the CTV surrounded by adequate margin to account for variation in patient position, organ motion, and other movement (Purdy 1999; Hall 2000).

Once target volumes and critical structures are defined, beam geometry and weighting are defined, and dose distribution is calculated (Purdy 1999). Selection of beam angles can be done by referencing axial images or by use of beam's eye view (BEV; Fig. 16.1). BEV allows the visualization of the relationship of tumor volumes to those of critical normal tissues, as if looking from the origin of the beam. This allows beam angles and beam shaping to be selected more intelligently. Once an initial plan has been developed, the resulting dose distributions are calculated and evaluated by the clinician. The plan can then be altered to improve on initial results, if necessary. The beam directions as well as their relative weights and shapes are modified to finally optimize the 3DCRT plan.

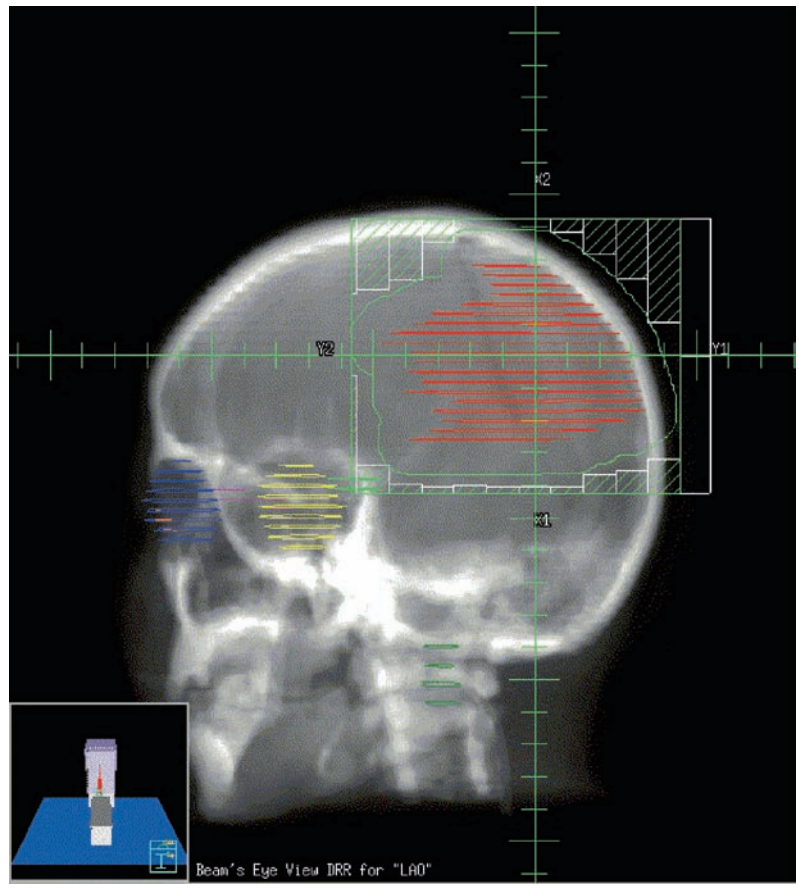


Figure 16.1
Beam's eye view of a left anterior oblique field in a patient with a supratentorial primitive neuroectodermal tumor (PNET). (Courtesy of Clayton Akazawa, Department of Radiation Oncology, UCSF)

Plans are evaluated by viewing isodose curves on serial images of a CT scan (Fig. 16.2a–c), as well as by the generation of dose–volume histograms (DVHs; Fig. 16.3). DVHs can be generated for a tumor volume or other organ of interest, allowing the clinician to evaluate the dose delivered to the total volume. DVHs typically graph percent volume of a given tissue on the *Y*-axis and dose on the *X*-axis. This allows a clinician to visualize what percentage of a defined structure is receiving a given dose. These data allow plans to be modified as needed to either increase dose delivered to tumor or decrease dose to a nearby critical structure.

16.3.3 Treatment Verification and Delivery

Once a satisfactory plan has been generated, DRRs corresponding to the planned radiation fields are generated. These DRRs typically display field shapes and tumor volumes, as well as standard radiographic information, such as anatomy. These serve as templates for design of cut blocks. Alternatively, and more commonly, block shape information can be transferred directly to the computer system that controls the MLC. Using a complex 3D plan, MLC allows for rapid change of field shape under computer control, dramatically shortening the time needed to treat a patient. Of note, studies have shown that dose

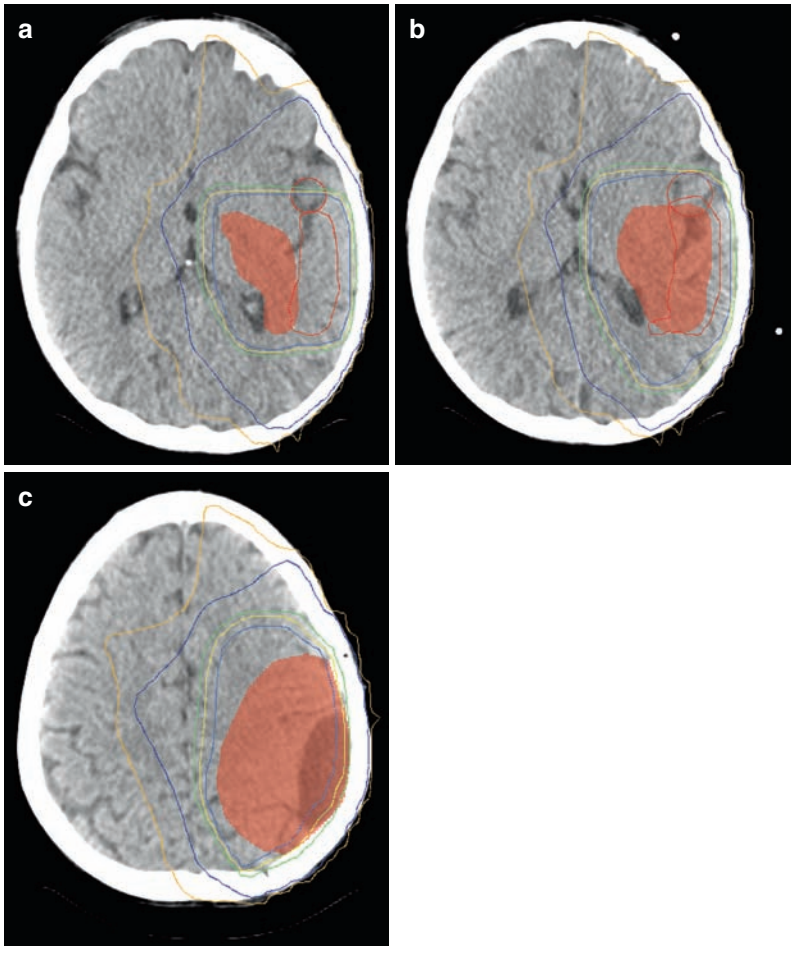
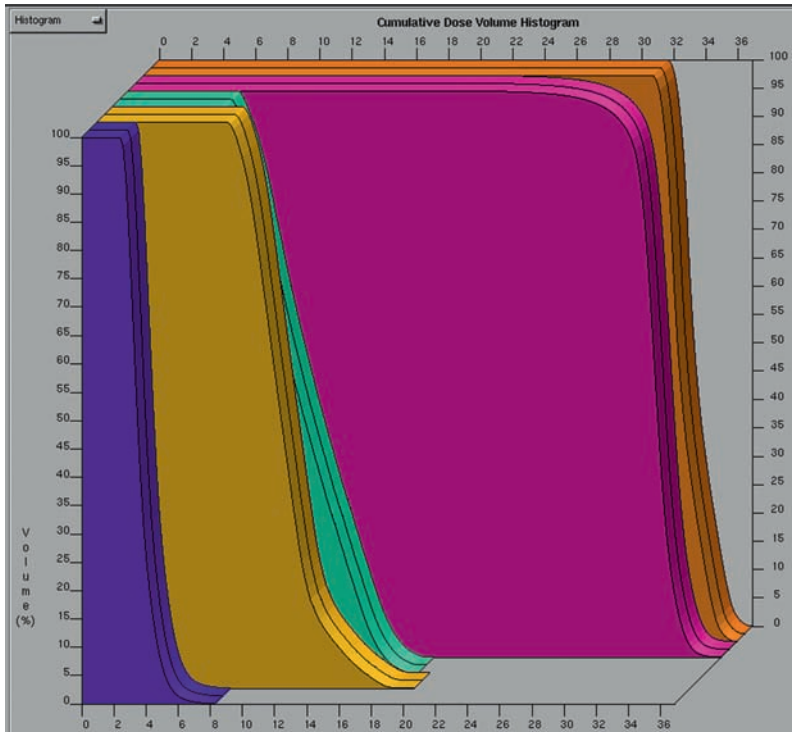


Figure 16.2

(**a–c**) Isodose curves of a three-dimensional conformal plan on serial axial slices in a patient with a supratentorial primitive neuroectodermal tumor (PNET). *Red line* depicts the 99% isodose line, *light blue* represents 95%, *yellow* depicts 93%, *green* depicts 90%, *blue* depicts 60%, and *gold* depicts 50%. (Courtesy of Clayton Akazawa, Department of Radiation Oncology, UCSF)

Figure 16.3

A dose–volume histogram for an intensity-modulated radiation therapy (IMRT) plan in a patient with a medulloblastoma. Clinical target volume (CTV) is depicted in *orange*, planning target volume (PTV) in *pink*, left ear in *light blue*, right ear in *orange*, and optic chiasm in *dark blue*. (Courtesy of Pam Akazawa, Department of Radiation Oncology, UCSF)



distributions produced with MLC are equivalent to those with cut blocks.

A verification simulation can be performed to check the validity and accuracy of the fields. First-day portal films are also generated to confirm accuracy of patient positioning and beam angles. This can be done with conventional portal films, or with the use of an electronic portal-imaging device (EPID). Because there is no development time (as there is with conventional portal images), the use of an EPID can significantly shorten the time needed to take portal images of complex multifield plans.

16.4 New Technical Approaches

16.4.1 Intensity Modulated Radiation Therapy

While 3DCRT allows for selection of beam shapes and angles to conform to a particular tumor volume, IMRT allows modulation of intensity within each given beam (Purdy 1999; Webb 2000). The initial form this approach took was the use of "beam within beam" planning with standard 3DCRT systems to treat static-shaped fields. The use of MLC makes this fairly easy to achieve. This process is typically referred to as "forward-planned" IMRT (Verhey 1999). More recently, a process called inverse planning has been developed. As with forward planning, critical structures and tumor volumes are identified. The desired dose distribution is then defined, including desired tumor dose and maximum allowable dose to critical structures. The planning algorithm then computes a plan compatible with the desired distribution. Optimization of inverse-planned IMRT requires adjustment of the dose parameters (Verhey 1999). The putative clinical advantage of IMRT resides in its demonstrated ability to improve dose conformity and spare normal tissue. Prospective trials designed to demonstrate survival benefit have yet to be conducted; however, there is recent evidence that, at least

in medulloblastomas, IMRT does significantly reduce auditory toxicity (Huang et al. 2002).

A number of techniques developed to deliver IMRT treatments have become commercially available in recent years. Most of these use MLCs to treat several static field shapes from each beam angle. Each MLC shape is referred to as a segment. Greater numbers of segments lead to longer treatment times. Other techniques include computer-controlled dynamic MLC, the use of custom compensators, and rotational therapy combined with dynamic MLC.

Using these techniques can result in dramatic dose gradients, allowing high doses to tumor, with rapid dose fall-off (Verhey 1999). An example of an IMRT plan is shown in Fig. 16.4. Because of rapid fall-off of dose, immobilization systems for IMRT are of particular importance to avoid under-dosing the target. Another issue that must be noted when using IMRT is integral dose. With IMRT, the total number of monitor units delivered to the patient is higher than with conventional treatments. This led to concerns that dose inhomogeneity might lead to an overall increase in total dose delivered. Initial studies provided conflicting results. A more recent study found that, in high-grade gliomas, IMRT actually decreased integral dose by 7–10% relative to 3DCRT (Hermanto et al. 2007). However, dose inhomogeneity also results in hot spots within the treated volume. Although these hot spots typically fall within the tumor volume, the significance of having regions of extremely high dose is unclear.

In the use of any of these conformal therapies, it is important to consider anatomy. Particularly in the use of inverse planning, if an area is not contoured as tumor, it will likely receive suboptimal dose. Areas of subclinical disease must also be taken into account. Only through careful consideration of anatomy and dose can IMRT be safely applied. Figure 16.5 compares axial sections planned with either 3DCRT or IMRT, demonstrating the sparing of inner structures achieved with IMRT without compromise of the dose delivered to the target volume.

To address patient immobilization and daily positioning, some centers use image-guided techniques. These new approaches allow the radiation oncologist to confirm the tumor location every day. One of the most exciting techniques to minimize tumor and patient movement is the use of a CT image of the patient using the "cone beam" technique that generates an image of the tumor and all surrounding normal structures using the same linear accelerator with which the patient is being treated. Appropriate adjustments can then be made daily to ensure that the tumor is receiving the prescribed dose of radiation, and normal tissues are receiving doses within their tolerance range.

The emerging concept of image-guided motion management is taking hold within the radiation oncology community, and many centers are learning not only to optimize patient immobilization techniques, but also to use novel technology to assure ever-increasing accuracy in radiation delivery.

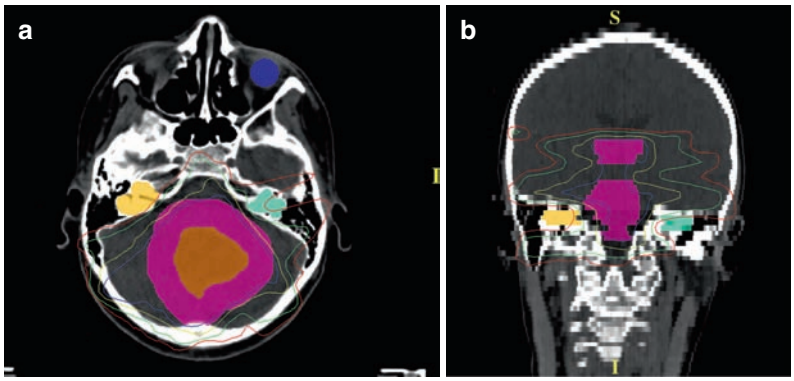


Figure 16.4

Axial (**a**) and coronal (**b**) images showing isodose curves for an intensity-modulated radiation therapy (IMRT) plan in a patient with a medulloblastoma. *Blue line* depicts the 83% isodose line, *yellow* depicts 70%, *green* depicts 50%, and *red* depicts 40%. (Courtesy of Ping Xia, Department of Radiation Oncology, UCSF)

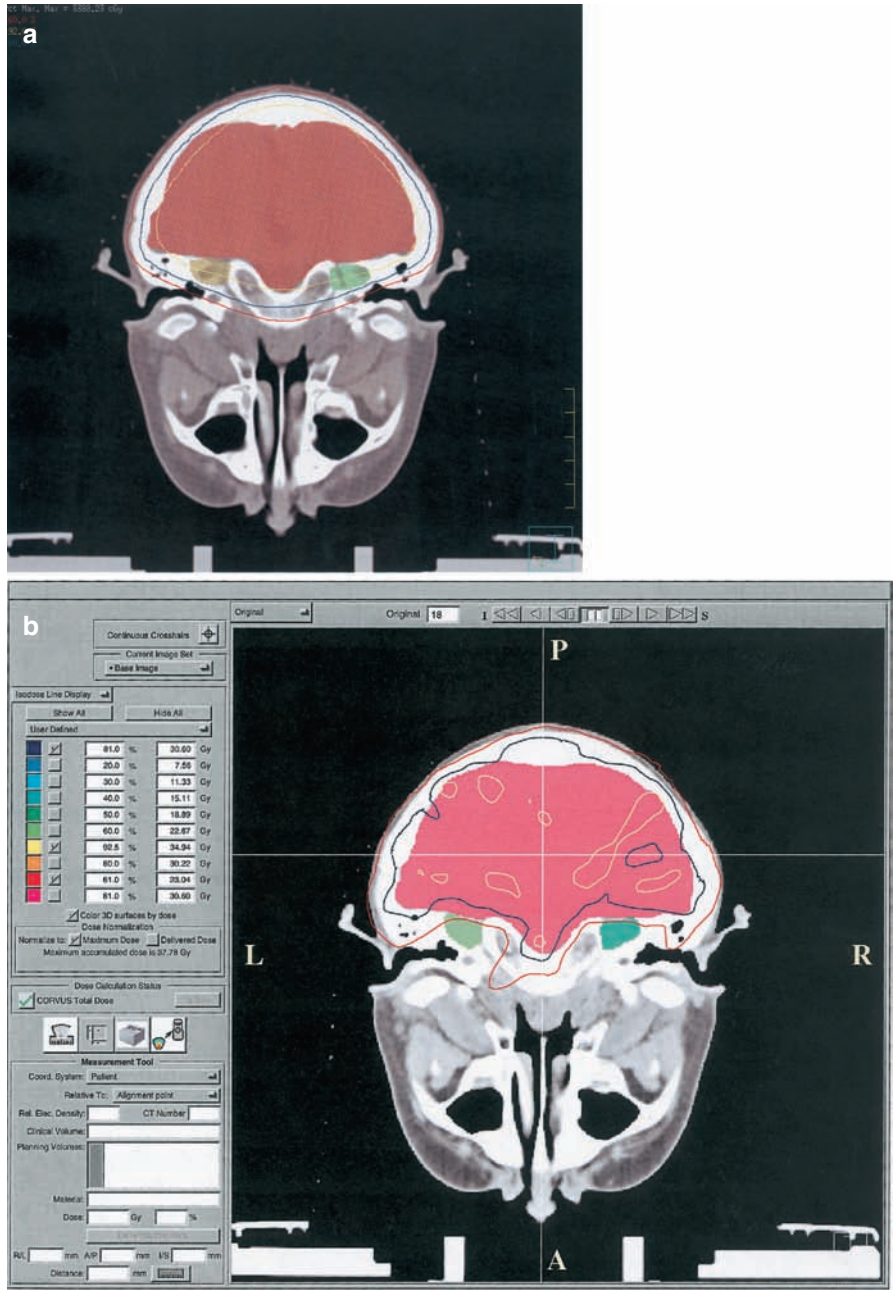


Figure 16.5

Comparison of axial sections planned with either three-dimensional conformal radiation therapy (3DCRT) (**a**) or intensity-modulated radiation therapy (IMRT) (**b**), demonstrating the sparing of inner structures achieved with IMRT without compromising the dose delivered to the target volume

16.4.2 Proton Beam Therapy

Although proton radiation has similar inherent biological effectiveness as conventional radiation, it has physical characteristics that allow precise control of dose fall-off, especially beyond the target volume (Yang 1999). Specifically, a properly focused proton beam results in both rapid fall-off of dose immediately distal to the target (a feature known as the "Bragg peak") and a smaller proximal dose than achieved with photon therapy. This allows for potential sparing of critical structures. It is conventionally accepted that proton beam therapy is superior to standard radiotherapy for skull-base chondrosarcomas and chordomas, but its effectiveness compared to radiosurgery or conformal radiotherapy has yet to be demonstrated in randomized clinical trials.

The physical advantages of proton beam radiotherapy must be weighed against proton-beam contamination by neutrons that may contribute significantly to risks of second malignancies, particularly in children. Such increased risks may be mitigated in the future as passive scatter techniques, currently used in the United States, are replaced by active scanning approaches that offer better conformity of highest doses, potentially lower doses to normal structures, and reduced beam contamination by neutrons.

Despite the lack of Level 1 evidence, retrospective studies do exist to support its use in specific subtypes of pediatric intracranial lesions. Macdonald et al. found that in pediatric ependymomas, local control, progression-free survival, and overall survival rates were comparable to those published in the literature for photon radiotherapy. As anticipated, traditional proton therapy and intensity modulated proton therapy (IMPT) resulted in greater sparing of normal tissue compared to photon-based IMRT (MacDonald et al. 2008). Using a model designed to predict neurocognitive dysfunction after radiation therapy, Merchant et al. concluded that the reduction in lower-dose volumes and mean dose afforded by proton therapy might reduce the incidence of late-term sequelae in children with medulloblastomas, craniopharyngiomas, and optic-pathway gliomas (Merchant et al. 2008). Specifically, they found that small, critical, and normal structures such as the cochlea and hypothalamus, which were anatomically separated from the PTV, received substantially less radiation using protons compared with photons. Proton radiotherapy would therefore be expected to reduce the risks of endocrine deficits and hearing loss. In addition, protons lowered the low (0–20 Gy) and intermediate (20–40 Gy) doses to the cerebrum in patients receiving focal radiation. Using longitudinal models of radiation dose-cognitive effects, the data indicated that proton radiotherapy would mitigate intelligence quotient (IQ) loss.

The benefit of proton beam radiotherapy in children is well-exemplified by its use for craniospinal irradiation. Comparisons of proton beam, conventional 3D radiation, and IMRT for treatment of the posterior fossa and spinal column suggest superior sparing of normal structures by protons. In particular, protons are likely to mitigate long-term toxicities related to hearing, endocrine, and cardiac functions. For example, 90% of the cochlea received 101.2% of posterior fossa boost dose with conventional radiation techniques, 33.4% with IMRT, and only 2.4% with protons. Similarly, 50% of the heart received 72.2, 29.5, and 0.5% of the posterior fossa boost dose for conventional X-ray therapy, IMRT, and proton beam therapy, respectively (St Clair et al. 2004).

16.4.3 Intraoperative Radiotherapy

Intraoperative radiotherapy (IORT) typically involves the delivery of a single large fraction of radiation therapy at the time of open surgery (Willett 2001). Radiation is most commonly given to the resection cavity using electrons. Depth of dose is controlled by choice of electron energy and use of bolus. Fall-off is rapid beyond the effective range of the selected electron energy. There is little data regarding either the efficacy or the side-effect profile of IORT in the treatment of primary pediatric CNS lesions. However, a recent Phase I study using the Photon Radiosurgery System found that IORT to a dose of 10 Gy prescribed to 2-mm depth was feasible and safe; the authors cautioned though that, when dose was maintained, but

depth increased to 5 mm, side effects, namely radiation necrosis, increased (Kalapurakal et al. 2006).

16.4.4 Temporary or Permanent Brachytherapy

Interstitial brachytherapy allows for the delivery of high doses of radiation to a tumor region. Brachytherapy entails the placement of radiation sources either directly in tissues or into catheters placed within tissues. As dose falls off with the square of the distance away from the radiation sources and is further attenuated by tissue, normal structures can be spared (Hall 2000).

Temporary brachytherapy typically entails the implantation of catheters in the tumor or tumor bed. Following placement of catheters, radiation sources are loaded into the catheters to deliver the desired dose. Historically, a variety of radioactive sources, including radium and cesium, have been used. In current practice an ^{192}I source is frequently used, utilizing a robotic remote afterloading system to minimize dose to medical personnel.

Permanent brachytherapy implants can also be performed. Radioactive sources are inserted into tumor tissue or placed in regions surrounding a resection cavity. For permanent brachytherapy, sources containing ^{125}I and ^{103}Pd are frequently used in clinical practice. Both of these approaches can allow delivery of a very high dose of radiation, while limiting dose to normal tissues.

A recent retrospective study reported a large series of pediatric brain tumors treated with ^{125}I brachytherapy (Sneed et al. 1996). Twenty-eight children were treated with temporary, high-activity ^{125}I brachytherapy for recurrent or persistent supratentorial, unifocal, well-circumscribed tumors less than 6 cm in diameter that had previously received external beam radiation therapy. Exclusion criteria included tumors with diffuse margins, corpus callosum involvement, or subependymal spread. The most useful result from this study is the documentation of acute and late toxicities. Outcome data, however, are less reliable, given the variety of brain tumors included in the analysis. No Grade III or IV acute or late toxicities occurred. However, 22 patients (79% of 28 total patients) required at least one reoperation following brachytherapy, and 17 of these 22 patients had evidence of necrosis in the resected specimen.

In an effort to reduce the incidence of radiation necrosis, an additional retrospective pediatric study looked at permanent low-activity ^{125}I seed implants for primary pediatric CNS lesions. Six patients with recurrent disease were enrolled, 5 of whom had received prior EBRT, and all of whom had reoperations after recurrence; only 2 patients had local failures at the first site of recurrence, leading the authors to conclude that low-activity permanent ^{125}I seed implants can help to provide good local control while diminishing the risk of significant treatment-related morbidity (Rostomily et al. 2001).

16.4.5 Stereotactic Radiosurgery and Radiotherapy

Conceptually, stereotactic radiosurgery (SRS) consists of multiple beams of radiation, all converging at the designated target volume. The patient's head is first immobilized using a stereotactic frame and then a Gamma Knife® with 201 collimated beams of cobalt-60 radiation, or a specially adapted linear accelerator, delivers a single high-dose fraction of focused radiation to a small intracranial target. Frequently, sensitive normal structures lie near the target volume. Rapid fall-off of radiation dose outside the target spares adjacent normal tissues and maintains a safe, acceptable level of irradiation. For primary brain tumors, no published, prospective, randomized trials have evaluated the role of SRS. However, the value of SRS has been demonstrated by many retrospective studies, which include a variety of benign and malignant brain tumors (Kondziolka et al. 2000). Benign tumors tend to shrink slowly over years after radiosurgery, while brain metastases generally shrink more rapidly. With the exception of metastases less than 1 cm in diameter, tumors, whether benign or malignant, generally do not disappear completely following radiosurgery treatment.

Radiosurgery use in pediatric populations is less frequent; however, retrospective case series have proven its feasibility. One of the few outcome studies retrospectively examined a population of 90 pediatric patients, the majority of whom were diagnosed with

medulloblastoma, anaplastic astrocytoma, glioblastoma, or primitive neuroectodermal tumor (PNET). In some patients, SRS was used as an initial treatment, while in others it was implemented at the time of recurrence. The study confirmed the safety of SRS in pediatric patients, with a minimal side-effect profile; there was an apparent reduction in local failure at the site of first recurrence compared to historical controls, and efficacy was increased when SRS was used as initial management rather than as salvage. The authors concluded that, in cases where residual or recurrent tumor is focally unresectable, an SRS boost might be beneficial (Hodgson et al. 2001).

Stereotactic radiotherapy (SRT) uses a noninvasive immobilization device and fractionates dose. Again, the literature is lacking in randomized controlled trials, but a recent prospective trial studied the effect of SRT in 50 pediatric patients with low-grade astrocytomas, including optic pathway gliomas. All the children were treated with SRT for progression following either surgery or chemotherapy. The total dose delivered was 52.2 Gy in 1.8-Gy daily fractions. Overall survival was 97.8% at 5 years and 82% at 8 years. Because tight margins were used in the hope of reducing late sequelae, there was some concern over marginal failures, but none were observed within a median follow-up of 6.9 years. The excellent local control observed supports the use of SRT for small, localized, low-grade CNS lesions (Marcus et al. 2005).

16.4.6 Neutron Beam Therapy

Neutrons deposit their dose more densely than conventional photon radiation, and the increased relative biological effect results in greater cell death. In addition, hypoxic cells exhibit less resistance to neutron radiation than to conventional photon radiation. Although clinical trials of neutron beam therapy in the treatment of malignant gliomas have resulted in a higher rate of tumor control than treatment with photons, no improvement in survival was demonstrated, likely due to increased necrosis associated with neutron therapy (Battermann 1980; Catteral et al. 1980; Griffin et al. 1983; Laramore et al. 1988). In a randomized study examining the optimal dose of neutrons for a limited-volume neutron boost combined with photon whole brain radiotherapy, no beneficial combination was documented (Laramore et al. 1988).

16.4.7 Boron Neutron Capture Therapy

Boron neutron capture therapy (BNCT) was first proposed in 1936, but has yet to make a significant mark on the clinical treatment of human malignancies. A stable isotope of boron, ^{10}B, is administered to patients in a pharmacologic preparation and accumulates in tumor cells. Normal and tumor tissues are then irradiated by broad-beam, low-energy thermal or epithermal neutron irradiation. The ^{10}B nuclei have a high probability of thermal neutron capture that results in nuclear fission. High LET particles are created with a range of only one cell diameter, killing only the cells in the immediate vicinity of the boron compound.

The clinical utility of BNCT depends on developing new ^{10}B-containing compounds that accumulate more selectively within tumor cells and achieve higher concentrations in these cells than within blood, scalp, and normal brain tissues (Diaz et al. 2000). The major compound used in clinical trials to date, *p*-boronophenylalanine (BPA), produces ^{10}B concentrations 3.5-fold higher in tumor and 1.5-fold higher in scalp than in blood (Chadha et al. 1998). Recent preclinical research in a rat model used a boronated monoclonal antibody (L8A4) directed against EGFRvIII, a mutant form of the EGF receptor. The authors found a statistically significant increase in overall survival when compared to intravenous BPA; the combination of intravenous BPA and boronated L8A4 proved still more potent, leading to an increase in overall survival greater than that achieved with either therapy alone (Yang et al. 2008).

16.5 Toxicity of Radiation Therapy

A wide range of potential toxicities complicates the implementation of radiation therapy in the treatment of tumors of the craniospinal axis. These toxicities

can be severe and debilitating, particularly in pediatric patients (Donahue 1992; Syndikus et al. 1994; Kalapurakal and Thomas 1997). Care should be taken to minimize these effects. Treatment of intracranial tumors can result in damage to the eye, ear, brain, and hypothalamic-pituitary axis, as well as impairment of normal growth. Treatment of the spine can result in growth deficits and damage to the spinal cord. Specific potential acute side effects of radiation to the central nervous system include epilation, skin reactions, otitis, hematopoietic depression, and somnolence. Specific late toxicities of radiation include radionecrosis, myelopathy, leukoencephalopathy, vascular injury, neuropsychologic sequelae, endocrine dysfunction, bone and tooth abnormalities, ocular complications, ototoxicity, and induction of second primary tumors (Donahue 1992; Syndikus et al. 1994; Kalapurakal and Thomas 1997). Table 16.1 delineates the radiation doses associated with late toxicities that may result from radiation therapy to the CNS.

16.5.1 Spinal Cord

Although rare, severe damage to the spinal cord can result following radiation therapy, with transection of the cord at the affected level being the most severe potential consequence. This usually takes the form of chronic a progressive myelitis. Wara et al. reported a 1% incidence of spinal cord damage at 42 Gy, and a 5% incidence at 45 Gy. A number of reports have indicated that tolerance of the cervical spinal cord to radiation toxicity is somewhat higher than 45 Gy in adults (Wara et al. 1975). However, it is unclear what the cervical spinal cord tolerance is in pediatric patients. Radiation to the spinal cord can also result in Lhermitte's syndrome, which is characterized by tingling, numbness, and a sensation of electric shock. Symptoms are often present only with neck flexion. Lhermitte's syndrome is typically self-limiting, presenting within the first 1–3 months following radiation, and having an average duration of 3–4 months. Craniospinal radiation can result in decreased truncal, or sitting, height. This is due to decreased growth of the vertebral bodies following radiation therapy, and becomes clinically evident at doses greater than 20 Gy.

16.5.2 Brain

Acute reactions during radiation therapy, thought to result from disruption of the blood–brain barrier, are uncommon. However, there are reports of edema following single conventional fractions (Kramer and Lee 1974). Clinically apparent acute changes are more common with hypofractionated doses, such as those used in radiosurgery (Loeffler et al. 1990). Steroids can be administered to address edema.

Subacute reactions are more common, and are thought to be due to transient demyelination (Boldrey and Sheline 1966). These effects typically occur within the first few months following radiation and usually resolve within 6–9 months. Delayed, transitory clinical manifestations of radiation,

Table 16.1. Late toxicities of CNS irradiation

Structure	Late effect	Threshold dose (Gy)
Spinal cord	Chronic progressive myelitis	45
Brain	Radiation necrosis	60
	Intellectual deficits	12–18
Eye		
Lens	Cataract formation	8
Retina	Radiation retinopathy	45
Optic nerve	Optic neuritis	50
Inner ear	Sensorineural hearing loss	40–50

including somnolence syndrome, are seen in a large number of patients receiving prophylactic craniospinal radiation along with intrathecal chemotherapy for acute lymphoblastic lymphoma (ALL) (Littman et al. 1984). Severe subacute effects such as rapidly progressive ataxia are rare and are generally associated with fractions larger than 2.0 Gy and total doses larger than 50 Gy (Lampert and Alegria 1964).

The late effects of radiation are primarily due to radiation necrosis. Symptoms are related to the neuroanatomical location of necrosis (sensory, motor, speech/receptive deficits, seizures), and may also be caused by increased intracranial pressure. Focal necrosis is uncommon with doses below 60 Gy given with conventional fractionation (Halperin and Burger 1985). As the number of survivors of childhood cancers increases, it is becoming apparent that those who received cranial irradiation are at increased risk for the later development of primary CNS neoplasms. A recent retrospective case-control study looking at survivors of childhood cancer found an increase in the incidence of glioma (OR = 6.78, 95% CI = 1.54–29.7) and meningioma (OR = 9.94, 95% CI = 2.17–45.6), with most of the excess risk attributable to radiation exposure (Neglia et al. 2006). These children were treated between 1970 and 1986, before the advent of IMRT. There is some concern that IMRT, because of increased radiation leakage and integral dose, may further increase the incidence of secondary neoplasms (Hall 2006); however, mechanisms do exist to mitigate scattering and leakage. Finally, in addition to secondary CNS neoplasms, children that receive cranial irradiation are also at elevated risk for stroke and cerebrovascular accidents (Bowers et al. 2006).

With large-volume radiation therapy, diffuse white matter changes can be seen. Clinically, these can result in lassitude, personality change, or neurocognitive deficits. Multiple studies have examined the effect of whole-brain radiation therapy on intellect in patients treated for leukemia. Radiation-associated depression in IQ has been noted by a number of authors (Rowland et al. 1984; Copeland et al. 1985). Halberg et al. compared three groups of patients. The first group received 18 Gy (1.8 Gy per fraction) of cranial irradiation, while the second received 24 Gy of cranial irradiation. The third group consisted of other oncology patients who did not receive cranial irradiation. Lower IQ scores were noted in the group receiving 24 Gy (Halberg et al. 1992). High-dose methotrexate and female sex appear to increase risk of intellectual deficits (Waber et al. 1992). The effects of cranial irradiation are also more severe in younger children. Intellectual deficits resulting from radiation most commonly result in difficulty acquiring new knowledge, decreased processing speed, and memory deficits (most frequently short-term memory) (Mulhern et al. 1992).

Children irradiated for primary brain tumors have also shown intellectual deficits. Effects of radiation are more difficult to evaluate in this setting, as most of these patients have also had surgical resection. However, similar to patients with ALL, younger age appears to result in a higher rate of neurocognitive deficits. Larger fields and higher doses also appear to cause higher rates of toxicity.

Attempts to avoid the cognitive sequelae of cranial irradiation tend to involve the sparing of certain critical structures. Because adult patients who receive whole-brain radiation therapy are at increased risk for dementia, attempts have been made to develop plans, using conformal technology that spare critical memory structures such as the hippocampus (Gutierrez et al. 2007). Additional effort has focused on creating conformal plans that spare the neural stem-cell compartments (subventricular and subgranular zones) in the hope of further mitigating neurologic impairment secondary to radiation (Barani et al. 2007).

Finally, alternative modalities of radiation have the potential to lessen neurocognitive toxicities. Merchant et al. compared models of photon radiation to those of proton radiation and predicted the relationship of each to cognitive function in children treated for brain tumors (Merchant et al. 2008). These investigators utilized models of radiation dose-cognitive effects developed from patients with four types of childhood brain tumors chosen for their characteristic location, volume, and radiation dosimetry. These included optic pathway glioma, infratentorial ependymoma, craniopharyngioma, and standard-risk medulloblasotma. They found

that, compared to photon-based radiation plans, proton beam radiotherapy delivers smaller doses to critical normal structures that were not adjacent to the tumor volume, specifically the cochlea and hypothalamus. Furthermore, protons resulted in a smaller proportion of normal supratentorial brain receiving low- and intermediate-dose radiation. Thus, superior dose distributions of proton beam radiotherapy were likely to translate into less radiation-induced cognitive dysfunction in children with optic pathway glioma, infratentorial ependymoma, craniopharyngioma, and standard-risk medulloblastoma.

16.5.3 Eye

The lens of the eye is exquisitely sensitive to radiation. Radiation-induced cataracts are caused by damage to the germinal zone at the equator of the lens. Initially, this results in a central opacity that progresses to an opaque cortex. The threshold for radiation damage is 8 Gy in a single fraction, or 10–15 Gy in fractionated doses. More rapid cataract formation is associated with higher doses of radiation. Radiation-induced retinopathy appears to have a threshold of 46 Gy at conventional fractionation (1.8–2.0 Gy per fraction), but is rare below doses of 50–60 Gy. Retinopathy is typically seen beginning from 6 months to 3 years following radiation. It is characterized by macular edema, nonperfusion, and neovascularization. The optic nerves and chiasm are also at risk for damage from radiation. Damage to the optic nerve is characterized by a pale optic disc, abnormal papillary response, and visual deficits. Damage to the optic nerve or chiasm is potentially blinding. The threshold for this damage is 50 Gy. Every effort should be made to keep these structures below their tolerated doses (Emami et al. 1991).

16.5.4 Ear

Radiation-induced sensorineural hearing loss is dose-dependent and is more severe in younger patients. Hearing loss can result from doses greater than 40–50 Gy, usually developing within 6–12 months of treatment (Grau et al. 1991; Grau and Overgaard 1996). High-frequency hearing loss is seen in 25–50% of patients who received greater than 50–60 Gy to inner ear structures (Anteunis et al. 1994). Hearing loss is typically attributed to radiation changes induced in the cochlea and vasculature. Ototoxicity related to cisplatinum chemotherapy is well documented (Schell et al. 1989). Cranial irradiation prior to or concurrent with cisplatinum chemotherapy enhances ototoxicity (Schell et al. 1989; Walker et al., 1989). Chronic otitis can also develop following radiation therapy, due to obstruction of the Eustachian canal.

16.5.5 Endocrine

Whole cranial irradiation or focal radiation that includes the hypothalamic-pituitary axis can result in neuroendocrine abnormalities. The neuroendocrine complications that can result from radiation therapy are summarized in Table 16.2. Growth hormone (GH) production appears to be the most prone to disruption by radiation therapy. GH deficiency worsens over time and may follow radiation doses as low as 12 Gy (Merchant et al. 2002). This appears to be a result of decreased GH-releasing hormone (GHRH) in the hypothalamus, as GH deficiency is seen in patients undergoing hypothalamic radiation with pituitary sparing. Clinically, GH deficiency can result in short stature, bone loss, and metabolic abnormalities. Treatment with synthetic GH can allow children to maintain their expected growth percentile, despite irradiation.

Other endocrine deficiencies, including decreased

Table 16.2. Endocrine abnormalities resulting from radiation to the hypothalamus and pituitary gland

Hormone abnormality	Threshold dose (Gy)
Growth hormone deficit	18–25
ACTH deficit	40
TRH/TSH deficit	40
Precocious puberty	20
LH/FSH deficit	40
Hyperprolactinemia	40

thyroid stimulating hormone, adrenocorticotrophic hormone (ACTH), follicle stimulating hormone (FSH), and lutenizing hormone (LH) appear to have a higher threshold. These effects are typically seen following doses greater than 40 Gy. It is important that children treated for tumors in the region of the hypothalamic-pituitary axis be followed closely for endocrine abnormalities, so that timely replacement therapy can be initiated.

16.6 Molecular Targets for Radiosensitization

16.6.1 Tyrosine Kinase Receptors

Tyrosine kinase receptors (RTKs) play a variety of roles in maintaining homeostasis. They regulate cellular proliferation, survival, adhesion, and differentiation, and their function is tightly regulated (Levitzki and Gazit 1995; Porter and Vaillancourt 1998; Hunter 2000). RTKs include molecules with a ligand-binding extracellular portion, a transmembrane section, and an intracellular portion that contains the tyrosine kinase catalytic domain (Pawson and Scott 1997). This family includes the epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGF), stem-cell factor receptor (SCFR), and nerve growth factor receptor (NGFR). Inactivating mutations that confer ligand-independent phosphorylation and activation of the kinases occur in various domains of the protein, including cytoplasmic juxtamembrane, extracellular, and kinase domains (Demetri 2001). Several human malignancies develop as direct consequences of tyrosine kinase activation, and the specific molecular defect can influence prognosis (Lasota et al. 1999; Taniguchi et al. 1999).

Monoclonal antibodies and small molecules have been developed to inhibit RTKs by targeting specific extracellular or intracellular domains. Monoclonal antibodies block signaling through growth factor receptors by preventing binding of ligands (Drebin et al. 1985, 1986). Initial problems associated with rodent antibodies have been alleviated by advances in antibody construction (Fan and Mendelsohn 1998). Small-molecule inhibitors block signaling through RTKs by competing with adenosine triphosphate (ATP) for its binding site in the receptor (Levitzki and Gazit 1995). Both these agents, when used in combination with ionizing radiation, can cause radiosensitization of cancer cells.

16.6.1.1 Epidermal Growth Factor Receptor Family Inhibitors

The EGFR family consists of four different receptors: ErbB-1 (also known as EGFR), ErbB-2 (also known as HER2/neu), ErbB-3 (also known as HER3), and ErbB-4 (also known as HER4) (Klapper et al. 2000; Mendelsohn and Baselga 2000; Olayioye et al. 2000). The *EGFR* gene, located on chromosome 7p12, plays a key role in oncogenesis of glioblastoma (GBM). It is the most commonly amplified oncogene in GBMs, with amplification seen in 40% of tumors (Wong et al. 1987; Ekstrand et al. 1991; von Deimling et al. 1992). One third of GBMs in which *EGFR* is amplified contain a mutant form, the EGFRvIII mutant, in which deletion in the extracellular domain results in constitutive tyrosine kinase activity (Ekstrand et al. 1992; Wikstrand et al. 1997). Mechanisms of *EGFR* activation include amplification, overexpression, and expression of a truncated constitutively active form.

Small-molecule inhibitors of EGFR target the ATP-binding site of the receptor (Fry et al. 1994; Klohs et al. 1997). Two such inhibitors, gefitinib and erlotinib, both oral agents, have entered clinical trials for the treatment of gliomas. To date, clinical trials have shown some activity against glioma, and tumors that coexpress both PTEN and EGFRvIII have proved the most sensitive to these small-molecule inhibitors (Mellinghoff et al. 2005).

Monoclonal antibodies (mAbs) raised against the extracellular domain of the receptor can also inhibit EGFR signaling. Human/murine chimeric antibodies offer the advantage of reduced immunogenicity, while preserving potency. Cetuximab is an example of such an antibody whose administration delays growth of tumors overexpressing ErbB-1 in a xenograft model (Goldstein et al. 1995). An ongoing Phase I/II trial of cetuximab at the University of Heidelberg aims to determine feasibility and safety, along with

effect on progression-free survival and overall survival, when combined with radiation and temozolomide (Combs et al. 2006).

16.6.1.2 Platelet-Derived Growth Factor Receptor Inhibitors

Imatinib is a small molecule that specifically inhibits the tyrosine kinases Abl, PDGFR, and Kit (Sawyers 2002). PDGFR-α and PDGFR-β are two distinct receptors that bind the PDGF ligand. Clinical trials have documented efficacy of imatinib in the treatment of chronic myeloid leukemia, a malignancy driven by constitutive activation of Abl resulting from a chromosomal translocation called Bcr-Abl. Overexpression of the PDGF ligand and its receptor (PDGFR) is observed in all glioma grades (Maxwell et al. 1990; Hermanson et al. 1992, 1996), and is the rationale for using imatinib to treat gliomas. Aberrant PDFR signaling in low-grade as well as high-grade gliomas suggests a role for this signaling cascade in the initiation and progression of this neoplasm (Westermark et al. 1995; Hermanson et al. 1996). Imatinib as a single agent has minimal activity against malignant gliomas (Wen et al. 2006). However, for recurrent grade III gliomas, a recent Phase II trial has shown that an imatinib/hydroxyurea combination is both tolerable and has antitumor activity in some adult patients (Desjardins et al. 2007). An additional trial found similar results in adult patients with recurrent glioblastoma (Reardon et al. 2005).

16.6.1.3 Vascular Endothelial Growth Factor Receptor Inhibitors

Tumor growth relies not only on uncontrolled cell proliferation and survival, but also on the development of new blood vessels. Vascular endothelial growth factors (VEGF) are proangiogenic molecules that transmit their signals through Flt-1 (also known as VEGF-R1) and Flk-1/KDR (also known as VEGF-R2) receptors (Carmeliet and Jain 2000). Whereas VEGF ligands are secreted by tumor and stromal cells, VEGF receptors are expressed mostly by endothelial cells. As with other RTKs, small-molecule inhibitors and antibodies directed against the receptor or ligand are used to block signaling through VEGF pathways. A variety of small-molecule inhibitors of the VEGF receptors have been developed. They include semaxinib, which selectively inhibits Flk-1/KDR and Flt-1 (Fong et al. 1999); SU6668, which exhibits wider specificity toward other proangiogenic RTKs, including Flk-1/KDR, PDGF, and FGF receptors (Laird et al. 2000); cediranib, which blocks both VEGF receptors and PDGF receptors; vatalanib, which selectively antagonizes VEGF and EGF receptors; sunitinib, which inhibits PDGFR-α and PDGFR-β, as well as VEGFR-1 and -2, KIT (SCFR), and FLT3 (Fms-like tyrosine kinase-3 receptor)(Laird et al. 2000); sorafenib, which inhibits VEGFR-2, PDGFR-β, and Raf; and vandetinib, another inhibitor of both VEGFR and EGFR.

There are a variety of ongoing clinical trials examining these small-molecule inhibitors. A Phase II trial of cediranib in patients with recurrent glioblastoma found that the compound resulted in vascular normalization and a decrease in vasogenic edema, itself a significant cause of morbidity in GBM patients. Even more promising is the possibility that this vascular normalization will improve delivery of chemotherapy and, by increasing oxygenation, enhance radiation sensitivity. Such effects might lead to improved progression-free and overall survival in these patients (Batchelor et al. 2007). Besides cediranib, both vatalanib and vadetinib are currently being evaluated in trials – vadetinib in a Phase I/II trial being conducted by the NIH and vatalanib in an EORTC Phase II trial in combination with temozolomide and radiation therapy (Fine 2007).

In addition to small-molecular inhibitors, antibodies directed against VEGF or its receptor have entered clinical trials (Presta et al. 1997). A study combining the anti-VEGF monoclonal antibody bevacizumab with irinotecan found a relatively high radiographic response rate, with an encouraging 6-month progression-free survival rate and median survival (Vredenburgh et al. 2007). A further Phase II pilot study looking at bevacizumab in combination with radiation and temozolomide found tolerable toxicities and encouraging mean progression-free survival (Lai et al. 2008).

16.6.1.4 Farnesyltransferase Inhibitors

Intracellular signaling cascades triggered by activation of growth factor receptors use intermediate molecules to propagate their signals to downstream pathways. The Ras proteins are examples of such intermediaries and mediate many functions, including proliferation, survival, cytoskeletal organization, differentiation, and membrane trafficking. Ras cycles between an active guanosine 5′-triphosphase (GTP)-bound state and an inactive guanosine 5′-biphosphate (GDP)-bound state. Ras proteins are synthesized as cytosolic precursors and are converted to membrane-bound forms through post-translational modifications (Bourne et al. 1990; Lowy and Willumsen 1993; Downward 1996). Such post-translational modifications begin with the addition of a 15-carbon farnesyl moiety (a lipid) to a specific portion of Ras proteins called the CAAX box (A is an aliphatic amino acid and X is methionine or serine) of Ras (Rowinsky et al. 1999). This reaction is catalyzed by an enzyme called farnesyltransferase.

Farnesyltransferase inhibitors (FTIs) directly block the function of Ras, but may also interrupt the effects of tyrosine kinase receptors that signal through Ras. Although gliomas rarely contain oncogenic forms of Ras, other alterations such as EGFR over-expression that rely on Ras signaling may be susceptible to targeting by FTIs. The precise mechanism of FTI action remains unclear and an enlarging body of evidence suggests that FTI activity is mediated in part through inhibition of farnesylation of other Ras family members, such as RhoB (Lebowitz and Prendergast 1998; Du et al. 1999; Reuter et al. 2000). Treatment of gliomas in vitro with FTIs results in decreased proliferation and induction of apoptosis. However, a Phase II clinical trial of the FTI tipifarnib in children with sPNET, high-grade gliomas, or brain-stem gliomas, found that although the drug was well-tolerated as a single agent, it exhibited little antitumoral activity (Fouladi et al. 2007). In adult populations, a recent Phase II study demonstrated that, in recurrent GBM patients not receiving enzyme-inducing antiepileptic medication, single-agent treatment with tipifarnib had some modest therapeutic benefit (Cloughesy et al. 2006).

16.6.1.5 Mammalian Target of Rapamycin Inhibitors

Mammalian target of rapamycin (mTOR) is a key downstream component of the phosphoinositide 3-kinase (PI3K)/Akt pathway (Fan and Weiss 2006). In GBM patients, PTEN mutation (occurring in approximately 30–40% of cases) results in constitutive activation of the Akt pathway. It has therefore been hypothesized that inhibition of downstream effectors in this pathway might prove beneficial in the treatment of gliomas; preclinical models bore this out, with data suggesting that PTEN-deficient tumors were sensitive to extant mTOR inhibitors. A Phase II trial of the mTOR inhibitor temsirolimus showed a measurable radiographic response in 36% of patients, with an accompanying increase in time to progression (Galanis et al. 2005). More recently, attention has focused on trials involving synergistic multidrug therapy. Results of a Phase II trial using the EGFR tyrosine kinase inhibitor geftinib and the mTOR inhibitor everolimus in unselected patients with recurrent GBM showed a response rate of 26%. Despite this, there was no concomitant increase in progression-free or overall survival compared to historical controls (Nyugen et al. 2006). The eventual hope is that selection of patients based upon the biological characteristics of their individual tumors will result in improvements in clinical response.

16.6.2 Molecular Targeting and Radiosensitization

Inhibitors of cell signaling are most likely to impact the treatment of human cancers when combined with standard forms of antineoplastic therapy such as chemotherapy and radiation. Such clinical impact is maximized if novel inhibitors sensitize human malignancies to standard cytotoxic agents. Many studies, most commonly of cell lines in vitro or xenograft tumor models in rodents, indicate that treatment with signaling inhibitors augments tumor response to radiation (Jones et al. 2001). These findings have been used to justify some of the multimodal trials mentioned earlier. Molecular mechanisms implicated

in radiosensitization associated with signaling inhibitors include effects on cell proliferation, survival, migration, invasion, angiogenesis, and DNA repair. The precise molecular mechanisms, however, remain elusive.

The strongest data for radiosensitization exist for agents that block EGFR signaling. EGFR overexpression correlates with resistance to radiation in vitro and in vivo (Wollman et al. 1994; Sheridan et al. 1997; Miyaguchi et al. 1998; Pillai et al. 1998). EGFR overexpression correlates with radiographically measured radiation response of human GBM in vivo (Barker et al. 2001). In a model of human squamous-cell carcinoma cells grown in mice, administration of cetuximab together with radiation resulted in complete regression of established xenograft tumors (Huang et al. 1999; Milas et al. 2000). Impressive efficacy of concurrent cetuximab and radiation has also been documented in intracranial tumors of human glioma cells grown as xenografts in athymic mice. Small-molecule inhibitors of EGFR, such as gefitinib and CI-1033, similarly sensitize human malignancies to radiation in cell lines in vitro and in animal models of human malignancies in vivo (Mendelsohn and Baselga 2000). Mechanisms for this sensitization by EGFR inhibitors inevitably vary, but may include elimination of cancer stem cells, modification of signal transduction, inhibition of DNA repair, and improved oxygenation (Baumann et al. 2007). These studies establish the rationale for current clinical trials examining concurrent administration of gefitinib or erlotinib and radiation in the treatment of adult and pediatric gliomas.

Similarly, FTIs reverse the radiation resistance of cell lines containing mutant Ras without affecting the radiosensitivity of cells expressing wild-type Ras (Jones et al. 2001). A critical unanswered question is whether FTIs will also preferentially radiosensitize cells with aberrant signaling cascades that rely on Ras as an intermediary. Direct evidence is lacking for radiosensitization by signaling inhibitors that target other RTKs such as PDGF and VEGF receptors. However, indirectly blocking VEGF signaling with antiangiogenic drugs augments the cytotoxic effects of radiation in vivo (Gorski et al. 1999). In vivo experiments have also shown that anti-VEGF therapy may, by normalizing tumor vasculature, improve oxygenation and thus heighten radiation sensitivity.

16.6.3 P53 Tumor Suppressor Protein

P53 regulates apoptosis, proliferation, differentiation, angiogenesis, and cell–matrix interactions in a tissue-specific manner, and is mutated in over 50% of human cancers. For example, in vitro irradiation of hematologic malignancies, such as leukemia and lymphoma, produces rapid p53-dependent apoptosis. A clinical corollary of this laboratory observation is that radiation treatment of hematologic malignancies produces a rapid and durable response. Similarly, in many pediatric tissues, apoptosis plays a key role during organogenesis, and pediatric solid tumors, such as Wilms' tumor and neuroblastoma, exhibit significant apoptosis and excellent cure rates when treated with radiation. In contrast, in many adult solid tumors such as astrocytoma, apoptosis plays a minor role and the balance of p53-mediated functions tilts toward proliferation and differentiation.

Although in glial neoplasms, the role of p53 inactivation in mediating radiation resistance remains unclear (Nozaki et al. 1999), enhanced radiosensitivity of glioma cells occurs after reconstitution of p53 function (Lang et al. 1999). Two main approaches have been utilized to restore wild-type p53 function and overcome resistance to radiation: gene therapy and pharmacologic molecules that confer wild-type function on mutant forms of p53. Many impediments to gene therapy have arisen, including inefficient delivery and detrimental immune responses. Pharmacologic agents that impinge on p53 functions hold greater promise for translational clinical practice. Some mutated forms of p53 are amenable to treatment with either synthetic peptides or monoclonal antibodies that can restore wild-type p53 function.

16.7 Conclusions

Radiation is a key therapeutic modality in the treatment of brain tumors and plays a role in the multimodality approach to virtually every pediatric CNS malignancy. Efforts to increase the efficacy of

radiation using IMRT, high-LET particles, BNCT, radiation modifiers, and altered fractionation have contributed to enhanced cure rates for pediatric patients. Nevertheless, great opportunities exist in improving prognosis for children with brain tumors, while reducing long-term side effects of treatment. Novel pharmacologic agents, such as signaling inhibitors, particularly in combination with standard therapies such as radiation and chemotherapy, hold great promise for scientific and clinical breakthroughs.

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Late Effects of Treatment and Palliative Care

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Anuradha Banerjee

Contents

17.1 Introduction

Identifying late effects of treatment and integrating palliative care when appropriate, are increasingly recognized as important elements of childhood tumor management. Patients with CNS tumors are at high risk for mortality, and survivors have high morbidity rates related to the late effects of treatment. While intensified therapy has improved survival in patients with pediatric brain tumors (Packer et al. 1999, 2003), it has also increased the long-term consequences. Survivors may develop a spectrum of late effects ranging from subtle memory loss and cosmetic anomalies to severe neurological disabilities and recurrent neoplasms. While seemingly quite different, both palliative and late-effects care focus on improving quality of life for patients, and need to be integrated into the overall care plan.

17.2 Late Effects

Late effects of cancer therapy are defined as toxicities that manifest after therapy, influenced by growth, development, and aging. Treatment-related complications include secondary malignancies, organ-system dysfunction, psychosocial difficulties, cognitive disabilities, and death. Characterization of late effects associated with novel therapies will become increasingly important as these therapies are integrated into pediatric brain tumor management.

17.2.1 Mortality

Patients treated for CNS malignancies are at risk for late mortality. The Childhood Cancer Survivor Study (CCSS) is a large cohort study of childhood cancer survivors treated from 1970 through 1986 that included newly diagnosed patients who survived at least 5 years after cancer diagnosis. This cohort of patients has been used to examine late effects of pediatric oncology treatment, including the risk of late mortality (Mertens et al. 2001). Survivors had higher mortality rates compared to age-adjusted survival rates for the US population. The cumulative mortality for the survivors of childhood cancer was 6.4% at 10 years from diagnosis, 9.3% at 15 years, 11.4% at 20 years, and 14% at 25 years. The risk of death is increased even when mortality from disease progression or recurrence is excluded, suggesting that it is related to radiation and chemotherapy exposure. The CNS tumor survivors had the worst overall survival with a cumulative mortality rate of 16.8% at 20 years. The major cause of death (67%) among the 5-year survivors was recurrence of the original cancer, and the rate of death due to disease recurrence was 0.9% per year. The risk for death from disease recurrence was greatest in the time period of 5–9 years after initial diagnosis (Fig. 17.1).

17.2.2 Secondary Malignancy

Chemotherapy-associated hematopoietic second malignancies typically occur within the first decade after treatment of the primary malignancy. Solid tumor secondary malignancies are usually radiation related and occur late, even several decades after initial therapy. In a study using CCSS data to assess secondary malignancies, the cumulative incidence of secondary malignant neoplasms in survivors was 3.2% at 20 years from diagnosis (Neglia et al. 2001). In this study, the absolute excess risk for developing a secondary cancer was higher for patients who had primary CNS tumors than the risk of developing cancer in the general population, but slightly less than the risk of a secondary cancer in the entire cohort. This may be because of the greater likelihood of disease recurrence and mortality in this population. The delayed nature of secondary malignant neoplasms associated with radiation therapy may lead to early underestimation of risk (Schiff and Wen 2006). The most common radiation-associated brain tumors are meningiomas, followed by gliomas and sarcomas (Behin and Delattre 2002). The CNS secondary malignancies occurred in survivors of other malignancies more often than in survivors of a CNS primary cancer. In all survivors of childhood cancer,

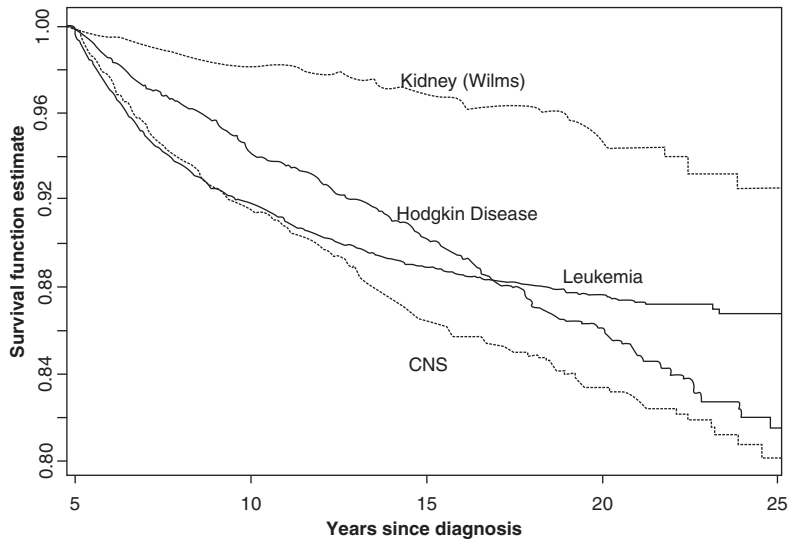

Figure 17.1

CNS tumor cumulative mortality rate is 16.8% at 20 years with worse overall survival than Wilm's tumor, Hodgkins disease, and leukemia (Mertens et al. 2001). Reprinted with permission ©2008 American Society of Clinical Oncology, all rights reserved

the significant risk factors for a secondary malignant neoplasm adjusted for therapeutic radiation exposure included female sex and young age at diagnosis.

17.2.3 General Late Effects

In addition to the increased risk of secondary cancer and death, survivors of childhood CNS malignancies are at risk for morbidity related to injury from the tumor itself and long-term effects of radiation, surgery, and chemotherapy (Butler et al. 1994; Packer and Mehta 2002; Nathan et al. 2007). The CNS tumor survivors have among the highest morbidity rates of all pediatric cancer survivors (Hays et al. 1992; Foreman et al. 1999).

Patients with brain tumors treated with radiotherapy alone (55%) have an increased risk of late adverse events when compared to patients treated with chemotherapy (15%) or surgery (25%) alone (Geenen et al. 2007). The CNS injury from radiation and chemotherapy is primarily due to cortical and subcortical white-matter changes, including glial-cell damage, and demyelination (Nathan et al. 2007). Radiation injury to CNS microvasculature results in hypoxia, as well as impairment of normal neurogenesis (Tofilon and Fike 2000; Schiff and Wen 2006).

Oeffinger used the CCSS database to assess chronic health conditions in pediatric cancer survivors. His analysis found that survivors were 3.3 times as likely as their siblings to have a chronic health condition. The CNS tumor survivors were among the survivors at highest risk for a Grade 3 or 4 chronic health condition using the Common Terminology Criteria for Adverse Events, Version 3 (Fig. 17.2). Female survivors of any cancer were found to be at greater risk for any, a Grade 3 or higher, and multiple chronic medical conditions. For all diagnoses, the cumulative incidence of chronic health conditions continued to slowly increase over time (Oeffinger et al. 2006).

The CCSS examined general health outcomes among 9535 childhood cancer survivors. The CNS tumor survivors reported increased adverse outcomes in general health, functional status, and activity status, and were twice as likely to have at least one

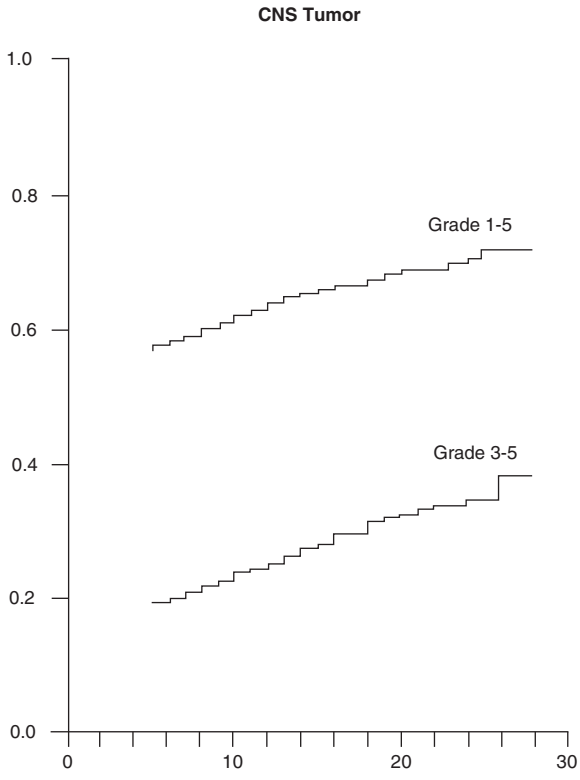

Figure 17.2

In 1,322 adult survivors of pediatric CNS tumors, the incidence of chronic health conditions continues to increase over time (Oeffinger et al. 2006). Copyright 2006 Massachusetts Medical Society. All rights reserved

negatively affected domain when compared to other pediatric cancer survivors (Hudson et al. 2003). The most commonly affected medical domains for CNS tumor survivors include neurologic, neurocognitive, neuropsychological, endocrine, and other organ dysfunction (Table 17.1).

17.2.4 Neurologic

Packer et al. analyzed questionnaire data from CCSS primary CNS tumor patients to assess long-term neurologic and neurosensory deficits (Packer et al.

Table 17.1. Chronic health conditions in pediatric CNS tumor survivors

Organ system	Chronic health condition
Neurological	Paralysis
	Seizure
	Fatigue
	Chronic pain
	Spasticity
	Ataxia
	Dysarthria
Ocular	Diplopia
	Cataracts
	Visual loss
Auditory	Tinnitis
	Hearing loss
Neurocognitive	Learning deficits
	Executive function (planning and organization)
	Sustained attention
	Memory
	Processing speed
	Visual–motor integration
	Diminished IQ
	Behavioral change
Neuropsychiatric	Social withdrawal
	Depression
	Anxiety
	Posttraumatic stress
Endocrine	Gonadal dysfunction, gonadotropin deficiency, infertility
	Metabolic syndromes, obesity
	Growth hormone deficiency
	Precious puberty
	Hyperprolactinemia
	Central hypothyroidism
	Central adrenal insufficiency
Pulmonary	Pulmonary fibrosis
	Interstitial pneumonitis
	Restrictive lung disease
	Obstructive lung disease
Gastrointestinal	Dysphagia
	Esophageal stricture
	Bowel obstruction
	Chronic enterocolitis
	Fistula
	Strictures
	Hepatic dysfunction
Cardiac	Congestive heart failure
	Cardiomyopathy
	Pericarditis
	Pericardial fibrosis
	Valvular disease
	Myocardial infarction
	Arrhythmia
	Atherosclerotic heart disease
Renal	Impaired function
Dental	Tooth/root agenesis
	Root thinning/shortening
	Enamel dysplasia

2003). When compared to the sibling group, survivors were at a significant increased risk for late onset of legal blindness, cataracts, and double vision. Twelve percent of patients reported hearing impairment with a statistically significant relationship to posterior fossa irradiation greater than 50 Gy. Children with primitive neuroectodermal tumors (PNET) were at higher risk for developing hearing deficits than other CNS tumor survivors (Packer et al. 2003). Focal neurologic dysfunction was common, with 49% of patients reporting coordination problems and 26% reporting a motor control problem. Seizure

disorder was reported in 25% of patients and 6.5% of this group reported the first seizure 5 or more years after initial diagnosis. Seizures, hand-eye coordination problems, and hemiplegia have been associated with supratentorial tumors, while ataxia and balance have been associated with infratentorial tumors (Lannering et al. 1990). Survivors are also at increased risk for stroke, especially if they have received greater than 30 Gy of cranial radiation (Bowers et al. 2006). Chronic progressive radiation myelopathy can occur following spinal radiation (Schiff and Wen 2006). Fatigue has been shown to be associated with a poor health-related quality of life in pediatric cancer survivors (Meeske et al. 2007). However, the impact of cancer therapy on long-term fatigue has not been well-defined (Zebrack and Chesler 2002; Langeveld et al. 2003). In a study of 176 childhood cancer survivors, including 19 CNS tumor patients, all study enrollees reported ongoing fatigue on a quality-of-life questionnaire (Zebrack and Chesler 2002). Conflicting with this outcome, a report of 416 pediatric cancer survivors, which included 30 CNS tumor survivors, found no evidence of excess fatigue in brain tumor survivors or pediatric cancer survivors overall (Langeveld et al. 2003). Chronic pain has also been reported as a late effect in 19–33% of pediatric brain tumor survivors in series of 52 and 44 patients, respectively (Barr et al. 1999; Foreman et al. 1999).

17.2.5 Neurocognitive

Neurocognitive dysfuntion can be a debilitating consequence and a predominant late effect of cancer therapy. Between 40 and 100% of pediatric CNS tumor survivors report neurocognitive problems (Moleski 2000; Oeffinger et al. 2008). Severity and probability of neurocognitive deficits are related to age at diagnosis and treatment, dose and volume of radiation given, and tumor type, size, and location (Packer et al. 1989; Radcliffe et al. 1992; Ris et al. 2001; Oeffinger et al. 2008). Socioeconomic status has also been identified as a risk factor in some studies (Nathan et al. 2007). It is essential to monitor at-risk patients over time as a nonlinear decline in intellectual function is often seen. Although earlier-learned information is typically retained, the ability to acquire new information at the same rate as one's peers is impaired (Mabbott et al. 2005). Children who have received brain irradiation may have cognitive dysfunction years after treatment, that is independent of the number of school days missed due to therapy (Oberfield et al. 1986; Radcliffe et al. 1992; Ris et al. 2001).

The most common neurocognitive impairments are problems with attention and concentration, processing speed and visual perceptual skills, executive function, and memory (Mulhern et al. 1998; Moleski 2000; Oeffinger et al. 2008). Deficits in full-scale intelligence quotient, verbal intelligence quotient, performance intelligence quotient, nonverbal memory, and somatosensory functioning have also been reported. Intelligence quotient scores have been shown to decrease as much as 15–25 points from baseline (Nathan et al. 2007). The CCSS reported that 18% of 18- to 24-year-old brain tumor survivors had not completed high school. In the CCSS, about 70% of brain tumor survivors diagnosed before the age of six required special education services in school. A small study of 24 adults who had CNS tumor treatment with irradiation showed improvement of cognitive functioning after treatment the acetylcholinesterase inhibitor donepezil (Shaw et al. 2006). Further studies are needed to see if therapeutic interventions can improve cognitive function.

17.2.6 Neuropsychology

Neuropsychological effects of brain tumor therapy include general behavioral problems, maladjustment, depressive symptoms, and poor self-concept (Carpentieri et al. 2003). Some more severe psychiatric complications include emotional dysfunction and psychosis. Seventeen percent of CCSS survivors have depressive, somatic, or anxious symptoms (Hudson et al. 2003). Specifically, cerebellar damage can been associated with neuropsychological and psychiatric problems (Steinlin et al. 2003). There is some

evidence to suggest that survivors of CNS tumors are at increased risk of hospitalization for psychiatric disorders (Ross et al. 2003).

17.2.7 Psychosocial

Using CCSS self-reported employment history, Pang and colleagues examined survivor employment status. Of the cancer survivors, 5.6% had never been employed compared to 1.2% of the sibling group. The CNS tumor survivors had the highest risk of having never been employed (odds ratio [OR] = 9.9), although all survivors were at increased risk (OR = 3.7). Within the group of CNS tumor survivors, risk for unemployment by treatment modality was also evaluated: surgery alone (OR = 3.7), radiotherapy and surgery (OR = 11.8), and chemotherapy, radiotherapy, and surgery (OR = 10.7) (Pang et al. 2008). Survivors of CNS tumors have a lower rate of marrying when compared to other pediatric cancer survivors as well as the general population. Many are unable to live independently (Ross et al. 2003).

17.2.8 Endocrine

Endocrine dysfunction is common in CNS tumor survivors. Children with suprasellar brain tumors have a high incidence of hormonal dysfunction (Ogilvy-Stuart et al. 1991; Sklar and Constine 1995). Patients who have received high-dose irradiation to the hypothalamic region can develop delayed-onset hormonal deficiency (Oberfield et al. 1986; Ogilvy-Stuart et al. 1991; Sklar and Constine 1995). Specific endocrinopathies include hypothyroidism, growth hormone deficiency, precocious puberty and/or gonadotropin deficiency, adrenocorticotropic hormone deficiency, panhypopituitarism, and diabetes insipidus (Rutter and Rose 2007; Nandagopal et al. 2008). Overall, patients treated with surgery alone manifest much lower rates of endocrine abnormalities than patients who also received radiation and/or chemotherapy (Gurney et al. 2003a). Young age at diagnosis increases risk of hypothalamic–pituitary axis dysfunction (Gleeson and Shalet 2004) (Gurney et al. 2003b).

Growth hormone deficiency is the most common endocrinopathy in pediatric CNS tumor survivors (Muirhead et al. 2002; Gurney et al. 2003a; Nandagopal et al. 2008). Livesey's series of 144 CNS tumor survivors showed laboratory evidence of growth hormone deficiency in 97% of the survivors at a median follow-up time of 9.6 years (Livesey et al. 1990). One of the primary risk factors for growth hormone deficiency is radiation dose. Cranial radiation doses as low as 18 Gy can affect the growth hormone axis (Brownstein et al. 2004). Growth hormone deficiency in children results in growth failure and short stature. Recent studies have also demonstrated that growth hormone deficiency can have effects on adults including abnormal body composition, reduced lean body mass, increased abdominal adiposity, reduced strength and exercise capacity, impaired psychological well-being, depressed mood, reduced vitality and energy, emotional lability, impaired self-control, anxiety, and increased social isolation (Carroll et al. 2000). Investigations have shown no increased risk for disease recurrence in CNS tumor survivors treated with growth hormone therapy (Moshang et al. 1996).

Central thyroid dysfunction in addition to growth hormone dysfunction can cause obesity syndrome due to the compounded effects on linear growth, in addition to the effects of hypothyroidism. These hormonal imbalances likely contribute to the increased incidence of obesity in female survivors of pediatric brain tumors. Abnormal thyroid function may also contribute to learning disabilities in this population (Anderson 2003). Gonadal dysfunction often occurs later than other endocrinopathies in pediatric CNS tumor survivors, and may not be detected until puberty or early adulthood. Gonadal dysfunction includes a wide range of abnormalities from precocious puberty to infertility. Livesey found that following spinal radiation, 35% of females had ovarian dysfunction, while only 3% of males had testicular dysfunction (Livesey et al. 1990). The use of cyclophosphamide increases the risk of gonadal failure. Panhypopituitarism is usually only diagnosed in patients who

have received greater than 40 Gy of cranial radiation. Central adrenal deficiency may present as failure to thrive, anorexia, dehydration, hypoglycemia, and hypotension. Hyperprolactinemia often manifests as galactorhea and menstrual abnormalities.

17.2.9 Other

The cardiovascular system can be affected by CNS tumor treatments, and in an evaluation of 1607 CNS tumor survivors, 18% of patients reported problems including primary arrhythmia, stroke, blood clots, and angina-like symptoms (Gurney et al. 2003a). Spinal irradiation may contribute to cardiac injury (Jakacki et al. 1993). Pulmonary disease following treatment is often linked to the use of nitrosoureas in this patient population. Cranial radiation is associated with low bone mineral density in brain tumor survivors. Methotrexate and steroids used in treatment may also contribute to this problem (Nandagopal et al. 2008).

17.2.10 Patient Factors

17.2.10.1 Age

Children less than 3 years of age at the time of therapy are thought to be at greatest risk for late effects due their immature stage of brain development. These patients almost universally require special education services and are unlikely to live independently as adults (Nathan et al. 2007). Many CNS tumor treatment protocols have recently attempted to postpone and reduce cranial radiation in young children.

17.2.10.2 Site

There is controversy over the role that tumor location plays in outcome (Mulhern et al. 1992; Ater et al. 1996; Steinlin et al. 2003). Multiple studies have demonstrated that supratentorial tumors confer worse morbidity than infratentorial tumors (Ellenberg et al. 1987; Lannering et al. 1990). Tumors in the cerebral hemispheres can cause problems with performance intelligence quotient, academic achievement, memory, motor skills, and attention. Posterior fossa tumors are associated with memory and motor deficits (Ater et al. 1996). Tumors that involve the hypothalamic and parasellar region are related to growth hormone deficiency. Children treated with surgery alone for benign cerebellar lesions showed deficits in attention, memory, processing speed, and visual-constructive copying (Steinlin et al. 2003). Late effects associated with particular tumor locations are shown in Table 17.2 (Ellenberg et al. 1987; Lannering et al. 1990; Livesey et al. 1990; Mostow et al. 1991; Constine

Table 17.2. Central nervous system tumor locations and associated late effects

Region	Histology (percentage of primary CNS tumors)	Important associated late effects
Supratentorial	Low-grade astrocytoma (15–20%), High-grade astrocytoma (8–12%), Other glioma (5–10%)	Poor cognitive function, Poor manual dexterity, Emotional difficulties, Seizures, Poorer overall quality of life
Hypothalamic/Parasellar	Craniopharyngioma (6–10%), Optic pathway glioma (4–8%)	Growth hormone deficiency with hypothyroidism and hypogonadism
Infratentorial	Primitive neural ectodermal tumor, Cerebellar astrocytoma (12–15%), High-grade pontine glioma (5–10%), Ependymoma (4–8%)	Ataxia, Primary thyroid dysfunction, Ovarian dysfunction

Anderson et al. (2001). Copyright 2001 American Cancer Society. This material is reproduced with the permission of Wiley-Liss, Inc., a subsidiary of Wiley

et al. 1993; Syndikus et al. 1994; Ilveskoski et al. 1997; Foreman et al. 1999).

17.2.10.3 Genetics

Variation in patient response to treatment and neurocognitive outcomes may also depend on genetic polymorphisms. Currently, enzymes that effect chemotherapy metabolism and clearance are under investigation, including glutathione *S*-transferase and enzymes involved in folate metabolism. Signaling pathways known to be dysregulated in solid/brain tumors such as ErbB1-4, mTOR, IGF-IR, and PTCH1 are under investigation as future targets for therapy. In addition, identification of molecular markers predictive of outcome, survival, and treatment response may allow more patient-specific treatment plans in the future with the aim of cure and minimal late effects.

17.2.11 Treatment Factors

17.2.11.1 Radiation

The most common delayed toxicity of radiation therapy is cognitive impairment (Schiff and Wen 2006). The risk of neurocognitive late effects increases with the cumulative cranial radiation therapy dose given (Mulhern et al. 1998; Grill et al. 1999; Ris et al. 2001). Larger individual radiation fractions and larger fields of radiation also increase the risk of neurocognitive sequlae. A Pediatric Oncology Group study compared radiation doses and outcomes in medulloblastoma patients and found a decrease in neuropsychiatric toxicity in patients treated with 23.4 Gy instead of 36 Gy (Packer and Mehta 2002). The current Children's Oncology Group low-risk medulloblastoma study protocol is analyzing the effects craniospinal radiation dose reduction in children age 3–7 years in coordination with adjuvant chemotherapy. The CNS tumor survivors who are treated with cranial radiation have greater deficits in neurocognitive functioning than those who do not receive cranial radiation. Neuropathologic changes following whole-brain radiation include leukoencephalopathy, mineralizing microangiopathy, subacute necrotizing leukomyelopathy, and intracerebral calcifications, commonly with subsequent cerebral atrophy and microcephaly.

17.2.11.2 Chemotherapy

Methotrexate, corticosteroids, and possibly cytarabine hydrochloride can be associated with long-term neurocognitive dysfunction. Methotrexate can cause a syndrome termed methotrexate leukoencephalopathy, most common in patients who have had treatment with both intravenous and intrathecal methotrexate therapy, in addition to whole-brain radiation therapy (Pizzo et al. 1979). Methotrexate has also has been shown to increase the effect of cranial radiation on the neurocognitive function (Waber et al. 1995; Moe and Holen 2000; Moleski 2000). Chemotherapy may have synergistic toxicity when given in combination with radiation therapy due to radiation-induced increase in blood–brain barrier permeability (Schiff and Wen 2006).

17.2.11.3 Surgery

A study of 28 children who were treated for medulloblastoma showed that neurologic deficits, meningitis, shunt infections, or the need for repeat surgery increased the risk of late neurocognitive deficits (Kao et al. 1994). In addition to neurocognitive affect, cerebellar dysfunction, including ataxia and cranial nerve palsy, may occur. Transient cerebellar mutism is often present following midline posterior fossa tumor resection, although its resolution may take many weeks.

17.2.12 Recommendations for Late Effects Care

In order to provide appropriate care for pediatric CNS tumor survivors, a plan for follow-up screening,

surveillance, and prevention based on the individual's cancer and treatment history as well as family history, lifestyle behaviors, and comorbid conditions should be established and communicated to the patient as well as their primary-care provider. Multiple studies have shown significant deficits in survivors' knowledge regarding their diagnosis, completed treatment, and cancer-related health risks (Byrne et al. 1989; Hudson et al. 2002; Kadan-Lottick et al. 2002). It is essential that patients receive a summary of their treatment and appropriate recommendations for follow-up. Risk-stratified, life-long medical monitoring can improve quality of life through early detection and intervention. In order to properly address the neuropsychological deficits in CNS tumor survivors, a comprehensive neuropsychological assessment upon entry to a late-effects or follow-up clinic is necessary, regardless of patient or family report of deficits. For providers of late-effects or follow-up care for CNS tumor survivors, it is important to consider that many insurance companies may not provide coverage for neuropsychological testing (Oeffinger et al. 2008).

There is controversy regarding the optimal setting for pediatric cancer survivor follow-up. Some pediatric cancer survivors may have minimal risk for late effects and could receive follow-up by a local primary care physician with guidance and support from a pediatric oncology treatment group. Pediatric brain tumor survivors are at high risk for a large variety of significant late effects and would be best served by continued follow-up at a multidisciplinary late-effects clinic at a center that provides pediatric oncology care. The Children's Oncology Group is a group of 240 institutions that has developed "Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young-Adult Cancer," available at www.survivorshipguidelines.org.

17.3 Palliative Care

Cancer is the leading disease-related cause of death in children less than 20 years of age, excluding infants (Ries 1999). The CNS malignancies are the second-most-common type of cancer diagnosed in children (Bleyer 1999). Surveillance, Epidemiology, and End Results (SEER) registry data show 5-year relative survival rates of brain and other nervous system malignancies in children aged 0–19 from 1995 to 2000 to be 72% for males and 75% for females (Jemal et al. 2004). These mortality data define the important role of pediatric palliative care in the management of pediatric CNS malignancies.

Palliative care for children is an active and total approach to care, embracing physical, emotional, social, and spiritual elements (Korones 2007). This approach focuses on enhancing patient's quality of life and support for family by managing distressing symptoms and providing respite and care through treatment, death, and bereavement. Care can be provided in multiple locations including the hospital, a hospice facility, or within the child's home. The family-centered approach requires a multidisciplinary team. Optimally, palliative care is not separate from curative care and should be integrated into the overall care plan from the point of initial diagnosis for patients with a life-threatening illness, but instead is increasingly incorporated into treatment planning, as prognosis for cure becomes less likely (Fig. 17.3).

Concerns regarding growth and development uniquely separate pediatric palliative care from adult palliative care. Developmental differences among infants, children, and adolescents must be considered when designing and implementing a pediatric palliative care program. In addition, pediatric palliative care encounters different obstacles than adult palliative care (Korones 2007). Overall, only 25% of childhood deaths are from a complex chronic medical condition and therefore suitable for involvement of a pediatric palliative care team. When combined with the overall lower mortality rate in children, this creates a relatively small population of pediatric patients compared to the adult population utilizing palliative care services. On average, a general pediatrician in North America cares for less than three children who die per year. Limited experience contributes to physician discomfort when providing pediatric palliative care (Kolarik et al. 2006).

The Medicare hospice benefit is primarily targeted for adults, and requires patients to forgo curative or life-prolonging therapy. Pediatric palliative care strives to integrate curative and palliative care in combination, and thus this reimbursement approach often directly conflicts with care plans. Typically, pediatric care does not require a do-not-resuscitate order or prognosis for short-term survival. Pediatric providers and families often choose to continue supportive measures such as blood transfusions and supplemental feeding with the goal of contributing to the overall well-being of the child (Sirkia et al. 1997).

Inadequate training is another barrier to providing good palliative care. In a survey of medical staff, 49–54% of attending physicians and residents responded that they felt inexperienced in providing pain management for dying patients (Contro et al. 2004). Pediatric patients have unique medical and psychosocial needs that adult-trained palliative care providers may feel unequipped to address. Limited clinical and community resources for hospice, homecare, and pediatric end-of-life services further complicates efforts to maximize quality of care outside of the hospital.

Many paradigms have been developed to conceptualize how and when medical treatment transitions from curative care to palliative care. In a treatment model where palliative care is considered only when curative treatment is abandoned, the patient may suffer unnecessarily as interventions to improve quality of life and comfort are deferred. An abrupt shift from curative to palliative care can be emotionally difficult for the patient, family, and medical team, creating barriers to providing the many beneficial aspects of palliative care (Fig. 17.3a). This model may also foster a feeling of abandonment in the patient and his or her family when the transition is made. Wolfe et al. documented that pain related to end-of-life was more common and severe in patients whose primary physicians were not involved in end-of-life care (Wolfe et al. 2000). Some treatment models include palliative care as an early component of overall medical care,

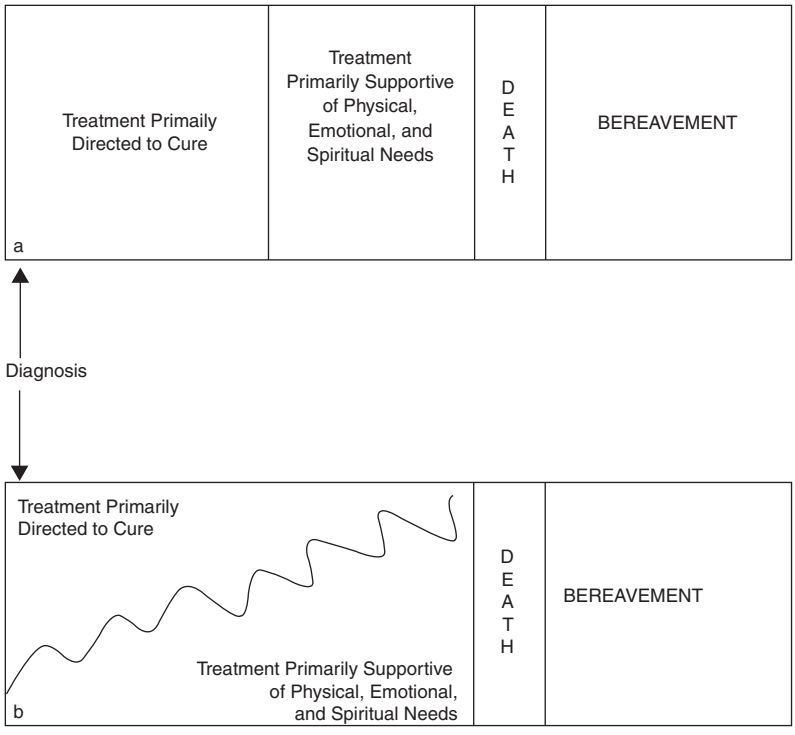

Figure 17.3

Models for incorporating palliative care. (**a**) Palliative care is introduced only after treatment directed to cure is completed. (**b**) Palliative care is introduced early on during treatment directed to cure and begins to comprise a larger component of care over time (Sahler et al. 2000). Reproduced with permission from Pediatrics, ©2000 by the AAP

regardless of whether the provider anticipates cure, chronic disease, or death (Fig. 17.3b). The transition to a primarily palliative care model is made slowly and gradually allowing appropriate consideration of comfort and quality of life without forcing the patient, family, and medical-care providers to discontinue curative efforts (Sahler et al. 2000).

17.3.1 Developmental Stage

Pediatric palliative care providers must always consider the age and developmental stage of each patient in care decisions. The role of the child in discussions and medical decision-making is an obvious example, but developmental stage must also be considered in pain assessment, techniques for communication, and conversations about death and dying.

A child's ability to understand death evolves as they mature. In addition, each child is unique and a discussion of death and dying must be directed to match understanding at the time of communication. A general knowledge of children's developmental understanding of death by age can be helpful in approaching these challenging conversations (Table 17.3). Children and adolescents with chronic disease can have advanced comprehension of death for their chronological age (Poltorak and Glazer 2006).

Initially, some parents express the desire to exclude their children from conversations regarding their diagnosis, prognosis, and treatment plans in order to protect them. Respect for these fears and concerns enable a relationship of trust between medical provider and family. Once this trust is established, the provider can more effectively communicate the importance of providing the child with honest, developmentally appropriate information, as well as a genuine willingness to listen to questions. This can help alleviate the anxiety that the child may be experiencing, and provide a safe environment for discussion of the child's own fears and concerns. In a study of 429 parents who had a child that died of cancer none of the parents who had discussed death with their child had regrets (Kreicbergs et al. 2004). Of the parents who did not discuss death with their child, 27% did have regrets. Many parents prefer to inform the child themselves of new information. The physician and medical team can be of great help by providing communication techniques as well as being available for support and to answer questions. Children may have significant anxiety and depression when faced with end-of-life issues. Play therapy is an excellent tool to elicit these feelings. Often, giving voice to these concerns is a significant first step in treating the child's anxiety and/or depression. For patients who require additional intervention, combined

Table 17.3. Understanding of death based on age

Age (years)	Understanding of death	Interventions
0–2	Death is interpreted as separation or abandonment, No cognitive understanding of death	Consistency, Physical comfort, Familiar people and objects
3–6	Death is interpreted as reversible or temporary, Often seen as a punishment, Magical thinking: wishes can come true	Minimize separation from family, Clarify that illness is not a punishment
7–12	Gradual awareness of irreversibility and finality, Specific death of self or loved one difficult to understand, Concrete reasoning: can see cause and effect relationships	Be truthful, Allow participation in decision making
>12	Death is irreversible, universal, and inevitable, All people and self die: usually see self death in far future, Abstract and philosophical reasoning	Promote independence, Allow expression of emotions, Be truthful, Allow participation in decision making

counseling and medical therapy with antidepressants and anxiolytics can be beneficial.

17.3.2 Communication

Innovative efforts to define communication as a skill, institute formal education in communication during physician training, and develop tools to help physicians improve their communication skills, all emphasize the essential role that communication plays in the patient–provider relationship. Effective and compassionate communication is paramount when conveying bad news and addressing end-of-life issues. In order to address the unique needs of each patient and family, the palliative-care team must establish ongoing open communication. This also allows improved support for each family's religious customs and cultural needs.

A survey of 228 pediatric oncologists was completed in 1998 by the American Society of Clinical Oncology (ASCO) (Hilden et al. 2001). Providing education focusing on communication skills when discussing the transition from curative to palliative care with pediatric patients and their families was found to need improvement. Families of 44 children who received palliative care reported confusing, inadequate, ineffective, and insensitive communication from the treatment team (Contro et al. 2004). Another study showed that physicians recognize that a child no longer has a realistic chance of cure well before the parents do (Wolfe et al. 2000). These findings indicate a need for improved provider communication.

To address the shortcomings of physician communication in this field, it is essential to acknowledge that sharing bad news and discussion of difficult issues is not an innate, but a learned skill (Korones 2007). Multistep communication tools can aid physician education in this arena. Von Gunten, Ferris, and Emanuel developed a 7-step communication tool to provide clinicians with a formal approach to structuring conversations with families (von Gunten et al. 2000). In this model, the physician should begin (Step 1) by preparing for the discussion by confirming medical facts of the case, designating an appropriate time and location for the conversation, and ensuring that everyone the family who would like to be present can attend. Next (Step 2), the physician should clarify what the patient and family understand about the current medical situation of the patient using open-ended questions to elicit the active involvement of the family and patient in the conversation. Step 3 aims to identify the developmentally appropriate manner in which the patient and family would like to handle new information. Step 4 focuses on delivery of information in a clear and sensitive manner followed by time for questions. In Step 5, the physician responds to the emotional reactions of the patient, parents, and others present. Next (Step 6), the physician begins to establish goals for care and treatment priorities. Finally (Step 7), the group establishes a plan. These steps may seem intuitive, but a study analyzing 398 clinic conversations between 51 adult oncologists and 270 patients found that the doctors responded to empathic opportunities only 22% of the time (Pollak et al. 2007). Role play and standardized patient interactions provide safe and effective teaching environments to build and improve communication skills.

Although a do-not-resuscitate order is not a requirement for palliative-care team involvement, there is often a point in the child's care when this issue should be addressed. Providers often wait until respiratory or cardiac arrest is a significant possibility before initiating do-not-resuscitate discussions because of the emotionally charged nature of the discussion. Discussion of wishes regarding resuscitation earlier in the clinical course, in a calm and nonacute setting, has many advantages, allowing the provider to shift the emphasis to maximizing quality of life, and avoiding interventions with low likelihood of benefit, but high likelihood of suffering. The parents should understand that a do-not-resuscitate (DNR) decision can be changed at any time.

Siblings of patients are often inadvertently neglected during treatment and throughout the pediatric palliative care process. These children have increased risk for multiple problems including school issues, negative interpersonal relationships with their parents, and other psychological and social problems. To assure that sibling needs are appropriately met, the Society of Paediatric Oncology (SIOP) working

committee on psychosocial issues in pediatric oncology generated a report with general principles and specific treatment phase guidelines (Spinetta et al. 1999). Siblings should be involved early to avoid feelings of isolation and abandonment. Parents should be encouraged and supported to have open and honest conversations with siblings on a regular basis in a developmentally appropriate manner. Evading the truth can create feelings of fear, isolation, guilt, and resentment. Families should be provided information support groups and other resources for their children.

17.3.3 Team Approach

The multidisciplinary team involving physicians, nurses, social workers, psychologists, child-life specialists, clergy, and family members must also communicate well to optimize patient care. In family meetings, each member of the medical team plays an important role to ensure effective and thorough conveyance of information. A study of 95 pediatric oncology patients including 25 brain tumor patients demonstrated that most pediatric oncology patients who die of progressive disease die at home (Klopfenstein et al. 2001). Continued communication between the care providers in the home and the hospital-based providers can be challenging.

17.3.4 Pain and Symptom Management

One of the primary goals of pediatric palliative care is to ensure the highest quality of life for the patient. Pediatric cancer patients often have poorly controlled symptoms and ongoing suffering. Wolfe and colleagues found that pain, fatigue, and dyspnea were the most frequent symptoms during end-of-life care as reported by 103 parents of pediatric oncology patients (Fig. 17.4) (Wolfe et al. 2000).

17.3.4.1 Pain

Pain is often not recognized or appropriately treated in children. Wolfe's study of symptom management in children dying of cancer found that only 27% of patients received successful pain treatment (Wolfe et al. 2000). Yet, the 1998 ASCO survey on practicing pediatric oncologists found that 91% of providers reported proficiency in end-of-life pain management (Hilden et al. 2001). There is clearly a disconnect between provider and parent perceptions of pain management. Using basic guidelines for pain management in children can help physicians to recognize and assess pain (Hain et al. 2004). The tool used to assess pain in a child must be appropriate to the child's developmental level. Although not all children are capable of self-report, it is the gold standard for pain measurement. In order to ensure accurate pain reports from children, the provider needs to establish a relationship of trust with the child by promptly and effectively responding to pain reports. The physician must also prevent and treat adverse effects of medical interventions. Use of developmentally appropriate language for pain (e.g., *hurt, owie, boo-boo)* can improve communication. Pain changes over time, and therefore must be assessed regularly.

Assessing response to pain treatment is also essential for effective management. In a chronically or critically ill child, physiological indicators including pulse and blood pressure may not accurately represent pain. Behavioral indicators may also be inaccurate in this patient population. Lastly, a child that is playing or sleeping may still have pain. Some tools to assess pain in children are body charts, face scales, numeric scales, color tools, visual analog scales, and behavior observation (Goldman 1998).

The World Health Organization has created a 3-step analgesic pain ladder to guide pain management. For children who have moderate to severe pain, opioids are the primary pharmaceutical agent used for treatment (Korones 2007). However, there are some barriers to appropriate opioid dosing in pediatric palliative care. Often parents and even physicians are concerned about the risk of opioid addiction. When used for treatment of pain, this is quite rare. Concerns regarding possible drug overdose or respiratory depression can interfere with appropriate medication dosing and pain relief. In children greater than 3 months of age, the incidence of opioid-induced respiratory depression is similar to the adult rate of 0.9% (Sahler et al. 2000). There is no maximal

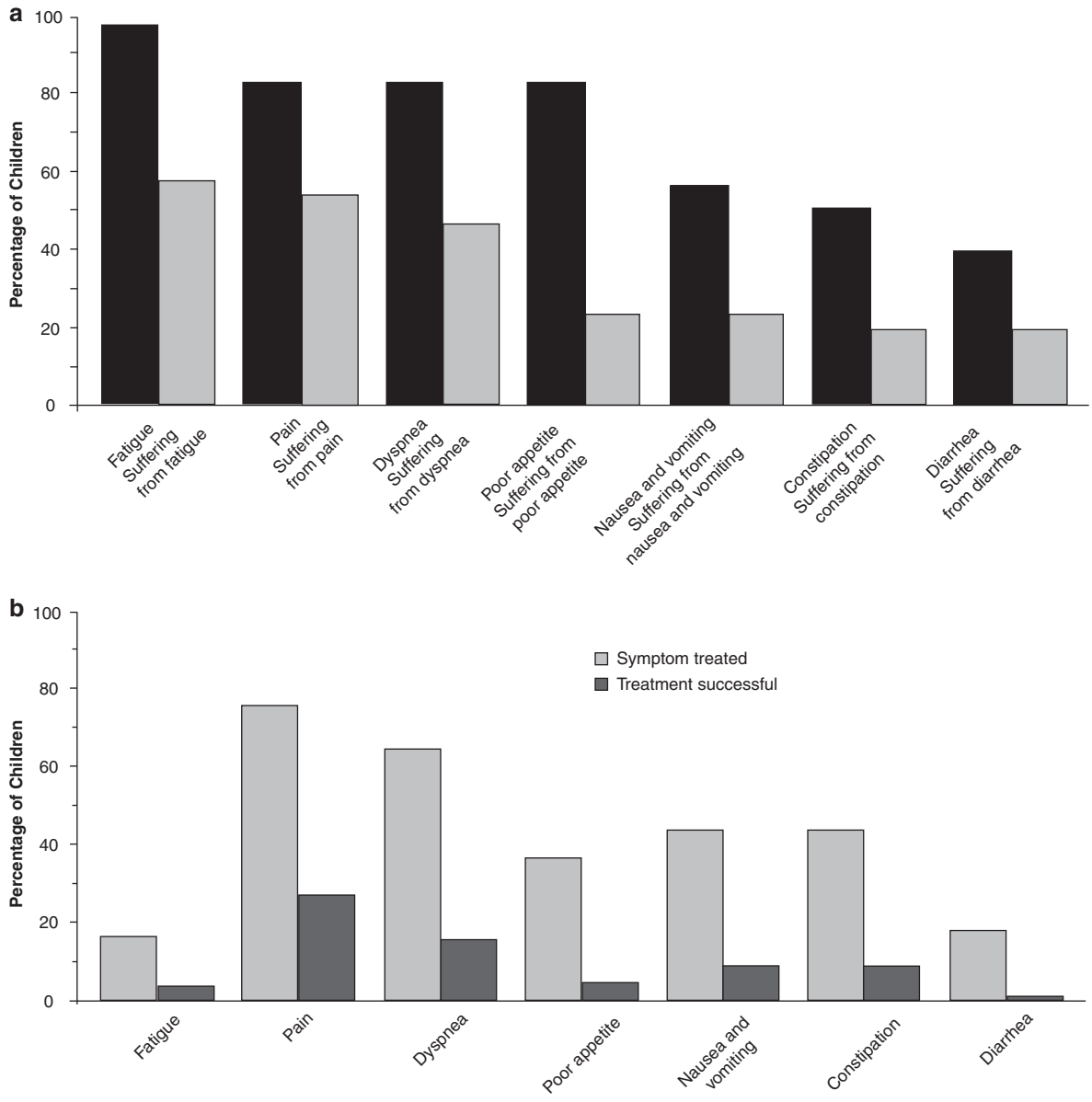

Figure 17.4

Symptoms in the final month of life of 103 pediatric cancer patients. (**a**) Percentage of patients with a specific symptom who had "a great deal" or "a lot" of suffering as a result of that symptom by parental report. (**b**) Percentage of children with a specific symptom that was treated, and where treatment was categorized as "successful" as opposed to "somewhat successful" or "not successful" by parental report (Wolfe et al. 2000).

dose for opioid medications. It is appropriate to continue dose escalation until there are either intolerable side effects or no improvement in analgesia.

Other medications are also used for treatment of specific types of pain. Neuropathic pain is treated using gabapentin, amitriptyline, or nortriptyline. Somatic pain in bone and soft tissues is often effectively reduced by nonsteroidal antiinflammatory drugs and glucocorticoids. For uncontrolled pain, a pain service consultation is available at many institutions and can provide the patient access to pain control techniques including nerve blocks. Alternative pain reduction techniques can also be employed, including hypnosis, distraction, biofeedback, massage, and acupuncture.

17.3.4.2 Seizure and Other Neurologic Symptoms

Pediatric CNS tumor patients are at significant risk for seizures. They can be quite distressing to both the family and child, and should be appropriately managed in consultation with a pediatric neurologist (Wusthoff et al. 2007). Daily antiepileptic drugs are often initiated. The medical team should also consider and plan for the possibility of status epilepticus. Families can administer rectal diazepam gel and other antiepileptic medicines if prolonged seizures occur outside the medical setting.

Agitation is often referred to as terminal restlessness and manifests as increased arousal with or without delirium. Some nonpharmaceutical methods of easing this agitation include familiar objects and reminders of orientation such as a clock or calendar. Pharmaceutical agents may be required. Some of the drug classes used for this purpose include benzodiazepines, neuroleptics, adrenergic agonists and antagonists, and in more severe cases, barbituates (Wusthoff et al. 2007).

Spasticity is defined as an increase in resistance to passive muscle stretch that is velocity dependent. When severe, it can cause significant pain as well complicate changing and positioning of the child. Physical therapy, positioning, and specific medical equipment can be used prior to initiation of medication. Some of the more commonly used agents are baclofen, α-adrenergic agonists, benzodiazepines, and dantrolene (Wusthoff et al. 2007).

17.3.4.3 Nutrition

Many families feel that continuing to provide nourishment for their child is essential. The primary goal should be comfort and enjoyment and risks of aspiration with oral feeding should be discussed with families and patients as developmentally appropriate. If nausea and vomiting from increased intracranial pressure or ongoing treatment are impairing a child's ability to eat and drink, appropriate pharmaceutical management should be initiated.

While some children and their families choose to spend the end of the child's life in the hospital, others prefer to be in their home. Efforts should be made to support the family in whatever they choose. In the past few years, more pediatric home health nursing and hospice services have provided the support families need at home. In this setting, pharmacologic therapy with antidepressants and anxiolytics can be beneficial.

It is important to address what can be expected during the actual physical process of dying with families and patients. Some general issues to include in this discussion are that in the days prior to death a child may have periods of confusion, restlessness, and agitation as well as deep sleep and lethargy. Oral intake as well as urine and stool output often decrease significantly. Some children may talk about death, heaven, and other related topics. In the time immediately preceding death, the child's skin may become cool. Breathing patterns may vary with gasping sounds and rattling sounds. These are not known to be uncomfortable or indicative of pain for the child, but can be quite distressing for observers. Having a health-care provider available to listen for heart rate and pronounce death is important for many families. Many parents request that nasogastric tubes, intravenous catheters, and other medical equipment be removed. The time after death can be an opportunity to cut locks of hair or create handprints for some families as well. Families should be encouraged to spend as much time as they would like with their child after they have died.

17.4 Ethical Considerations of Clinical Trials and Consent

Participation in clinical trials is an important option available to many pediatric brain tumor patients. Preservation of the patient's and the family's right to autonomy and self-determination in medical decision making is integral to good end-of-life care. Three specific areas to consider are the patient's role in decision-making, best interests, and determination of the course of care (Sahler et al. 2000). Often there are new chemotherapy protocols or Phase I or II experimental drug trials available to patients with progressive or relapsed disease. The physician must balance the hope offered by these treatment options with realistic expectations of long-term outcome (Levy 2005). Phase I trials are generally defined as the first stage of testing in human subjects to test safety, tolerability, pharmacokinetics, and pharmacodynamics of a drug. They can also include assessment of new combinations or dosing schedules of FDA-approved drugs (Horstmann et al. 2005). The estimated number of patients who can expect to have disease response is variable, based on the exact study design, but is estimated to be 4–6% for single-agent investigational trials (Kurzrock and Benjamin 2005). The primary benefit is to future patients. Phase II trials are designed to test the effects of the drug on a specific disease and learn more about the effects of the drug on the human body. The highest dose tolerated in the Phase I trial is the dose administered and although a few patients can show disease response, again the primary benefit is to future patients. Palliative chemotherapy is often an option especially if the selected agent is well-tolerated and easy to administer. The physician is responsible for clarifying that palliative chemotherapy aims to improve the quality of life, not eliminate the disease.

17.5 Bereavement

The time following a child's death is very difficult for the surviving family members and is a significant stressor (Wheeler 2001). The abrupt departure from the medical environment can cause additional feelings of loss and sorrow. Many families appreciate continued communication with members of the medical team. Other families desire privacy, and the needs of each family must be determined and respected individually. Support groups can be very helpful to grieving family members. A palliative care team should provide ongoing support and assessment to the family after a child's death. Bereavement counseling may be offered, if needed. The needs of the medical team are often neglected in discussions of grief and sadness after the death of a child. Often a debriefing session can be helpful, and allow providers to mourn the loss of a child.

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