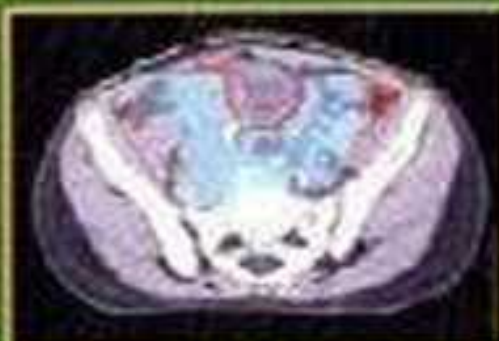


Pediatric Radiation Oncology

5TH
EDITION



Edward C. Halperin
Louis S. Constine
Nancy J. Turbell
Larry E. Kun



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Pediatric Radiation Oncology

F I F T H E D I T I O N

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Dedication

For our children

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Preface

Carl Sandburg is best known as a poet and biographer. He published one novel titled *Remembrance Rock* in 1948. In Chapter 2 he wrote:

A baby is God's opinion that life should go on . . . Never will a time come when the most marvelous recent invention is as marvelous as a newborn baby. The finest of our precision watches, the most super-colossal of our supercargo plants, don't compare with a newborn baby in the number and ingenuity of coils and springs, in the flow and change of chemical solutions, in timing devices and interrelated parts that are irreplaceable. A baby is very modern. Yet, it is also the oldest of the ancients. A baby doesn't know he is a hoary and venerable antique—but he is. Before man learned how to make an alphabet, how to make a wheel, how to make a fire, he knew how to make a baby—with the great help of woman, and his God and Maker.

In 1986, one of us (Edward C. Halperin) conceived the idea of a new textbook of pediatric radiation oncology. There were several general textbooks in radiation oncology on the market at that time. There was not, however, a textbook specifically devoted to the use of radiation therapy in the treatment of childhood cancer. Dr. Halperin thought that there would be a need for a focused text in pediatric radiation oncology and set out to write it. Initially he contacted several medical publishing companies in the United States in an attempt to “sell the idea.” The initial sample chapter, “Langerhans Cell Histiocytosis,” was submitted to these publishing companies along with a proposal letter. While he received several favorable reviews, most publishing companies rejected the book proposal on the grounds that the market was too small to sustain a book of this type. After several rejections, Raven Press of New York City agreed to publish the book.

Dr. Halperin, at that time a 32-year-old assistant professor, thought that this undertaking was too much for one person. He wrote to his colleague Larry E. Kun, at St. Jude Children's Research Hospital in Memphis, Tennessee, to persuade him to join him in the project. After a back and forth correspondence, Drs. Kun and Halperin drew up the outlines for the proposed book and added Drs. Nancy J. Tarbell of Boston and Louis S. Constine of Rochester to the team.

We had a very specific vision for this book. Most clinical radiation oncology textbooks were massive tomes perfectly appropriate for propping a door open or lifting up the slide projector for the morning lecture. In these encyclopedic volumes, each chapter was assigned to an individual author so that the book was written by several different experts. If a reader were to do justice to any individual chapter, several hours of study would be required—almost always with a highlighter in hand. Our opinion for *Pediatric Radiation Oncology* was considerably different. We envisioned a junior resident in radiation oncology working up a pediatric patient late one afternoon. The resident was responsible, in our imagination, for presenting the case to the attending physician the following morning. How would he or she get ready for the

presentation? Was there adequate time to go to the library, read several books, and make lengthy photostatic copies of the relevant journal articles? Probably not. (Furthermore, when we first envisioned this book, it was well before the age of computer-augmented searches for journal articles and the ability of a computer to “download” the pertinent references.)

Our view, therefore, was that we needed to create a book wherein each section would be devoted to a specific tumor and could be read by the hypothetical junior resident at one sitting within the space of an hour. We hoped that this hypothetical resident-in-training could find in our book enough background information to understand the disease that he or she faced, what was called for in diagnostic and staging studies, what the treatment strategy ought to be, and if, when, and how to employ radiation therapy. By the next morning's rounds, when the resident would face the attending physician, this young physician-in-training would not be able to present himself or herself as an expert, but could, at the least, be informed, competent, and ready to explore the topic in more depth.

It is hard to believe that almost a quarter of a century has passed since Dr. Halperin first had the idea, sitting in an office in Durham, North Carolina, to create this book. While much time has passed, however, certain principles of this book have remained unchanged. We have tried to write all of the chapters with a common voice, avoiding repetition and maintaining uniformity of style. We have paid respect to historical information and have paid due deference to the many controversies in the field. The passage of time has allowed us to witness considerable evolution in pediatric radiation oncology. When we wrote the first edition of this book, the role of radiation therapy in the treatment of childhood leukemia, retinoblastoma, neuroblastoma, Hodgkin disease, Wilms tumor, and Langerhans histiocytosis were all vastly different than they are now. The information that we were able to present to our readers about the late effects of cancer treatment and treatment-induced second malignant neoplasms was considerably less.

The challenge of pediatric radiation oncology derives from the broad spectrum of complex diseases, all with their own biology and natural history. The optimal and creative integration of radiation therapy into their management requires a sophisticated understanding of the disease as well as the adverse consequences of all treatment modalities. Pediatric oncology scares many radiation oncologists because each new patient opens a foreign world into which the doctor must not only enter but be successful. The stakes are high since most childhood cancers are curable, but the child can be injured and live a long time with the injury.

We have all aged almost a quarter of a century together through these editions. The reader will see evidence of the original authors getting ready to pass the torch to the new generation of pediatric radiation oncologists, many of whom we have now engaged in the writing of these chapters. In fact, a concern for the future is that radiation oncologists don't

become expert in pediatrics since it requires a huge investment of time and has little financial reward. One of our goals is to demystify pediatric radiation oncology.

The response to this book has been gratifying. We never imagined, in 1986, that there would be five editions of this book and that it would have assumed a niche in the medical literature. Indeed, we have sat at medical meetings and heard this text referred to simply as “the book.”

We hope that all five editions of this book have contributed to an improved understanding of the benefits and

risks of radiotherapy for children. We remain steadfast in our belief that the dissemination of knowledge about pediatric radiation oncology will improve the quality and quantity of life for children afflicted with cancer.

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October 20, 2009

Acknowledgments

For those children who have taught us about life, bravery, pain, and serenity, as well as what they have taught us about clinical pediatric radiation oncology, we are grateful beyond words. We pray that the fifth edition of *Pediatric Radiation Oncology* will serve, in the ultimate measure of our days, as some small payment for what our patients have given to us.

Much of the preparation and collation of the fifth edition of this book was done in Louisville, Kentucky, by Ruth Aultman. Were it not for her skill and devotion, four of the five editions of this book would never have been completed. Additional manuscript preparation was done by Rebecca

Bunker in Memphis, Laura Brumbaugh in Rochester, and Erin Cromack in Boston. Jonathan Pine and Emilie Moyer and the staff of Lippincott Williams & Wilkins were, at all times, courteous and helpful.

We are indebted to our mentors and teachers: J. Robert Cassady, Juan A. del Regato, Sarah Donaldson, Samuel Hellman, Henry Kaplan, Rita M. Linggood, Jay Loeffler, Donald Pinkel, Leon Rosenberg, Philip Rubin, Herman Suit, Samuel Thier, and John Truman.

The love of our families has been a source of constant strength to us.

The Cancer Problem in Children

Edward C. Halperin

In 1900, cancer trailed typhoid fever, malaria, smallpox, measles, scarlet fever, whooping cough, diphtheria, croup, influenza, dysentery, erysipelas, tuberculosis, sexually transmitted disease, meningitis, acute bronchitis, pneumonia, accidents, birth injuries, and violence as a cause of death in children in the United States (1,2). Cancer mortality constituted only 0.43% of mortality from all causes for children (1).

At the beginning of the twenty-first century in economically developed countries, many children die every year from preventable incidents such as traffic accidents, intentional injuries, drowning, falls, fire, and poisoning. The leading cause of death in children older than 1 year is murder by a close relative. Cancer in children has become a significant problem compared with other causes of childhood mortality (3). There were 12,486 new cases of cancer among children of age 1 to 14 years in the United States in 2005 (4,5). In 15- to 19-year-olds for the period 2001 to 2005 there were 5740 new cases. Cancer is the leading natural cause of death among children between the ages of 1 and 14 years in the United States (Table 1.1) (6). For the youngest children, however, cancer is not a major cause of mortality (7). The leading causes of death in infants are congenital anomalies, disorders related to short gestation and low birth weight, and sudden infant death syndrome. In late adolescence, homicide surpasses cancer as a cause of death.

The mortality rate from cancer for children is approximately 3 deaths per 100,000 population per year (5). In the United States, there are approximately 100 cancer deaths per year in 0- to 1-year-olds, 500 in 1- to 4-year-olds, and 1100 in 5- to 14-year-olds (Figs. 1.1 and 1.2) (8,9).

Although cancer is a major cause of childhood death in developed countries, it continues to trail infections as a cause of mortality in developing countries (10–14). In many parts of the world, nutrition, housing, climate, and sanitation conditions create childhood mortality statistics similar to those reported for industrialized countries in the early twentieth century. However, it is likely that future improvements in the standard of living, the success of immunization programs, and dissemination of medical services will make inroads against infectious disease and thereby make childhood cancer a major cause of death in developing nations. Finally, there is almost certainly some variation in childhood cancer rates between countries because of differing abilities to diagnose and treat cases.

RELATIVE FREQUENCY OF THE VARIOUS TYPES OF CHILDHOOD CANCER

The relative frequency of the various types of childhood cancer is influenced by whether we are examining incidence or mortality and by how we stratify by age, sex, or nation. Among the most commonly used data are those of the Surveillance, Epidemiology, and End Results (SEER) program. SEER is a project of the Biometry Branch of the U.S. National Cancer Institute (NCI). The program draws data from several population-based cancer reporting systems covering approximately 10% of the total population of the United States (5,6,15). The adjusted relative frequency of the common forms of childhood cancer from

Table 1.1

Ten Leading Causes of Death among US Children Aged 1–14 years, 2005

Rank	Cause of Death	Number of Deaths	Total Deaths (%)
1	Accidents (unintentional injuries)	4079	36
2	Cancer	1377	12
3	Congenital anomalies	918	8
4	Assault (homicide)	718	6
5	Heart disease	403	4
6	Intentional self-harm (suicide)	272	2
7	Influenza and pneumonia	216	2
8	Septicemia	166	2
9	Chronic lower respiratory disease	160	1
10	Cerebrovascular disease	157	1

Data from Jemal A, Thomas A, Murray T, et al. Cancer statistics. *CA Cancer J Clin*. 2008;58:71–96.

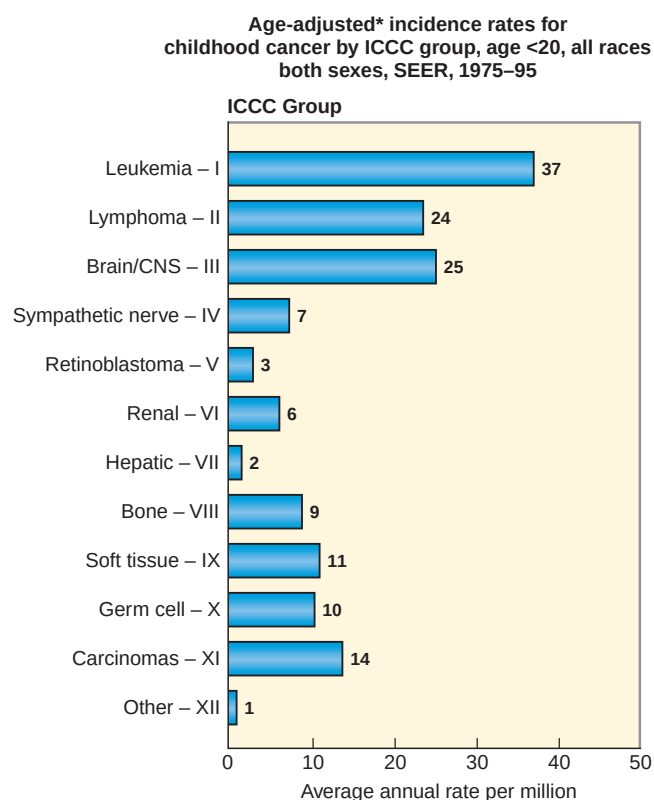


Figure 1.1 Age-adjusted US incidence rates for childhood cancers by International Classification of Childhood Cancer (ICCC) Group, age <20 years, all races, both sexes, SEER, 1975–1979 (<http://seer.cancer.gov>).

SEER is shown in Table 1.2. Leukemias, brain and spinal tumors, lymphomas, sympathetic nervous system tumors (neuroblastoma), kidney (Wilms) tumors, and soft tissue and bone sarcomas are the most common childhood cancers. The common epithelial tumors of adults are rare in children (Fig. 1.3).

Of the cancers that do afflict children, some are more common in specific age groups. For example, neuroblastomas are more common in infancy. The ratio of non-Hodgkin lymphoma to Hodgkin disease favors non-Hodgkin lymphoma in younger children, but the reverse is true in adolescents. There is a steep rise in bone cancers among children aged 11 through 15, which coincides with the adolescent growth spurt. The most common tumors of neonates (younger than 28 days of age), for example, are teratomas, retinoblastoma, rhabdomyosarcoma, and neuroblastoma (16,17). In 15- to 20-year-olds, the list is headed by lymphoma (25%), epithelial tumors (18%), and bone malignancies (15%), followed by leukemia, central nervous system (CNS) tumors, and gonadal and germ cell tumors (10% each) (Fig. 1.4) (18).

Childhood cancer death rates for the United States are shown in Table 1.3. In general, approximately one third of childhood cancer deaths are caused by leukemia, and about one fifth of these deaths are caused by brain tumors (5,6,19,20).

Childhood cancer incidence varies throughout the world. This may be related in part to fundamental issues of biology and demographics. It can also be related to the reporting system of a country and its level of economic development. For example, the distribution of childhood cancers in Uruguay is very similar to that of North America. Uruguay has a per capita income much higher than that of the rest of Latin America and the Caribbean (21). However, the frequency of malignant solid tumors in children in a report from Pakistan was distinctly different from that in the rest of the world. This may be related to

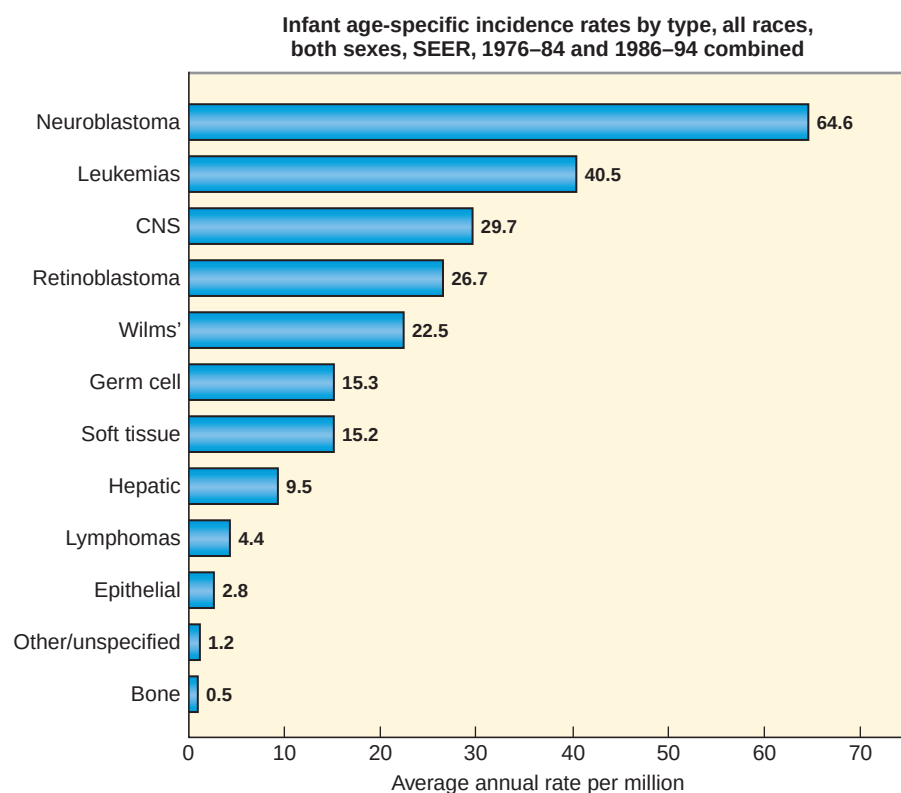


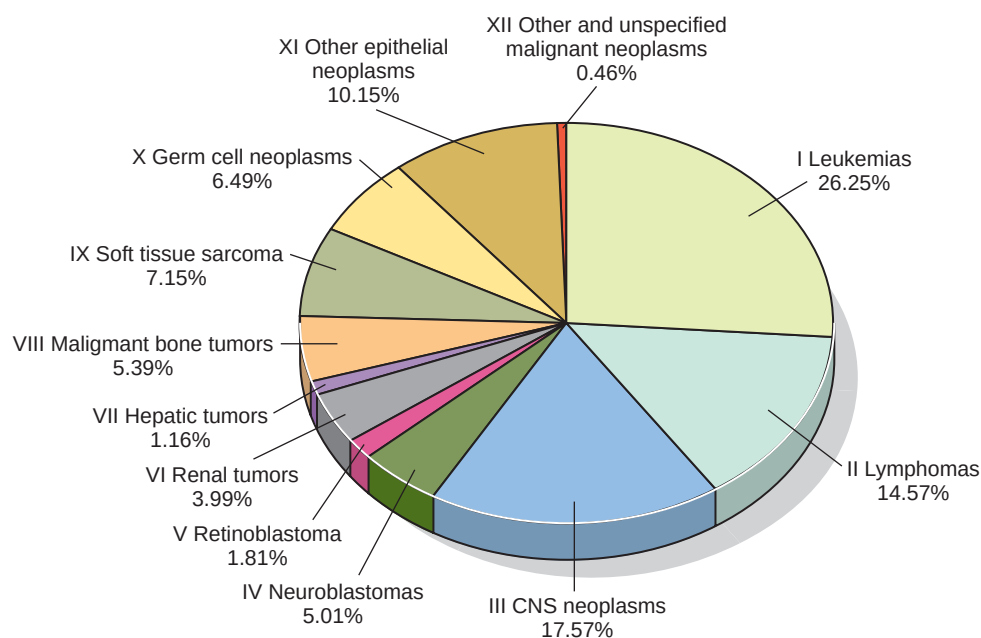
Figure 1.2 Infant age-specific cancer incidence rate by type, all races, both sexes, SEER, 1975–1984 and 1986–1994, combined (<http://seer.cancer.gov/publications/childhood/infant.pdf>).

Table 1.2**SEER Cancer Data: Percent Distribution of Childhood Cancer for <20-Year-Olds by ICCC Group**

ICCC Group	As a Percentage of All Childhood Cancer
I. Leukemia	25%
a. Lymphoid leukemia	19%
ALL	19%
Lymphoid excluding ALL	0.2%
b. Acute nonlymphoblastic leukemia	5%
c. Chronic myeloid leukemia	0.9%
d. Other specified leukemias	0.1%
e. Unspecified leukemias	1%
II. Lymphomas and reticuloendothelial neoplasms	16%
a. Hodgkin disease	9%
b. Non-Hodgkin lymphoma	5%
c. Burkitt lymphoma	1%
d. Miscellaneous	0.3%
e. Unspecified	0.6%
III. Central nervous system and miscellaneous intracranial and intraspinal neoplasms (germ cell are found in category X)	17%
a. Ependymoma	1%
b. Astrocytoma	9%
b. Primitive neuroectodermal tumors	3%
c. Other gliomas	3%
d. Miscellaneous	0.3%
e. Unspecified	0.4%
IV. Sympathetic nervous system tumors	5%
a. Neuroblastoma and ganglioneuroblastoma	5%
b. Other	0.2%
V. Retinoblastoma	2%
VI. Renal tumors	4%
a. Wilms, rhabdoid, clear cell sarcoma	4%
b. Renal carcinoma	0.2%
VII. Malignant bone tumors	6%
Osteosarcoma	3%
Chondrosarcoma	0.3%
Ewing sarcoma	2%
Other specified malignant	0.2%
Unspecified	0.1%
VIII. Soft tissue sarcomas	7%
a. Rhabdomyosarcoma and embryonal sarcoma	3%
b. Fibrosarcoma, neurofibrosarcoma, other	2%
c. Kaposi	0.1%
d. Other specified	2%
e. Unspecified	0.7%
IX. Germ cell, trophoblastic, and other gonadal neoplasms	7%
a. Intracranial and intrapial	1%
b. Other and unspecified nongonadal	1%
c. Gonadal germ cell tumor	4%
d. Gonadal carcinomas	1%
e. Other and unspecified malignant gonadal	0.1%
X. Carcinomas and other malignant epithelial neoplasms	9%
a. Adrenocortical carcinoma	0.1%
b. Thyroid carcinoma	3%
c. Nasopharyngeal carcinoma	0.4%
d. Malignant melanoma	3%
e. Skin carcinoma	3%
f. Other and unspecified	0%
XI. Other and unspecified malignant neoplasms	1%
All groups continued	100%

ALL, acute lymphoblastic leukemia; ICCC, International Classification of Childhood Cancer; SEER, Surveillance, Epidemiology, and End Results.

Data from SEER Cancer Statistics: <http://seer.cancer.gov>, <http://seer.cancer.gov/iccol>, and <http://seer.cancer.gov/publications/childhood>.



Cases = 36,446
Rate = 165.92 per million

Figure 1.3 Childhood cancer incidence in those aged 0 to 19 years in United States, 2001–2003. Rates are per million and were adjusted to the 2000 US standard population. Data are from population-based cancer registries that participate in the National Program of Cancer Registries (NPCR) or the SEER program. These data included malignant tumors only and cover 90.3% of the US population. (Reproduced from Li J, Thompson TD, Miller JW, et al. Cancer incidence among children and adolescents in the United States, 2001–2003. *Pediatrics*. 2008; 121:e1470–e1477, with permission.)

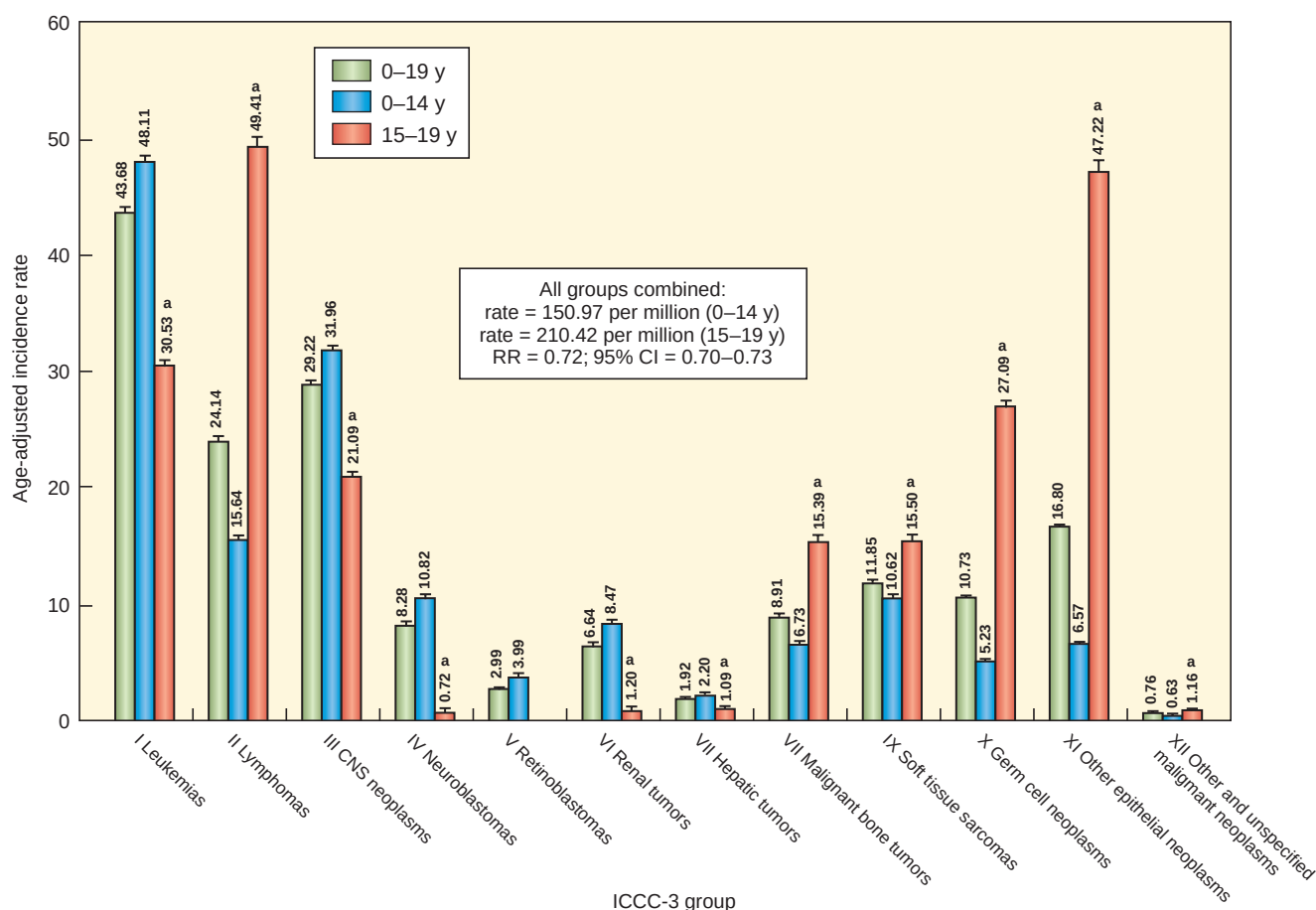


Figure 1.4 Age-specific childhood cancer-incidence rates according to ICCC-3 group: United States, 2001–2003.^a There is a significant difference between children (aged 0–14 years) and adolescents (aged 15–19 years). Retinoblastomas are not shown for those aged 15 to 19 years because there were fewer than 16 cases in this category. (Reproduced from Li J, Thompson TD, Miller JW, et al. Cancer incidence among children and adolescents in the United States, 2001–2003. *Pediatrics* 2008; 121:e1470–e1477, with permission.)

Table 1.3**Reported Deaths for the Five Leading Cancer Sites for Individuals <20 Years of Age, United States, 2005, by Sex**

Reported Number of Deaths	
Male	Female
All sites, 1261	All sites, 922
1. Leukemia, 382	1. Leukemia, 258
2. Brain and other nervous system, 298	2. Brain and other nervous system, 246
3. Bones and joints, 121	3. Bones and joints, 91
4. Other endocrine system, 109	4. Soft tissue, 87
5. Non-Hodgkin lymphoma, 78	5. Other endocrine system, 69

Data from Jemal A, Thomas A, Murray T, et al. Cancer statistics.2008. *CA Cancer J Clin.* 2008;58:71–96.

artifacts of data collection and reporting (14,22–26). Although the absolute frequency of certain tumors is reported to be higher in developing countries than in industrialized states, there is likely to be variation in reporting standards, diagnostic techniques, and histopathologic review (25,27). In Cuba, the most common childhood tumor is leukemia (31%), followed by lymphoma (18%), CNS tumors (15%), sympathetic nervous system tumors (7%), soft tissue sarcomas (6%), and renal tumors (5%) (11). In Thailand, leukemias are most common (40%), followed by CNS tumors (14%), lymphoma (12%), bone tumors (4%), and soft tissue sarcomas (4%) (28). In Eastern Nigeria, lymphoma leads the list (Table 1.4) (29).

TRENDS IN CHILDHOOD CANCER MORTALITY RATES

The mortality rate from childhood cancer has fallen dramatically in the United States. Particularly impressive gains have been posted for acute lymphocytic leukemia (ALL), bone tumors (predominantly osteosarcoma and Ewing sarcoma), Hodgkin disease, non-Hodgkin lymphoma, soft tissue sarcomas (including rhabdomyosarcoma and nonrhabdomyosarcoma soft tissue sarcomas), and Wilms tumor. Although gains have also been achieved for acute myelocytic leukemia, neuroblastoma, and brain tumors, the improvements have been less dramatic or confined to certain subgroups or stages (Tables 1.5 and

1.6). In general, however, the diagnosis and treatment of childhood cancer has been one of the success stories of modern medicine.

It is clear that when compared with adult cancer, childhood cancer is a vanishingly rare event. For example, in 2008 there were 162,000 reported deaths from lung cancer alone in the United States (5). The comparative infrequency of childhood cancer is highlighted by the fact that more people in the United States die of lung cancer in 1 week than children die of all forms of cancer in 1 year. Looking at the impact of cancer solely in this manner obscures the issue, however. If one looks at a death from cancer in terms of potential years of life lost, then the death of an 8-year-old from ALL has a greater statistical weight than the death of an 82-year-old from small cell carcinoma of the lung. Therefore, the success of medical treatment of childhood cancer has a significant public health impact when considered in terms of the person-years of potential life or lifetime earnings saved. A lifetime is saved for every child cured of cancer.

IS THE INCIDENCE OF CHILDHOOD CANCER INCREASING?

Some data suggest that the overall incidence of childhood cancer is rising in the United States. Experts disagree about what might account for this alleged increase. Some have asserted that new diagnostic techniques such as computed tomography (CT), magnetic resonance imaging, needle biopsy, and serum chemical markers are increasing the rate of diagnosis of childhood cancer. Thus, the increase in childhood cancer is merely

Table 1.4**Frequency of Histologic Types of Childhood Cancer in Eastern Nigeria, 1976–2004**

Cancer Types	Frequency (%)
Lymphoma	42%
Wilms	16%
Sarcoma	11%
Leukemia	9%
Retinoblastoma	7%
Neuroblastoma	4%
Other	10%

Data from Ocheni S, Bioha FI, Ibegbulam OG, et al. Changing patterns of childhood malignancies in Eastern Nigeria. *West African Med J.* 2008;27:3–6.

Table 1.5**Trends in US Childhood Cancer 5-Year Survival Rates for 0- to 14-Year-Olds**

Year of Diagnosis	Survival Rate (%)
1950–1954	20
1996–2004	81 (Total change: 61%)

Age adjusted to the 2000 population.

Data from SEER Cancer Statistics: <http://seer.cancer.gov/csr/1975-2005/results-single/sect-01-table.03.pdf>.

Table 1.6**Trends in 5-Year Relative Survival Rates^a for Children <15 Years of Age, United States, 1975–2003**

Diagnosis	Survival Rates (%)	
	1975–1977	1996–2003 ^b
All sites	58	80
Acute lymphatic leukemia	58	87
Acute myeloid leukemia	19	54
Bone and joint	51	72
Brain and other nervous systems	57	74
Hodgkin lymphoma	81	95
Neuroblastoma	52	69
Non-Hodgkin lymphoma	43	87
Soft tissue	61	72
Wilms tumor	73	92

^aSurvival rates are adjusted for normal life expectation and based on follow-up patients through 2004.

^bDifference in each rate, 1975–1977 vs. 1996–2003, $p < 0.05$.

Data from Jemal A, Thomas A, Murray T, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58:71–96.

an artifact of improved diagnostic techniques. The counterargument is that the rise in the incidence of childhood cancer is real and may be linked to environmental toxins. So far, alleged links include pelvic radiography of mothers during pregnancy, the use of radioactive nucleotides during pregnancy, exposure to electromagnetic fields, radon, solvents, parental occupational exposure, diet, environmental tobacco smoke, alcohol, and infection. The alleged link to agricultural and home pesticide use is weak, and many studies find no correlation (30,31). While it has been suggested that exposure to magnetic fields emanating from electric transmission and distribution lines and certain electrical household appliances may be associated with some childhood tumors, the available studies are contradictory (32).

SEER, the Manchester Children's Tumor Registry in northwestern England, a registry for Queensland, Australia, the Greater Delaware Valley Pediatric Tumor Registry, and a study from Canada indicate an increase in cancer incidence in children of approximately 1% per year (32–35). Although a study in Denmark did not find a rising incidence, overall the evidence supports an increase in childhood cancer incidence (22).

The data concerning changes in the incidence of acute leukemia in childhood are somewhat conflicting. Some reports indicate that it is rising, and some show it to be stable. Improvements in diagnosis have decreased the number of children labeled as having "leukemia, not otherwise specified" and increased the number of children given a specific leukemia type as a diagnosis. However, most studies indicate an increase in the incidence of childhood brain tumors and lymphoma (33,34).

If we accept the premise that the overall incidence of childhood cancer is rising, then we must bear in mind two potential confounding factors. First, the frequency of childhood cancer is so low that it takes only a few cases, in registries covering a small population base, to suggest a change

in incidence (35). Second, as the diagnostic tools of modern medicine improve, more children will be correctly diagnosed with cancer as opposed to another diagnosis. This may be particularly important for brain tumors (34). The consensus, an explanation for the increase in childhood cancer incidence has not been established.

WHAT DOES CURE MEAN IN PEDIATRIC ONCOLOGY?

The English word "cure" is derived from the Latin term "cura" and the Old French term "cure," both meaning "care." The generally accepted definition in medicine for cure is "successful medical treatment; the action or process of healing a wound, a disease, or a sick person; restoration to health" (36). There are several mathematical and statistical definitions of cure. In 1963, Easson and Russel suggested a definition for cure that was a modification of an earlier definition proposed in 1929 by Greenwood (37,38): "We can speak of cure when in time—probably a decade or so after treatment—there remains a group of disease-free survivors whose progressive death rates from all causes is similar to that of a normal population of the same sex and age constitution." Patients and clinicians, during the 1960s and 1970s, became comfortable with transitioning from the concept of "indefinite remission" to "cure" (39). Frei and Gehan (40) suggested that survival should also be unassociated with continuing morbidity from the disease or its treatment. Cure is not achieved when treatment stops or even after a 5-year disease-free period. For each child with cancer and his or her family, the meaning of cure is different. For some patients, it is the knowledge that the disease is gone and never coming back. To others, it is the statement that they are well today and want to be so tomorrow. For all children with cancer, hope is the common denominator and getting on with life is the goal (41).

One way of expressing the probability of survival is a relative survival rate. The relative survival rate is the ratio of the observed percentage of survival to the percentage expected on the basis of general population experience, adjusted for age, sex, race, and calendar year. Using this definition, a population of patients would be cured when a graph plotting relative survival rate showed a horizontal line (40).

Pinkel (42) summarizes the criteria of biologic cure as completion of all cancer treatment, continuous freedom from cancer relapse, and minimal or no risk of subsequent relapse. It is important to consider the continuous cancer-free survival (other commonly used terms are relapse-free survival and event-free survival) and the overall survival in constructing survival curves. Overall survival rates reflect factors other than biologic curability, including death caused by complications of treatment and subjective factors such as the patient's will to continue living with cancer or its repeated relapses, the physician's determination to keep the patient alive, and the technical and financial resources available to the physician and the patient.

The reported cure rates in pediatric cancer may be affected by artifacts of data acquisition and analysis. The zero time shift or lead time bias will extend the statistical length of survival without prolonging life. This phenomenon occurs when a new screening test or imaging study leads to the detection of a previously unknown tumor. Even if therapy is

THE WILL ROGERS EFFECT

The Will Rogers effect occurs when a new staging test, such as diagnostic imaging, is introduced into cancer management (43). Assume that you evaluate 100 children with a specific histologic type of cancer. After they complete a staging work-up, they are assigned a stage. For example, Stage I—localized; Stage II—regional spread; Stage III—metastatic. Let's say the 100 patients are distributed as follows.

Stage	Number of Patients
I	50
II	30
III	20
Total	100

Now we'll enter the 5-year survival probabilities and determine the overall survival; in this case 44 of the 100 patients.

Stage	Number of Patients	Five-Year Survival (%)	Number of Survivors
I	50	60	30
II	30	40	12
III	20	10	2
Total	100		44

Then a new staging test is discovered. By detecting small foci of tumor spread, some patients are moved from Stage I to Stages II or III. By removing these bad prognosis patients from Stage I, the survival for Stage I rises—even if therapy is not improving. Some patients who were formerly Stage II are

reassigned to Stage III because of the detection of tumor spread. Similarly, the survival rate of Stage II rises by extracting these “bad actors” from the pool of Stage II patients. The Stage III patient group enlarges—having acquired patients with minimal-volume metastatic disease. These patients with low-volume metastatic disease do better than the traditional patient with metastatic disease. (Imagine the difference between lung metastases detected by CT, for example, vs. conventional chest x-ray.)

The survival rates of Stages I, II, and III have risen as a result of restaging with new technology and stage redistribution, but not as a result of improved therapy.

Stage	Number of Patients	Old 5-Year Survival (%)	New 5-Year Survival (%)	Number of Survivors After the New Test
I	30	60	67	20
II	40	40	45	18
III	30	10	20	6
Total	100			44

Interestingly, although the survival probability for every stage of disease rose, the overall survival is still 44 out of 100 patients. The introduction of a new test that more precisely stages patients has deceived us into thinking that our therapy has improved—but it has not. As described in the text, this is “The Will Rogers effect.”

ineffectual, survival is increased by the interval provided by the earlier detection of the cancer. The Will Rogers effect occurs when there are improved techniques for detecting cancer metastases. These new data allow patients to migrate from lower stages of cancer to higher. Such migration improves survival in lower stages by eliminating those with metastatic disease. Survival also improves in higher stages because of the addition of people with minimal metastatic disease. Survival improves in each stage, but overall survival for the cancer is unaffected. This phenomenon is named after the American humorist Will Rogers, who is reputed to have remarked during the economic depression of the 1930s that “when the Okies left Oklahoma and moved to California, they raised the average intelligence in both states” (43). (See Sidebar.)

THE GROWING POPULATION OF CHILDHOOD CANCER SURVIVORS

With improving cure rates in childhood cancer, it is apparent that we must move beyond the statistical definition for cure (20,44) (Table 1.7). Cure is more than the absence of disease. It is important to provide the child with a functional cure, regaining or retaining the ability to function in society without major handicaps and minimizing the need for a significant support. There are about 270,000 survivors of childhood cancer in the United States (45,46). The prevalence will reach 1

in 450 young adults by 2010. This means that the average primary care physician will have several long-term survivors of childhood cancer in his/her practice.

The Childhood Cancer Survivor Study is a multicenter study funded by the NCI. This study of more than 14,000 survivors of childhood cancer shows that survivors are at a higher risk of impaired pulmonary function, growth abnormalities, endocrine dysfunction, obesity, physical limitations, infertility, cardiac problems, reduced quality of life, depression, special educational needs, and second malignant neoplasms (47). Pulmonary complications may develop years after treatment. Cancer survivors have higher rates of lung fibrosis, emphysema, pneumonia, pleurisy, and a need for oxygen compared with sibling control subjects. Survivors of childhood acute lymphoblastic leukemia treated with more than 20 Gy of cranial radiotherapy were significantly more likely to be overweight or obese than sibling control subjects (48).

Planning for adequate limb function, ambulation, and activities of daily living is crucial in planning a course of treatment. Rehabilitation including physical, occupational, and recreational therapy plays an important part in follow-up care. A comprehensive pediatric cancer rehabilitation program requires people with expertise in prosthetics, orthoses, ostomy care, gait training, and pain management (23,49–52).

Attention to the child's emotional status is also important. This includes preserving and nurturing a sense of well-being on the part of the child and his or her family. Childhood

Table 1.7
All Cancer Sites (Invasive) Survival Rates^a, by Year of Diagnosis and for All Races, Males and Females, Ages 0 to 14

Year of Diagnosis	Relative Survival Rates (SEER ^b)		
	5-Year	10-Year	20-Year
1975–1979	60.0	55.8	52.9
1980–1984	65.9	62.5	58.9
1985	69.6	64.8	62.6
1986	68.7	66.8	
1987	70.3	67.1	
1988	72.5	70.1	
1989	71.5	67.3	
1990	74.2	71.2	
1991	75.3	72.8	
1992	77.5	75.5	
1993	76.4	74.5	
1994	78.2	75.9	
1995	77.3	74.3	
1996	80.1		
1997	78.9		
1998	77.6		
1999	78.9		
2000	80.4		

^aSurvival rates are relative rates expressed as percentage.

^bRates are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).

Data from http://SEER.cancer.gov/csr/1975_2005/results_single/sect_28_table.10.pdf.

cancer survivors are more likely than their siblings to suffer symptoms of depression and somatic distress (53). The family should be given every measure of support in dealing with illness and restoring health. The diagnosis and treatment of cancer exert severe emotional and financial strains on a family. The term “psychological cure” refers to the ability to put cancer behind you and move on with life (39).

Parental separation and divorce, sibling behavior problems, and the weight of family responsibilities during adversity complicate the treatment and rehabilitation of the child with cancer (54,55). The pediatric radiation oncologist should ensure an ongoing relationship with the child and family after treatment to contribute to rehabilitation. As the survival rates for pediatric cancers improve, we will have an increasing population of young adults who are cancer survivors. These people will pose new problems for medicine and society: What will be appropriate medical surveillance for late effects of treatment, including secondary malignancy? How shall these patients be counseled concerning reproduction? What special needs will such people have concerning employment, disability and health insurance, and psychological support? (51). A survey of 1437 childhood cancer survivors, >18 years old and >10 years postdiagnosis, showed decreased marriage rates in irradiated hematologic malignancy survivors and generally lower employment (Table 1.8) (56). The pediatric radiation oncologist will play an important role in understanding these issues and implementing solutions (57,58).

SITE OF CARE AND THE PEDIATRIC CANCER TEAM

The 1969 edition of *Nelson Textbook of Pediatrics* reported that childhood “leukemia is a uniformly fatal malignant disease.” Advances in the treatment of pediatric malignancies in the subsequent three decades have been remarkable. This success is the result of a complex, multidisciplinary process administered by a team of professionals (59).

Combined-modality therapy has been a rewarding approach. A coordinated group of medical and surgical specialists with expertise in the clinical care of children with cancer and in basic and clinical research best direct the child’s care. The complete pediatric cancer center is staffed by a pediatric medical oncologist, specially trained nurses, a pediatric diagnostic radiologist, surgeons with expertise in pediatric oncology, anesthesiologists, psychiatrists, physiotherapists, physicians’ assistants, and social workers. The group must also include a radiation oncologist committed to pediatric care and with experience in radiotherapy for children (59,60) (Table 1.9).

Participation of the patient’s parents and other significant family members is an integral part of the team approach. Parents will soon become extremely knowledgeable about their child’s illness, its treatment, and the associated complications. They will become careful observers of physical signs and symptoms and their report of changes in the child’s well-being will be invaluable to caregivers. Parents often develop important skills such as the care of indwelling venous access devices. Parents may be taught to administer medications, titrate their dosages, and oversee symptom management.

Going to school is the normal daytime activity for most children. The child with cancer should be encouraged to live as normally as possible. Participation in school is encouraged to whatever degree is reasonable. Many hospitals maintain a program for schooling children during their cancer care. In some states, the hospital itself is accredited as a public school and certified teachers are on staff. These teachers, working closely with the local school districts, can help children keep up with their studies and be more readily integrated back into their classrooms at home.

There is evidence that the diagnosis and treatment of some pediatric malignancies, particularly those dependent on complex radiotherapy, are better conducted at university-affiliated medical centers. The available data suggest that there is a benefit to treatment at a university-based or regional cancer center when the treatment is rapidly evolving and when complex treatment approaches with technically difficult surgery or radiotherapy are needed. However, it appears that the site of treatment does not alter survival rates for patients in whom a cure may be achieved with surgical intervention alone, for tumors for which there is no significant curative treatment, and for tumors necessitating multimodality therapy when the most up-to-date protocol information and the services of a consulting expert are available in the community hospital (61–66).

POSTGRADUATE TRAINING IN PEDIATRIC RADIATION ONCOLOGY

There are serious gaps in residency training in pediatric radiation oncology in the United States. The incidence of childhood cancer is low. In addition, only a portion of childhood

Table 1.8

Marriage, Employment, and Health Insurance in Adult Survivors of Childhood Cancer: A Survey of 1437 Survivors >18 Years of Age and >10 Years Postdiagnosis Treated at St. Jude Children's Research Hospital

Diagnosis	National Average Patients (%)					
	Married	Separated or Divorced	Never Married	Married	Separated or Divorced	Never Married
Hematologic						
RT	52	10	38	44	13	43*
No RT	34	6	60	35	7	57
Solid tumor						
RT	52	10	37	50	11	39
No RT	44	8	47	44	8	52
CNS tumor						
RT	40 (employed full-time)	7 (employed part-time)	53 (unemployed)	25 (employed full-time)	0 (employed part-time)	75 (unemployed)
Hematologic						
RT	85	13	4	68*	10*	22*
No RT	76	18	6	72	8*	20*
Solid tumor						
RT	83	13	4	71*	7*	23*
No RT	80	15	5	67	8*	25*
CNS						
RT	78 (private health insurance)	17 (public health insurance)	6 (no health insurance)	44* (private health Insurance)	6 (public health insurance)	50* (no health insurance)
Hematologic						
RT	70	7	23	69	13*	18*
No RT	63	8	28	69	10	21*
Solid tumor						
RT	70	7	23	76	15*	10*
No RT	67	8	28	65	17*	19
CNS tumor						
RT	65	8	27	30*	45*	25

* = $p \leq 0.05$ vs. national average; RT = radiation therapy.

Derived from Crom DB, Lensing SY, Rai SN, et al. Marriage, employment, and health insurance in adult survivors of childhood cancer. *J Cancer Surv.* 2007;1:237–245.

Table 1.9

Requirements for a Pediatric Cancer Center

The **medical staff** should include a qualified pediatric hematologist or oncologist; a pediatric radiation oncologist; a pediatric general surgeon; surgeons with pediatric expertise in neurosurgery, urology, and orthopedic surgery; a pathologist with expertise in tumors of children adolescents; and pediatric subspecialists in anesthesiology, diagnostic radiology, intensive care, infectious disease, cardiology, endocrinology, nephrology, and neurology

The **allied health staff** should include pediatric nurses, social workers, pharmacists, psychologists, child life specialists, recreational therapists, physical therapists, and chaplains with expertise in childhood cancer

The **physical plant** of the hospital or medical center should include an appropriate inpatient unit for the care of children with cancer, an ambulatory clinic for treatment and monitoring of children with cancer, a pediatric intensive care unit, a hematopathology laboratory capable of performing cell phenotype analysis, a clinical chemistry laboratory able to monitor antibiotic and antineoplastic drug levels, a blood bank, a pharmacy capable of preparing and dispensing antineoplastic agents and total parenteral nutrition, a diagnostic radiology suite, and a radiation oncology department

The **institution** should conduct a regularly scheduled multidisciplinary pediatric cancer center and role of such centers in diagnosis and treatment

Based on American Academy of Pediatrics. Guidelines for the pediatric cancer center and role of such centers in diagnosis and treatment. *Pediatrics* 1986;77:916–917.

cancer cases are appropriate for radiotherapy. When one also considers the fact that pediatric cancer cases are not uniformly distributed among the radiation oncology training programs in the United States, one can readily understand why many residency programs see fewer than five pediatric cancer cases per year. In some residency programs the few pediatric radiation oncology cases that are seen are heavily weighted toward palliative cases, total body irradiation for bone marrow transplantation, or late adolescents with Hodgkin disease. Therefore, it is very likely that a person could go through 4 years of postgraduate training in radiation oncology and never see a case of retinoblastoma, neuroblastoma, Wilms tumor, or Langerhans cell histiocytosis.

There is an intrinsic problem with the way academic medical centers count the number of pediatric radiation oncology cases for residency training accreditation. In adult radiation oncology, guidelines exist for the appropriate number of lung, colorectal, breast, head and neck, and genitourinary malignancies necessary for training. In the case of pediatric cancer, however, all forms of cancer are lumped together to reach an acceptable number. Such a policy would never be acceptable in taking an inventory of the appropriate number of adult cases for training.

Some residency programs try to solve the problem by sending residents for away rotations. With a 1-month rotation at another center, residents are expected to acquire sufficient training to last them for the 4 years of the residency program. In 1 month, it is entirely likely that a resident would never see a patient taken from consultation through simulation and all the way through completion of a course of treatment. Long-term follow-up is also impossible.

Some have proposed eliminating pediatric radiation oncology training from general radiation oncology training. By this line of argument, pediatric radiation oncology would become a subspecialty, which would entail a separate fellowship at the end of a residency. Another proposed solution is to designate only certain residency programs as capable of providing pediatric radiation oncology training by virtue of the adequate number of cases and faculty with sufficient expertise. It is highly unlikely that there will be approved subspecialty training in pediatric radiation oncology in the near future. The designated accrediting boards in the United States have a series of requirements for subspecialty designation that are too formidable to be met in the case of pediatric radiation oncology. Therefore, it remains likely that for the foreseeable future pediatric radiation oncology residency training will continue to be inadequate (57,67).

THE PROBLEM OF EVIL AND CHILDHOOD CANCER

The philosophical problem of severe illness and death in children poses a tremendous challenge to the pediatric radiation oncologist. Why does premature death take the innocent? This question has troubled philosophers, theologians, and physicians.

Physicians use several defense mechanisms in dealing with adults with cancer. When faced with someone with advanced bronchogenic carcinoma, physicians may say to themselves, "The prognosis is grim. However, the patient has a long history of cigarette smoking." Faced with a patient with advanced car-

cino-ma of the cervix, the physician may think, "The patient has a very bad malignancy, but this is almost certainly associated with significant risk factors associated with sexual behavior." When etiologic rational defenses do not come to mind in adult oncology, the physician may turn to the age defense: "The patient is 85 years old, and no one lives forever." Such rationalizations are not useful when a 40-year-old is faced with widespread metastatic breast cancer. In most cases, however, they do help the physician get through the day (68–70).

Rationalization defenses based on age or etiology break down when the pediatric radiation oncologist faces a child with a malignancy. We have nothing and no one to blame for a child dying of pontine glioma. There is no obvious rationalization.

The problem of evil is a long-standing one in the history of philosophy. For the physician who believes in a rational order to the universe, most often in the context of religious faith, there is a classic dilemma: Why is there evil? If there really is a God who permits cancer in children, is God omnipresent but not omnipotent? If so, then a logical contradiction exists in the concept of an omnipresent, omnipotent God. On the other hand, is the explanation for childhood cancer that God is all powerful but not all merciful? If so, again a contradiction exists in the general monotheistic view of the Supreme Being. One could also conclude that there is no God. If this is the case, then there is no rational order to the universe, everything is random, and evil is simply one more random event. As Camus wrote in *The Plague*, any god worth believing in would not permit the sufferings and death of innocent children (71).

For some people, there is no response to the problem of evil. One Baptist minister wrote:

Silence may be the most truly faithful response. This holds true at least in a Christian understanding that God is found not in the whirlwind, but in the silence. . . . The Old Testament tells us that when Job cried out, "What does this all mean?" God responded, "Where were you when I created the heaven and the earth?" I think that this is a reminder that there are wisdom's beyond our wisdom. (71)

In some philosophical schools, the greatest sin is the lack of knowledge. For others, however, the greatest sin is to be separated from one's conception of a Supreme Being.

The authors of this book have no special knowledge concerning the problem of evil that enables us to counsel the pediatric radiation oncologist in training or to assuage the concerns of the long-standing practitioner. The child with cancer is discomfiting to the physician. However, this discomfort should not paralyze the physician with indecision or doubt about a course of therapy. It is reasonable for the physician to be angry and distressed about the child with cancer. We should be more concerned about the physician who lacks rather than possesses such feelings.

It is acceptable, in the context of the problem of evil, for physicians simply to accept the fact that they don't know the answer. In medieval times, the population often went to cathedrals to seek the answers to the great questions of life. In the modern world,

the grand complexes of medical centers supplanted cathedrals. We go into places like [a hospital] to seek our answers. [Physicians] are the new caste of priests. They are the persons to whom people come for the answers.

You are asked to be without blame, faultless, and have absolute answers. Part of your training is the classic rationalization of an education that does not give you permission not to know. That is the issue for many [physicians]. You have to know that you cannot know all of the answers (69).

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The full list of References for this chapter can be found online at the book's website. Listed here are References particularly recommended for further reading.

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Leukemias in Children

Larry E. Kun

Leukemias are the most common cancer types in children, representing nearly 30% of all childhood cancers in North America. The most common leukemia is acute lymphoblastic leukemia (ALL), accounting for 80% of childhood leukemias and nearly 24% of all cancers in children. Approximately 3000 children present with ALL annually in the United States. ALL was the prototype childhood cancer documenting response and, subsequently, cure with chemotherapy and the importance of combined modality therapy that incorporated irradiation for “sanctuary sites.” The development of therapeutic approaches in ALL sets another precedent in oncology, demonstrating the value of serial, prospective clinical trials to introduce progressively more successful treatment regimens. It is no exaggeration to attribute the early success in leukemia control to the introduction of central nervous system (CNS) irradiation, a fundamental component of the earliest successful leukemia regimens developed in the late 1960s that has been extensively studied in serial intervals, identifying subsets of ALL at higher risk for CNS disease and weighing relative effectiveness and toxicities of CNS-directed chemotherapy or irradiation (Fig. 2.1).

Approximately 20% of childhood leukemias are acute myeloblastic leukemia (AML), a disease that is more common in adults. Successful management of AML has lagged behind that of ALL historically, and the role of radiation therapy remains poorly identified. However, AML has been one of the more common indications for bone marrow transplant (BMT) in children, and the impact of total body irradiation (TBI) in this setting has been significant. Transplant regimens continue to evolve, with increasing indications for radiation immunosuppression, as the host pool for allogeneic transplants now commonly includes matched unrelated and haploidentical donors.

ACUTE LYMPHOBLASTIC LEUKEMIA

Biology

ALL results from a clonal expansion of dysregulated, immature lymphoid cells. The linkage of ALL subtypes to the major immunophenotypic lymphocyte lines provided the first biologic understanding of the disease types that correlate biologic characteristics with common clinical features. B-precursor leukemias account for 85% of ALL cases in children. Most cases of B-precursor ALL consist of leukemic clones from early pre-B-cell lines (55%; cytoplasmic immunoglobulin [cIg] negative) or pre-B-cell lines (25%; cIg positive); only 2–3% of B-progenitor ALL cases show mature B-cell differentiation with surface immunoglobulin that characterizes mature B cells. T-precursor

ALL accounts for 15% of cases of childhood ALL (1). B cell-derived ALL typically occurs in young children, associated with a wide range of clinical manifestations and initial white blood cell (WBC) counts. Classically, T-cell ALL occurs in older children (above 10 years) and has been associated with extramedullary involvement (in mediastinal lymph nodes and the CNS) and high presenting WBC (2).

Enormous advances in the understanding of ALL have accompanied studies of the cytogenetics of this disease (3) (Fig. 2.2). More than 60% of ALL cell lines in children are identifiable as specific genetic abnormalities. The earliest

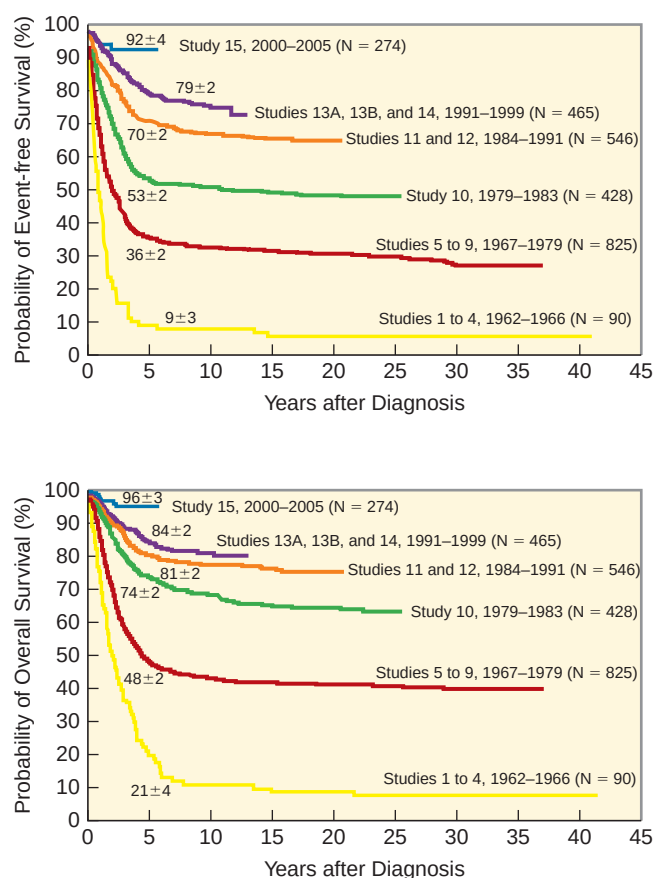


Figure 2.1 Outcome in childhood ALL—serial “total” therapy studies at St. Jude Children’s Research Hospital 1962–2005. EFS (top) and OS (bottom) for 2628 children treated on 15 consecutive trials. Reprinted from Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med.* 2006;354(2):166–178, with permission.

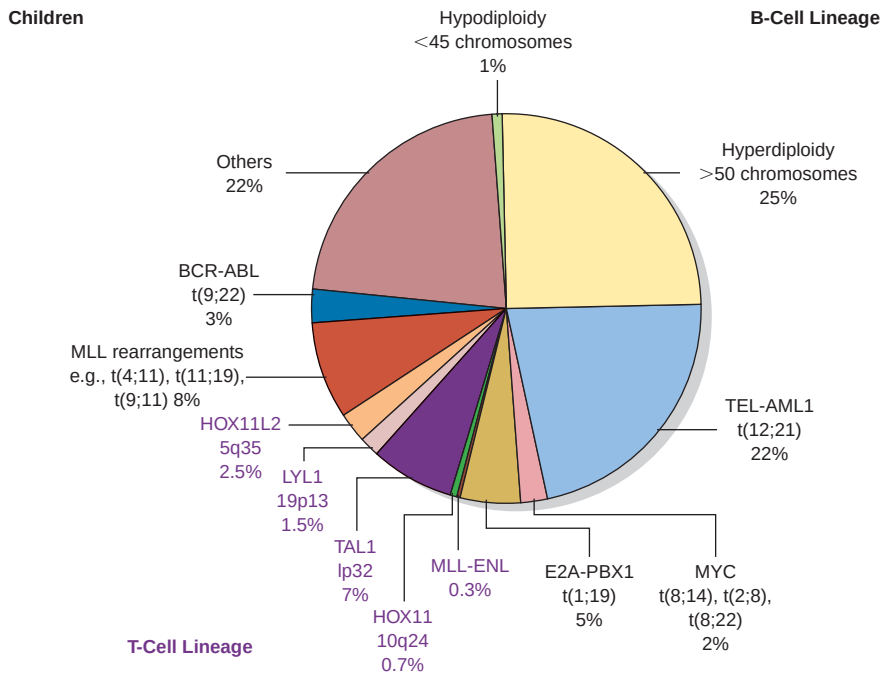


Figure 2.2 Genotypes in childhood ALL, including genetic findings in B-cell lineage or all ALL immunophenotypes; genetic findings unique to T-cell ALL are in purple shades. Reprinted from Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. *N Engl J Med.* 2004;350(15):1535–1548, with permission.

distinct molecular characteristic included chromosomal translocations: the demonstration of Philadelphia chromosome (Ph+), associated with chronic myelogenous leukemia in adults, in up to 5% of children with B-precursor ALL. P+h+ cases have translocation t(9;22) associated with the *BRC-ABL* fusion gene and a high risk of relapse, especially in adolescents (3,4). Unfavorable genetic findings include hypodiploidy and t(4;11) associated with the *MLL-AF4* fusion gene, found in half of the infants below 1 year (5). Lymphoblasts with deletion or mutation of *IKZF1* are associated with a twofold incidence of relapse and adverse events independent of age and initial WBC; the *IKZF1* deletion is associated with a threefold likelihood of minimal residual disease (MRD) at completion of induction therapy (6). Several chromosomal translocations (e.g., t(4;11), t(11;19), and t(1;11)) result in mixed-lineage leukemia (MLL) gene rearrangements, a genetic factor associated with a significantly lower disease control rate (7). Infants below 1 year often show MLL gene rearrangements (8,9). Biologic characteristics associated with favorable outcome in B-lineage ALL include hyperdiploidy (>50 chromosomes) and t(12;21), associated with *TEL-AML1* fusion gene present in 20% of children (3–5). Among the 12% of leukemic children and adolescents presenting with T-cell ALL, the finding of t(11;19) and related *MLL-ENL* is associated with positive outcome (3).

Clinical Presentation

The median age at presentation for ALL is 4 years, with a peak occurrence between ages 2 and 4 years. Boys are more commonly affected than girls; the male sex predominance is particularly notable in T-cell ALL. ALL is less common in African-American children. Earlier studies demonstrated unfavorable outcome in adolescents and in African-American children; more recent results are similar among children with standard-risk ALL (10).

The most common presenting symptoms include fever, bleeding, and bone pain. Findings at diagnosis include

ecchymoses or petechiae, signs of lymph node enlargement, and hepatosplenomegaly. The diagnosis is suspected with a complete blood count (CBC) demonstrating the presence of immature lymphoblasts in the peripheral blood or elevated WBC (WBC less than 10,000/mL in 50% of presentations, 10–50,000 in 30%, and more than 50,000 in 15–20% at diagnosis). Less often, clinical symptoms or signs are associated with extramedullary involvement of the CNS, testis, or kidney.

ALL is a systemic disease by definition, usually involving the bone marrow diffusely and associated with lymphoblastic infiltration, either microscopic or overt, in a number of organ systems (e.g., lymph nodes, liver, and spleen). CNS leukemia is usually asymptomatic; extensive leptomeningeal disease may be manifest clinically by irritability, headaches, sometimes vomiting or unanticipated weight gain (the “hypothalamic” syndrome), and, less often, cranial nerve palsies (especially VII; less often VI, III) or seizures. Advanced disease sometimes is manifest by papilledema and diffuse retinal infiltration (Fig. 2.3). The pathophysiology was demonstrated in Price and Johnson’s classic description of leukemic cells filling the subarachnoid space well into Virchow–Robin spaces and throughout the basal cisterns (11). CNS disease is associated with IL-15 expression (12).

Staging: Risk Categories for ALL

The clinical criteria used in determining “risk group” for pediatric ALL were agreed upon at an NIH-sponsored Consensus Conference in 1995. *Low risk* has been defined as B-precursor ALL in children between 1 and 10 years presenting with WBC less than $50 \times 10^9/L$ (50,000/mL) (13). Other features currently identified as *low risk* include DNA index of >1.16 or presence of *TEL-AML1* fusion (14). Infants below 1 year, children 10 years or older, B-cell lineage with WBC over 50,000/mL, all those with T-cell lineage, and cases with t(1;19)/*E2A-PBX1* fusion are now classified as *standard risk* at St. Jude Children’s Research Hospital (SJCRH) and in several cooperative groups (14). *High-risk* disease at diagnosis is limited to those with

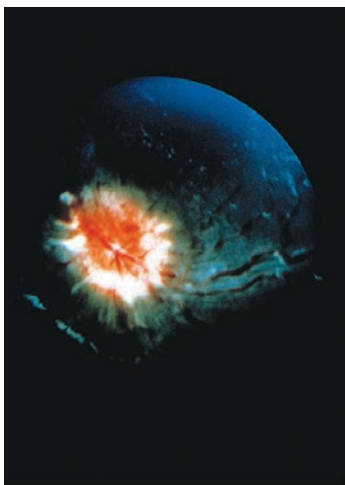


Figure 2.3 The retinal photograph demonstrates advanced CNS leukemia with papilledema and retinal infiltrate typical of ocular disease.

t(9;22)/*BRC-ABL* fusion (Ph+ ALL) (14,15). In addition to clinical and biological features at diagnosis, one of the most important predictors of outcome is early response to induction chemotherapy: patients with residual bone marrow leukemia (MRD quantitatively defined by immunohistochemistry or polymerase chain reaction [PCR] blasts defined as $\geq 1\%$ on day 19 of induction therapy or 0.1–0.99% at completion of 6-week induction therapy) are at higher risk for relapse and are staged as *standard risk* (rather than low risk); those with $\geq 1\%$ residual at the latter interval are all treated as *high risk* (14,16). Relative risk factors and the impact on therapeutic outcome are listed in Table 2.1. Recent studies show 45–50% of cases treated as *low risk*, 40–45% as *standard risk*, and 8–10% as *high risk* (14,17). With more aggressive, risk-adapted therapy, many of the outcome correlates are no longer significant, including mature B-cell or T-cell immunophenotypes, race, and gender (5,14,18).

Staging: CNS Involvement in ALL

The diagnosis of CNS disease in leukemia was standardized by the Rome Workshop as the presence of ≥ 5 WBC/ μL in the cerebrospinal fluid (CSF) with identifiable blasts or the presence of cranial nerve palsies believed to be related to CNS infiltration (19,20). Based on disease control in ALL studies through the 1990s, CNS disease is now classified as CNS 1 (no blasts), CNS 2 (blasts with <5 WBC/ μL), or CNS 3 (as above: ≥ 5 WBC/ μL and cytologic or biologic evidence of blasts in the CSF) (19). Studies at SJCRH showed that a traumatic lumbar puncture early in diagnosis/therapy (iatrogenic introduction of circulating blasts into the CSF) is equivalent to CNS 2 disease (21). The percentage of cases with positive CNS disease at diagnosis has been quite variable; recent large trials show 3–5% of children have CNS 3 status, but the proportion with CNS 2 status has varied between 5% and 10–30% (22). In most series, CNS 2 or CNS 3 at diagnosis is associated with a less favorable outcome; more intensive systemic and IT chemotherapy may reduce the impact of CNS 2, yet identifying CNS 3 as a negative finding at diagnosis (14,23).

Treatment: Chemotherapy

Therapy for ALL includes three components: remission induction, intensification (or consolidation), and continuation

therapy. Typical induction therapy combines corticosteroids (prednisone or dexamethasone), vincristine, and asparaginase or anthracycline (daunorubicin). Dexamethasone is often substituted for prednisone due to greater CNS penetration and longer half-life (5). Remission induction is successful in 97–99% of children (14,15).

Intensification (or consolidation) follows remission induction and incorporates aggressive drugs and regimens to continue maximal early cytoreduction. The most commonly used agents include methotrexate (MTX; at “high” dosages, typically 1–5 g/m² repeatedly during this phase), 6-mercaptopurine (6-MP), and asparaginase (also at high dosages). Reinduction is also a component of consolidation, shown to improve disease control (24,25). Patients with *BRC-ABL* fusion gene (Ph+) deficit and poor initial response (with (+) MRD) appear to benefit from allogeneic BMT in intensification (26).

Continuation therapy is a routine part of therapy for all ALL presentations except the rare mature B-cell type (the latter is treated with more intensive, less protracted chemotherapy). Continuation therapy is administered for ≥ 2 years (4,27). It is typically weekly MTX and 6-MP. The goal of continuation therapy is to eliminate residual, slowly replicating leukemic blasts or to sufficiently suppress leukemic cell division to allow programmed cell death to intervene.

Pharmacologic studies reveal biologically specific sensitivities to drug therapies: hyperdiploid cells show increased intracellular MTX, and lymphoblasts with TEL-AML1 expression are unusually sensitive to asparaginase—correlating with improved outcome in both biologic subsets given current therapeutic regimens (2,3,5). T-lineage lymphoblasts show lower concentrations of MTX’s active polyglutamate metabolites, correlating with improved outcome when treated with high-dose MTX regimens (2,3,5).

Long-term leukemia-free survival is now achieved in over 80% of children with ALL (28–30). Low-risk ALL can be cured in 90–95% of cases, while standard-risk patients can anticipate disease-free survival rates greater than 80%; children with high-risk features are reported to show EFS of 50–70% depending on the threshold for defining *high risk* (5,14,23,28,29).

Treatment: CNS Preventive Therapy Evolution of CNS Preventive Therapy in ALL

The initial concept for preventive CNS irradiation was derived from animal experiments with the mouse L1210 leukemia model: “leukemia control” was possible only when CNS irradiation was added to intraperitoneal chemotherapy (31). Investigators at SJCRH first applied the experimental model to children with ALL in the 1960s. Taking a “total” approach to the disease, they used induction chemotherapy (vincristine, prednisone) in sequence with prolonged, nonaggressive maintenance therapy (oral MTX and 6-MP) (32–34).

Early studies incorporated 5–12 Gy craniospinal irradiation (CSI) following the observation that CNS relapse was the dominant event once chemotherapy prolonged “hematologic remission” beyond 6–12 months (32). CNS preventive therapy evolved through serial studies at SJCRH and in Cancer and Leukemia Group B. CSI or cranial irradiation (CrI) to 24 Gy (the latter combined with intrathecal methotrexate [IT-MTX]) reduced the incidence of CNS

Table 2.1

Preventive CNS Therapy in Acute Lymphoblastic Leukemia—Major Recent Series

Series (Interval)	Subset	pCrI (% CrI) (Alternative pCNS Therapy)	n	EFS at 5 Years (%)	Isolated CNS Relapse (First Event) (%)
DFCC-95 ^a (1996–2000)	Standard risk (all)	CrI _{18 Gy} (100%) versus TIT ^j (0%)	272	86	0.7
			(CrI _{18 Gy} = 81) (TIT = 83)	86 83	0 2.4
	High risk	CrI _{18 Gy} (100%)	219	76	0.5
	Overall		491	82	
SJCRH TXIIIA ^b (1991–1994)	All	CrI _{18 Gy} (22%)	165	78	1.2
SJCRH TXIIIB ^c (1994–1998)	All	CrI _{18 Gy} (12%)	247	81	1.7
SJCRH TXV ^d (2000–2007)	All	Systemic, IT-MTX (0%)	498	86	2.7
CCG-1952 ^e (1996–2000)	CNS 3 Standard risk (all)	Systemic, IT-MTX (0%) IT-MTX versus TIT	9 2027	43 82	4.9 (1.6% CrI) ^k (5.9%) (3.4%)
ALL-BFM-95 ^f (1995–2000)	Standard risk	Systemic, IT-MTX (0%)	758	90	1.1
	Medium risk	Systemic, IT-MTX (0%)	1157	80	2.2
	High risk (and all T cells)	CrI _{12 Gy} (100%)	254	49	2.4
	CNS 3	CrI _{18 Gy} (≥ 2 year old)	16	59	
	Overall		2169	80	1.8
UK ALL 97/99 (1997–2002) ^{g,h}	Overall	CrI _{24 Gy} (3%)	1935	74–81	2.5–5
Dutch COG ALL-9 ⁱ (1999– 52004)	Overall	TIT (0%)	601	81	2.6
		TIT (0%)	21	67	14

^aMoghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood*. 2007;109(3):896–904.

^bPui CH, Boyett JM, Rivera GK, et al. Long-term results of Total Therapy studies 11, 12 and 13A for childhood acute lymphoblastic leukemia at St. Jude Children's Research Hospital. *Leukemia*. 2000;14(12):2286–2294.

^cPui CH, Sandlund JT, Pei D, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIB at St. Jude Children's Research Hospital. *Blood*. 2004;104(9):2690–2696.

^dPui CH, Campana D, Pei D, et al. Treatment of childhood acute lymphoblastic leukemia without prophylactic cranial irradiation. *N Eng J Med*. 2009;360(26):2730–2741.

^eMatloub Y, Lindemulder S, Gaynon PS, et al. Intrathecal triple therapy decreases central nervous system relapse but fails to improve event-free survival when compared with intrathecal methotrexate: results of the Children's Cancer Group (CCG) 1952 study for standard-risk acute lymphoblastic leukemia, reported by the Children's Oncology Group. *Blood*. 2006;108(4):1165–1173.

^fMoricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood*. 2008;111(9):4477–4489.

^gMitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukemia: results of the UK Medical Research Council ALL97 randomized trial. *Br J Haematol*. 2005;129(6):734–745.

^hVora A, Mitchell CD, Lennard L, et al. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukemia: a randomized trial. *Lancet*. 2006;368(9544):1339–1348.

ⁱVeerman AJ, Kamps WA, van den Berg H, et al. Dexamethasone-based therapy for childhood acute lymphoblastic leukemia: results of the prospective Dutch Childhood Oncology Group (DCOG) protocol All-9 (1997–2004). *Lancet Oncol*. 2009;10:957–966.

^jMethotrexate (IT), hydrocortisone, cytosine arabinoside.

^kCrI_{24 Gy} + Spl_{6 Gy} during consolidation for CNS 3 only.

relapse from >60% to <5–10% (32,35). Children in hematologic remission randomized to preventive CSI (24 Gy) or equivalent therapeutic CSI at the time of overt CNS relapse showed strikingly higher event-free and overall survival with preventive therapy (36). In addition, children cured following a CNS relapse had significantly greater functional deficits (e.g., seizure disorders and cognitive deficits) (37). Subsequent trials proved the relative equivalence of 18 Gy (at 1.5–1.8 Gy per fraction) and 24 Gy (similarly fractionated) for preventive CrI (38–41).

Other approaches to preventive CNS therapy were developed in the 1970s, with higher-dose systemic MTX and increased IT chemotherapy (39,40,42,43). Trials over the past 10–15 years have limited use of preventive CrI by progressively defining cohorts at higher risk for CNS relapse most likely to benefit from CrI—balancing the proven efficacy of CrI against radiation-related toxicities (in particular neurocognitive deficits and secondary neoplasms) and toxicities associated with the added CNS exposure to IT and systemic MTX (2,15,22,44–48). The Dana-Farber Cancer Institute (DFCI) Childhood ALL Consortium Protocol 95-01 included preventive CrI for 60% of children: all high risk (defined by WBC > 50,000/mL, T-cell ALL, Ph+ or t(9;22)) and, by randomization, half the standard risk (randomized to CrI vs. more intensive IT chemotherapy); girls with WBC < 20,000/mL were assigned to the IT arm. The high-risk cohort was randomized between 18 Gy in 10 fractions (180 cGy once daily) or in 20 fractions (90 cGy twice daily). The EFS and OS at 5 years were 82% and 90%, respectively; the rate of CNS relapse was 3% overall and 0.6% as an isolated event. CrI was associated with zero isolated or combined CNS relapses in the standard risk group; the IT group showed only <2% combined and 1% isolated CNS failures (2). There were no differences in neurocognitive function when intensive IT was compared to CrI₁₈ Gy (49). The German–Austrian–Swiss ALL-BFM-95 study limited preventive CrI (dose = 12 Gy) to those with T-cell ALL and high-risk disease above 1 year old (high early MRD, t(9;22) or BCR-ABL, or t(14;11) or MLL-AF4). Compared to the earlier ALL-BFM-90 trial, CrI was used in 10% instead of more than 50% of cases; even at higher thresholds of CrI, the BFM-95 therapy resulted in EFS of 80% and OS of 87% at 6 years. The rate of CNS relapse was 1.8% isolated and 4.1% overall (50). Comparing the earlier BFM-90 cohort (medium risk, age >1 year with pre-B-cell disease) to equivalent cases that did not

receive CrI on the BFM-95 trial, EFS was the same, but the overall (4.4% vs. 1.9%) and isolated CNS failure rates (2.2% vs. 0.5%) were statistically superior, if perhaps not clinically meaningful, following CrI₁₂ Gy. Isolated CNS failures occurred early and were associated with poorer outcome after therapy for CNS relapse, but represented a low percentage of events (50). The investigators noted not only the superiority of CrI, but also the higher rates of secondary carcinogenesis. Comparative outcome has also been addressed following CNS relapse in the BFM-95 trial; 58% secondary survival was observed 6 years after relapse and secondary brain tumors are yet at zero (3–4 years following CSI) (15). St. Jude Total XV trial was designed specifically to test eliminating preventive CrI and “therapeutic” CrI (i.e., for those with CNS 3 involvement at diagnosis), the first major US prospective trial assessing intensive IT and systemic chemotherapy to totally replace CrI (14). The impetus was based largely on the high rate of secondary neoplasms identified in the preceding St. Jude Total XII trial (12–20%) (28,51–53) (Fig. 2.4). Trials XIIB and XIIC had shown CNS relapse rates of 1.2% and 1.7%, respectively, with thresholds for preventive CrI resulting in 22% and 12% of participants receiving CrI, respectively (24). Total XV trial was powered to document a low rate of CNS relapse even in the highest-risk category, defined in the key Italian BFM report as T-cell ALL with WBC > 100,000/mL (14,54); only children with persistent CNS disease at conclusion of induction therapy were scheduled for CrI. On comparing the highest-risk cohort regarding CNS disease in Total XV trial with the 12% of similarly presenting patients who had received CrI on the earlier trial, EFS was statistically equal or better in the Total XV group without CrI (14). Despite the high overall EFS and low rate of CNS relapse, one must note the low rate of overall disease control (43%) in the CNS 3 small cohort with initial disease in a without use of CrI in this presentation (14,22,55).

Table 2.1 summarizes some of the major series reporting therapeutic approaches over the past 10–15 years. In sum, it is apparent that standard risk ALL can be treated without CrI (15,38,39,41,43). The group for which CrI may be beneficial is the cohort with T-cell ALL and presenting with WBC greater than 100,000/ μ L. Approximately 20% of children with T-cell ALL (or 2% of all children with ALL) present with high WBC and seem to benefit from preventive CrI (15,44). Because HD-MTX and IT-MTX have been associated with neurologic sequelae, there is also interest in considering

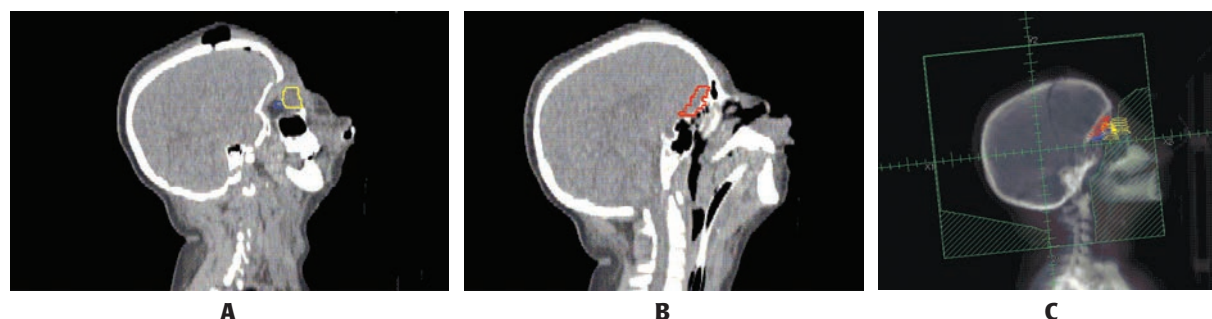


Figure 2.4 Craniospinal irradiation for CNS leukemia. **A:** Sagittal CT simulation reconstruction showing eye (yellow) and optic nerve (blue) at midorbital level; cranial irradiation for CNS leukemia includes the subarachnoid extension along the optic nerve sheath and the posterior retina (see Fig. 2.7). **B:** Midline sagittal CT simulation reconstruction showing the cribriform plate (red) along the lower midline skull base anteriorly; this is a critical target for full cranial irradiation. **C:** Outline of cranial irradiation volume providing margin at key anatomic regions (A and B) for craniospinal therapy in ALL.

further CrI dosage reduction (12 Gy/8 fractions in the more recent BFM studies) (39).

Current Recommendations for Preventive CNS Therapy

It is unclear whether absolute avoidance of CrI (preventive or “therapeutically” for overt CNS disease at diagnosis) reflects the best current understanding of the relative effectiveness and major toxicities of CrI and the more intensive MTX (systemic and IT) required in high-risk settings when not using CrI. Contemporary ALL regimens include indications for preventive CrI in 2–20% of children (22). There remain cohorts with T-cell disease and high WBC, Ph+ (t(9;22)) presentations, CNS 3 (and possibly CNS 2) at diagnosis, and B-cell precursor ALL with t(1;19) where the risk of CNS relapse exceeds 10% and the use of 18 (or 12) Gy preventive or therapeutic CrI may offer superior disease control (CNS, overall) with acceptable balance regarding known late toxicities (14,22,54–57). Major trials ongoing in 2009 are listed in Table 2.2, showing indications for preventive CrI.

Radiotherapeutic Management Volume

For preventive CNS therapy, the target volume includes the entire intracranial subarachnoid space. The key margins are at the skull base: the cribriform plate (the lowest point of the anterior cranial fossa, located in the midline at a level that is typically below the orbital roof) and the lower limit of the temporal fossa. It is a good practice to outline the cribriform plate to ensure adequate coverage (Fig. 2.5) (58). By convention, the lower border is at the inferior margin of the second cervical vertebra.

Documentation of retinal involvement as a late manifestation of CNS leukemia has led to a standard requirement to

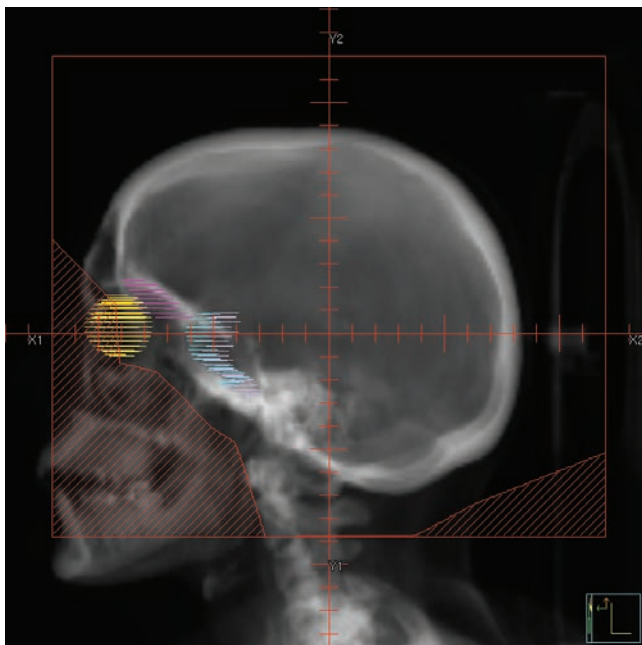


Figure 2.5 Lateral field for cranial irradiation in ALL. Note margin below cribriform plate (pink) and middle cranial fossa (blue). Targeted volume includes posterior eye (yellow) and orbit.

include the posterior retina and orbital apex, subtending the extension of the subarachnoid space around the optic nerves. Several techniques allow one to encompass the posterior orbit and globe while sparing the sensitive anterior aspect of the globe and lens. One approach uses inferior rotation of the gantry (i.e., angling the beam posteriorly for the supine patient) to achieve a parallel anterior margin at the bony orbital rim (59). Detailed studies indicate that one needs to accept a dosage approximating 20% to the lens in order to adequately cover the cribriform plate (60). Dosimetric studies have suggested that custom beam blocking may improve treatment when compared with a multileaf collimator alone (58).

Dosage

Dosages for preventive CrI range from 12 to 18 Gy in current protocols. Fractionation typically is at 150–180 cGy once daily (2,22,25). A study at DFCI in Boston showed no difference in efficacy or apparent toxicity between conventional irradiation (180 cGy $\times$ 10) and hyperfractionated CrI (90 cGy twice daily to 18 Gy) (2,41,49).

Treatment of Established CNS Leukemia CNS Leukemia at Diagnosis

CNS leukemia is present at diagnosis in 3–5% of children (19,50,61). Under the “CNS staging” system proposed by Mahmoud, up to 20% of children at diagnosis show positive CSF cytology, but the incidence of true CNS leukemia (CNS 3: positive CSF cytology and WBC greater than 5/ μ L) is approximately 5% (19,25,38,50,62). Earlier trials found CNS leukemia at diagnosis associated with a negative outcome. More intensive systemic and IT chemotherapy has successfully eliminated CNS relapse in children with CNS 2 disease (positive CSF cytology and WBC less than 5/ μ L) (19,25,38,50,62). Therapeutic CrI or CSI has been used in most series for children with CNS 3 disease; the impact of CNS involvement on outcome has been diminished and, in some series, eliminated with such intervention (50,61,63). Nevertheless, the ALL-BFM-95 trial showed 6-year EFS of only 58% with CNS 3 at diagnosis (following therapeutic CrI systematically at 18 Gy) compared to 80% overall 6-year EFS, and SJCRH Total XV trial showed 5-year EFS of 43% (with CrI only for residual CNS disease after induction) compared to 86% overall 5-year EFS (14,15). The latter series obviating irradiation except with residual CSF positivity after induction therapy showed excess CNS and hematologic relapse and death (14).

Radiotherapeutic Management

Most current protocols include consolidative CrI after intensification therapy for children with CNS 3 disease at diagnosis (Table 2.2). The recommended dosage of CrI is 18 Gy, based on 150–180 cGy fractions daily.

CNS Relapse

Despite CNS preventive therapy, 1–8% of children sustain an isolated CNS relapse (i.e., in the presence of continuous, maintained hematologic remission) (22). CNS relapse is asymptomatic at diagnosis (i.e., detected by routine surveillance lumbar puncture) in 75% of cases. Symptoms and signs are apparent in 25% of children with CNS involvement and include headaches with or without vomiting, papilledema, cranial nerve palsies

Table 2.2**Indications for Preventive Cranial Irradiation (pCrI)—Contemporary Studies (2009)**

Study Group or Institution	Indication(s)	% of All Cases Projected to Receive pCrI	CrI _{dose}
AIEOP (Italian Association for Pediatric Hematology Oncology)	T cell with WBC $\geq$ 100,000/dL	15	CrI ₁₂ Gy 1–2 year old
	B precursor with poor initial response to prednisone, t(4;11) or t(9;22), minimal residual disease (MRD) $>$ 0.1% at the end of induction		CrI ₁₈ Gy $\geq$ 2 year old
	CNS 3 at diagnosis		CrI ₁₈ Gy 1–2 year old CrI ₂₄ Gy $\geq$ 2 year old CrI ₁₂ Gy
BFM (European, German-led)	T cell and over 1 year old	10	CrI ₁₂ Gy 1–2 year old
COG	B precursor with high risk $>$ 1 year old		CrI ₁₈ Gy $\geq$ 2 year old CrI ₁₂ Gy
	CNS 3 at diagnosis	20	CrI ₁₈ Gy
	T-cell high risk		CrI ₁₈ Gy
DFCI (Dana-Farber Cancer Institute, Boston)	B precursor with slow early response (MRD $>$ 0.1% at the end of induction)		
	CNS 3 at diagnosis	20	CrI ₁₂ Gy
	T cell		CrI ₁₈ Gy
SJCRH Total XVI trial (St. Jude, Memphis)	B precursor with WBC $>$ 100,000/dL or rearranged MLL gene or hypodiploidy or MRD $>$ 0.1% at the end of induction		
	CNS 3 at diagnosis	0	
	None		
UKAU (United Kingdom)	CNS 3 $>$ 2 year old	2	CrI ₂₄ Gy

Modified and updated from Pui CH, Howard SC. Current management and challenges of malignant disease in the CNS in paediatric leukaemia. *Lancet Oncol.* 2008;9(3):257–268.

(most often VI and VII; also V), hyperphagia, and CNS hemorrhage (presenting with headaches, seizures, change in mental status, and/or focal neurologic signs) (22,64,65).

Therapy for isolated CNS relapse includes systemic chemotherapy for reinduction, IT chemotherapy (MTX alone or in combination with cytosine arabinoside and hydrocortisone) to clear the CSF, and irradiation. Clinical trials documented CNS control following neuraxis irradiation, but overall disease control was observed in only 50–70% of children after isolated CNS relapse following reinduction and consolidation chemotherapy with CNS irradiation (64,66–70). Recent documentation of “submicroscopic” bone marrow involvement (using PCR or PCR and immunoglobulin gene rearrangement) in children with “apparently isolated” extramedullary relapse has provided biological proof of the clinically long suspected link between overt extramedullary and occult bone marrow ALL (71).

Serial trials in the Pediatric Oncology Group (POG) confirmed the benefit of initial systemic and IT chemotherapy

for isolated CNS relapse: POG 9061 was the first large prospective experience interposing 6 months of chemotherapy prior to CSI (24 Gy/16 fx CrI, 15 Gy/10 fx SpI); secondary EFS was 71% (64). The study also confirmed that early CNS relapse ($<$ 18 months post-diagnosis) was much more aggressive, with secondary 4-year EFS only 46% compared to 83% for those who relapsed later than 18 months (64). As in most series after 1985, failures were predominantly in the bone marrow, leading to POG 9412 that tested 1 year of systemic and IT chemotherapy followed by delayed “risk-adapted” CNS irradiation: CrI to 18 Gy for CNS relapse $>$ 18 months after diagnosis and CSI to 24 Gy CrI/15 Gy SpI for earlier CNS relapse (72). Results were similar to the earlier trial: 52% 4-year EFS with early CNS relapse versus 78% with relapse $\geq$ 18 months post-diagnosis (72). The other significant factor related to outcome was the NCI risk group (high risk, age $<$ 1 or $>$ 10 years; WBC $>$ 50,000 mL at diagnosis); children in the high-risk group had a four-time greater likelihood of relapse following isolated CNS relapse (72).

Volume and Dose

CrI, as described above, is adequate for CNS relapse occurring beyond 18 months after diagnosis; the current standard is 18 Gy (at 150 cGy once daily). There is an ongoing assessment of further reducing the cranial dose in late-relapsing CNS leukemia to 12 Gy, but it is yet premature to use the data as a standard for management. For those with early relapse, CSI is standard with 24 Gy to the cranium and 15 Gy to the spine. Ongoing trials testing 18 Gy in the latter setting are yet inconclusive.

Techniques are identical to that described earlier in this chapter for CrI. For CSI, the basic technique is summarized in Chapter 4; noteworthy is the modification of the cranial volume to include the posterior ocular globe (unique to leukemia; an area not included with primary CNS tumors treated with CSI). Coordination of neuraxis irradiation and TBI during BMT is considered below.

Treatment of Other Extramedullary Sites

Testicular Leukemia

Treatment of ALL in the 1980s was associated with a significant risk of testicular relapse. Approximately 5–10% of boys presented with overt testicular leukemia representing 10–20% of all failures (70,73). Testicular relapse was typically a late event, occurring at a median of 3 years post-diagnosis (70,73). The occurrence was related to high-risk features (e.g., T-cell phenotype and high WBC at diagnosis) (70). Testicular relapse seems to represent a sign of inadequate systemic disease control rather than a true “sanctuary site” analogous to the CNS. Enhanced systemic disease control, particularly the introduction of high-dose MTX into prolonged intensification regimens, has largely eliminated the occurrence of testicular relapse since 1990 (74).

Radiotherapeutic Management

Treatment of testicular relapse involves systemic chemotherapy; systematic testicular irradiation has been eliminated from most current treatment regimens, reserving irradiation for documented residual testicular infiltration following reinduction chemotherapy (70,75). The ongoing national COG trial is prospectively reserving irradiation for disease persistent after high-dose MTX and induction chemotherapy (documented by biopsy of testes enlarged at completion of induction). The Dutch Late Effects Study Group has reported successful management of testicular relapse without local irradiation (75). Although late failure may be associated with only unilateral involvement, most instances present with clinical or histologic evidence of bilateral infiltration (73). When indicated, irradiation is directed to both testes, usually by *en face* electron beam, calculating the energy to deliver 90% of the dose to the posterior aspect of the testes based on measurements in the treatment position. Attention to daily positioning is important, ensuring the descent of the testes into the scrotum during therapy. The recommended dosage is 20–24 Gy, usually given at 200 cGy per fraction (73). The interest in limiting use of irradiation reflects the sterility and Leydig cell hypofunction following irradiation. There is yet preliminary data using chemotherapy alone, reserving orchiectomy for local disease control in boys who do not show prompt, histologically verified disease control.

Other Sites of Extramedullary Disease

Other sites of extramedullary relapse are uncommon, representing less than 2% of failures (70). An unusual pattern of involvement is disease confined to the anterior chamber of the eye. Unlike diffuse retinal disease that is associated with CNS leukemia, limited anterior chamber leukemia seems to be an isolated phenomenon. Management with *en face* electrons superficially irradiating the eye has been successful at dosages of 12 Gy/6 fractions (76,77). Other sites of extramedullary involvement have included lymph nodes, ovaries or uterus, and bone (70). In the uncommon situation in which local extramedullary disease fails to respond to reinduction chemotherapy, or in the rare patient with truly sizable local disease, it is appropriate to consider local irradiation as consolidation either after intensification chemotherapy or in conjunction with BMT.

ACUTE MYELOGENOUS LEUKEMIA

Approximately 20% of children with leukemia present with AML, representing nearly 500 children per year in the United States; over half the leukemic deaths in US children occur with this form of leukemia (78). The disease occurs throughout the pediatric age range, with greater frequency in newborns and during adolescence. There is a high incidence of AML among young children with Down syndrome (78). Presenting symptoms include pallor, fatigue, bleeding, infection and fever, or leukostasis. Organomegaly at diagnosis is less common than in ALL. Localized extramedullary tumor deposits (chloromas or “granulocytic sarcomas”) are rarely noted but can present as symptomatic masses involving the head and neck region, spinal cord, or brain. The initial WBC typically is below 50,000/mL; about 20% of cases present with hyperleukocytosis (WBC greater than 100,000/mL). Clinical features associated with outcome include ethnicity, age, and body weight: African Americans, older age (>2 years and increasing age), and overweight habitus are associated with poorer outcome (79–82).

CNS disease is documented at presentation in 5–15% of cases (22). CNS disease at diagnosis is associated with high peripheral WBC, age <2 years, and ironically favorable cytogenetic characteristics (t(1;11), t(8;21), inv(16)) (83).

AML has classically been categorized by cytomorphology, based on the French–American–British (FAB) classification and increasingly by molecular characteristics (79). The common morphologic feature is the presence of Auer rods in cytoplasm of leukemic blasts. Cell types indicate primarily myeloblastic, monoblastic, or megakaryocytic AML; the megakaryocytic form is common with Down syndrome and associated with favorable prognosis (78). Cytogenetic abnormalities have been documented in a majority of children with AML. One of the most common findings is translocation t(8;21), associated with *AML1*, a gene encoding *AML1*–*CBFβ*, a transcription factor essential for normal hematopoietic development (79,84). The t(8;21) is often combined with inversion of chromosome 16 (inv(16)) as “core binding factor” AML, commonly present in AML M2; the t(8;21) translocation and inv(16) identify favorable disease (79,84,85). The t(9;22) translocation is associated with a poor outcome. Favorable AML (with t(8;21), inv(16); MRD < 0.1% after induction), high-risk disease (t(6;9), –7, –5, –5q; FAB M0 or M6, FAB M7; MRD > 5% after the first induction or >1% after the second induction), and intermediate

risk AML (all others) are associated with 78%, 42%, and 55% 5-year survival, respectively (10,11,78, 79,86–88).

The mainstay of treatment for AML has been induction with daunorubicin (or idarubicin) in conjunction with cytarabine and etoposide; gemtuzumab may be included (79,89–92). Current regimens result in 40–50% event-free survival rates in children. Even more so than in ALL, the finding of MRD upon completion of induction, by molecular or genetic analysis, is associated with a poor outcome (88). Postinduction therapy is somewhat controversial, data suggesting either intensified consolidation chemotherapy or the use of matched sibling or matched unrelated stem cell transplant (SCT) (93). Although early experience in pediatric AML had failed to prospectively identify a benefit with marrow transplant, trials in POG and CCG demonstrated an apparent survival advantage for allogeneic transplant (matched sibling SCT) when compared with chemotherapy alone or autologous transplant (90,91,93). Conflicting data from the United Kingdom MRC studies show that even matched sibling donor SCT reduced the frequency of relapse without improving survival (92). Summary recommendations currently indicate use of SCT (matched, related donor; increasingly, also matched unrelated/haploidentical donor) with high-risk AML in first remission; indications in intermediate risk beyond poor early responses are controversial (79,94).

Extramedullary Disease

Extramedullary disease is relatively common in AML at diagnosis. A Japanese cooperative group series found signs of extramedullary leukemia in 23% of children. Disease was most often epithelial (skin as nodules or infiltration in 26% of such cases; gingival, 14%; CNS, 14%; bone, 10%; orbital, 8%) (95). The incidence of extramedullary disease in all sites in earlier BFM studies was similar, while POG reported a lower incidence of extramedullary AML outside the CNS (i.e., 7–10%) (95–97). Extramedullary involvement is associated with high WBC and myelomonoblastic or monoblastic subtypes (FAB M4, M5) (95,98). The incidence of CNS involvement at diagnosis exceeds that seen with ALL, approximating 10–15% in pediatric AML (22,45,51,83). In serial St. Jude trials, the incidence of CNS 2 disease (blasts present but WBC <5 mL in the CSF) was 12% (83). Associations with CNS disease at diagnosis are noted above; the combination of CNS disease at diagnosis with other extramedullary involvement and WBC > 100,000/mL has been related to a high frequency of relapse (95). The overall outcome in patients with CNS leukemia initially varies in the literature; the outcome over four consecutive St. Jude trials suggests better survival for those with CNS 3 at diagnosis, many of whom received CrI therapeutically as a part of primary therapy (83). More recent experience, with limited numbers, suggests similarly favorable outcome may relate more to associated favorable cytogenetics seen in the CNS cohort than an impact of therapy (83,95).

CNS Disease: Radiation Therapy

Preventive CrI has not been utilized in North American AML trials over the past two decades. The BFM group studied the impact of CrI prospectively in AML-BFM-87, randomizing children without CNS disease to 18 Gy CrI or enhanced systemic chemotherapy. The randomization was stopped early due to the lack of excess CNS relapse in the nonirradiated group, but final analysis actually showed a higher rate of both

CNS and systemic relapse in the cohort who did not receive CrI. Subsequent BFM trials have incorporated CrI for children >1 year old. Other studies without CrI over the same interval failed to show excessive CNS failure in AML (22,92,99,100). In the St. Jude trials using CrI only when blasts were present in the CSF, the incidence of CNS relapse was 3% for those with CNS 1 disease and 6% for CNS 2 disease without CrI (83). In the larger CCG 2891 trial, the 8-year cumulative risk of CNS relapse was 4.8%, essentially all within the first year of therapy (98). As in other reports, patients with isolated CNS relapse tended to be under 2 years of age and M5 subtype; other extramedullary involvement and high WBC were noteworthy at diagnosis (98).

Management of CNS relapse in AML is most often with intensified intrathecal cytosine arabinoside (ara-C, with or without MTX); it has been difficult to evaluate the potential efficacy of CrI in a setting where bone marrow relapse rapidly follows apparently isolated CNS failure (22,98). Treatment of focal infiltrates (“chloromas”) may be required for symptom control or consolidation, the latter primarily a concern for larger tumor-like infiltration in and around the CNS. AML is exquisitely sensitive to irradiation; symptomatic and measurable response is often apparent after 12–15 Gy. Consolidative therapy has been reported to be effective at 18 Gy; lesions that show incomplete response to chemotherapy may require 21–27 Gy focally in our experience (22,95).

Hematopoietic Stem Cell Transplantation (HSCT)

HSCT is a unique technique designed to allow higher dosages of antineoplastic agents (chemotherapy, TBI) that are concurrently immunosuppressive, then “rescue” the attendant hematosuppression by engrafting new hematopoietic stem cells from bone marrow or peripheral circulating stem cells to repopulate the bone marrow. HSCT can also result in an immunotherapeutic antineoplastic effect by tumor lysis releasing antigens that stimulate host T cells or by donor cells attacking residual host hematopoietic cells (101,102). Graft-versus-leukemia effects are associated with matched unrelated or haploidentical transplants (and typically not with matched sibling HSCT) (101,103). Developed initially by Donnell Thomas and colleagues at Fred Hutchinson Cancer Research Center, BMT has been used predominantly in leukemias, malignant lymphomas, and other hematologic disorders in both children and adults, as well as in genetic diseases (e.g., aplastic anemia, Fanconi syndrome, sickle cell disease, thalassemia, and osteogenesis imperfecta) (101–106).

The principles of HSCT include a conditioning regimen (“supralethal” doses of chemotherapy most often with TBI) and successful engraftment of extrinsic hematopoietic stem cells. Initial work in BMT focused entirely on allogeneic transplantation, typically relying on a sibling or related donor found to be histocompatible based on human leukocyte antigen (HLA) typing. In leukemias, the cytoreductive therapy is intended both to eliminate residual lymphoblasts or myeloblasts and to immunosuppress the host so that the donor marrow is accepted (102–104). The use of HLA-matched, unrelated donors necessitates more significant immunosuppression while providing more potent antineoplastic immunotherapy to patients who lack a matched sibling donor (105–107). Unrelated donor transplants are more problematic in that the greater degree of immunosuppression

needed to ensure engraftment and associated antihost immunoreactivity (graft-versus-host disease, GVHD) is associated with decreased relapse but increased treatment-related mortality (101,107,108). Syngeneic transplants (in which an identical twin is the donor) and matched sibling donor allogeneic transplants are better tolerated (i.e., less often associated with GVHD), but show higher rates of relapse (101,102).

Autologous transplants use the patient's own HSC (either from bone marrow or peripheral circulating stem cells), harvested and stored before the conditioning regimen, to repopulate the patient's own bone marrow following high-dose chemotherapy. Autologous procedures are used in hematologic malignant diseases and increasingly selected "solid tumors" in children and adults where drug intensity has been associated with improved outcome (93,94,101,106).

The "standard" conditioning regimen is high-dose cyclophosphamide (CY) and TBI (CY/TBI) (27,97,101, 103,107). The most commonly used non-TBI alternative is busulfan (BU) and cyclophosphamide (BU/CY) (107,109–111). Management of AML in remission and relapsed ALL are the most common indications for HSCT in children and adolescents; data suggest that CY/TBI is superior to BU/CY in the first or subsequent relapse of ALL, including a randomized trial showing 2-year EFS of 58% with TBI versus 29% with BU, differences favoring TBI being more significant with matched unrelated than sibling matched transplant (107,109).

HSCT in Children and Adolescents

Acute Myeloblastic Leukemia

Consolidation of remission in childhood AML was one of the earlier successes in BMT (112). The overall disease-free survival rates of AML approximate 50–60%. There has been a debate over the impact of postinduction intensification. Recent trials suggest a relationship between drug intensity and survival after remission (78,79,89–92, 106,113). Recent data further substantiate the advantage of myeloablative therapy with SCT (bone marrow or peripheral circulating stem cells) in children and adolescents with (1) intermediate or high-risk presenting biologic features (presence of isochromosome 7 or 5 [or –5q]) or FCT3 mutation, or (2) low-risk disease (inv(16) or t(8;21)) but clinical factors (age > 10 years, WBC > 50,000/mL) or response to induction therapy (MRD or >15% blasts at the end of induction, initial CR <1 year at relapse) requiring management as high-risk (79,80,87, 90,106). Initial intensive systemic induction chemotherapy induces remission in 80–90% of children/adolescents (79,89,90,92,113). AML treated in first remission (CrI) with matched sibling donor HSCT enjoy up to 70–75% 5-year EFS and OS; results are superior to those with autologous stem cell rescue (94,106,110,114). There appears to be advantage to matched unrelated donors where the inherent graft-versus-leukemia immunoregulation decreases the incidence of relapse; higher rates of treatment-related mortality in the latter setting limits the advantage in overall survival (106,110,111). For children with residual leukemia after induction or postinduction relapse, the only curative approach is transplantation. Allogeneic transplants (in second remission) result in survival rates of approximately 20–40%, depending on the length of first remission (84,114,115).

Acute Lymphoblastic Leukemia

The role of HSCT in pediatric ALL is typically limited to management of first or subsequent relapse; use in first relapse

when confined to extramedullary disease (especially isolated CNS relapse) is controversial (101,116,117). HSCT is considered in children with early relapse (within 3 years of initial remission); the use of higher-dose chemotherapy with HSCT *prior* to documented relapse is variably suggested with poor initial response to induction therapy or genetic determinants of high-risk disease (Ph+, t(9;22) or *BRC-ABL* or *MLL-AF4* fusion genes, or t(4;11)) (14,101,118,119). Outcome depends on disease state; several studies demonstrate long-term survival rates greater than 65% for high-risk ALL transplanted in first relapse (119–122). Comparable studies in relapsed ALL show an advantage for HSCT, particularly in children with early relapse (101,123).

Allogeneic transplantation in ALL results in low rates of transplant-related mortality following matched sibling transplant and low rates of relapse with matched unrelated or haploidentical transplants (101,107,108,118,120).

The role of TBI has been addressed in children with ALL treated with allogeneic transplant using HLA-matched sibling donors. Retrospective comparisons using data from the International Bone Marrow Transplant Registry have reported CY/TBI to be superior to BU/CY in preventing relapse, reducing treatment-related mortality, improving overall treatment failure, and reducing overall rate of mortality (107,117). The addition of etoposide to CY/TBI may further improve disease control and overall survival (124). For patients with extramedullary relapse (i.e., CNS, testis), the addition of local irradiation before (cranial) or during (testicular) the conditioning regimen results in excellent local disease control and outcomes equivalent to or better than those with hematologic relapse alone (116,117,119,120,125). Overall disease control following TBI-based HSCT has been excellent with isolated CNS relapse; series show 0–20% post-transplant relapse and 0–13% treatment-related mortality (both figures superior to HSCT data for hematologic response); the influence of timing of CNS relapse (prior to or later than 18 months after initial remission) is also documented in HSCT series (116,117,120).

Other Hematologic Diseases

Fanconi anemia is an autosomal recessive disease characterized by progressive pancytopenia, growth retardation, urinary tract abnormalities, microphthalmia, and cardiac malformations. The disease is associated with a number of chromosomal aberrations and is invariably fatal as a result of progressive marrow aplasia or the development of leukemia (126). HSCT is potentially curative as "genetic therapy," reversing the underlying genetic clone and reintroducing normal hematopoiesis in approximately half the children without leukemic conversion (126–128). Transplant programs at some institutions rely on cyclophosphamide alone for those without overt leukemia based on greater radiation sensitivity in children with Fanconi anemia. Other institutions use thoracoabdominal irradiation at reduced dose (typically 5 Gy in one fraction) (128). Patients with leukemic conversion are treated with TBI at standard or reduced dosages similar to techniques used in other acute childhood leukemia settings.

Aplastic anemia is characterized by marrow hypoplasia and pancytopenia. The disease may be associated with chemical exposures or abnormal response to infectious or other agents; often, the origin is not apparent. Allogeneic HSCT can be curative (110,129–131). Because it is a nonmalignant disorder, the conditioning regimen often is chemotherapy alone

(cyclophosphamide with an additional alkylating agent). When additional immunosuppression is needed (e.g., initial failure at engraftment, incompletely matched donor), TBI or, preferably, total lymphoid irradiation (TLI) is a part of the conditioning regimen (110,129,131). The latter has the advantage of sparing significant pulmonary irradiation while including sufficient volumes of the marrow and immune system to ensure engraftment (129).

Radiotherapeutic Management

Volume

TBI is a fundamental component of HSCT in most malignant hematologic and many genetic disease states. The target volume encompasses the entire body. Techniques include a variety of physical configurations to achieve a field size

adequate to subtend the entire body. For infants and small children, an anterior–posterior (AP:PA) configuration on the floor often allows sufficient field size and easy reproducibility. For larger children and adolescents, one of the extended distance techniques uses opposed lateral fields, providing stable positioning and some degree of tissue compensation from the arms to reduce the excess lung dose secondary to increased transmission through the lungs. AP:PA techniques (achieved with sitting or standing positions or with the supine or prone body rotated to be roughly perpendicular to the incident beam) offer the advantage of partial blocking for compensation or diminution of dose to critical structures (most often lungs; in some instances, kidneys) (132,133) (Figs. 2.6 and 2.7).

The incidence of interstitial pneumonitis is one of the major dose-limiting, regimen-related, often fatal acute

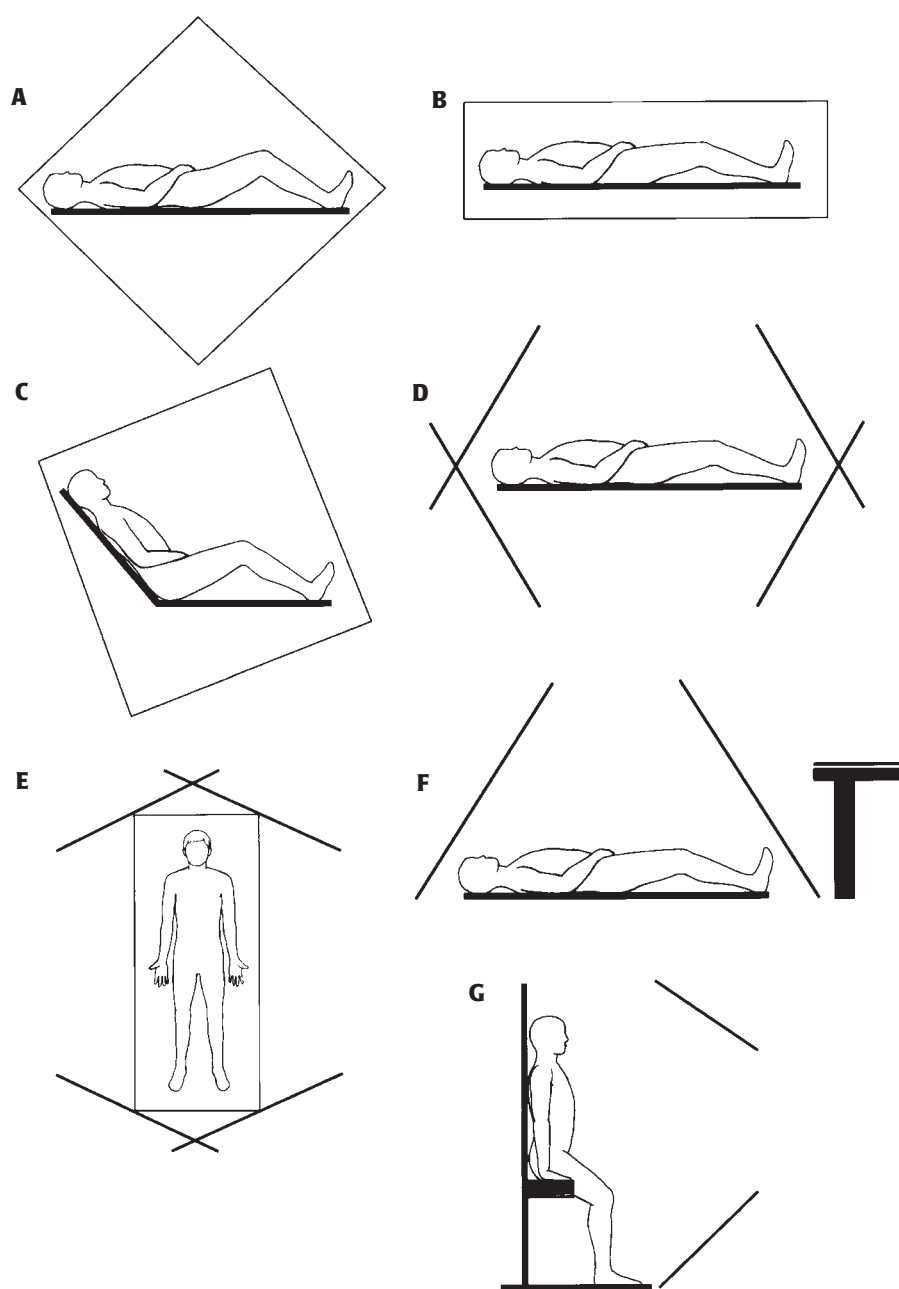


Figure 2.6 A: A wide variety of techniques are available for administering total body irradiation (TBI). The techniques include (A) a lateral approach with the patient supine and the collimator of the treatment machine rotated to fit the patient in the beam. B: A lateral approach with the patient supine and distant from the treatment machine so that a rectangular beam can be used. C: A lateral approach with the patient in a semirecumbent position and the collimator of the treatment machine rotated to fit the patient in the beam. D: A specially prepared TBI suite with one treatment machine mounted in the ceiling and one in the floor, with the patient placed on a treatment couch between the units. E: A specially prepared TBI suite with two machines mounted at opposite ends of the room, with the patient irradiated in the lateral position while on a treatment couch between the units. F: A conventional couch to obtain the necessary extended distance. G: The patient seated on a specially constructed seat to allow anterior and posterior treatment (some institutions use lung shielding during the photon treatment and then “boost” the ribs with electron beams).



A



B

Figure 2.7 A: “AP:PA” technique using supine/prone positioning, respectively, on rotating couch (St. Jude), patient secured with whole body Vac-Loc and rotated 90° to provide incident lateral beam. Shown PA with lung compensators. B: Simple “AP:PA” on-the-floor technique for infants subtended by vertical beam. Show PA with lung compensators.

toxicities; the cause is multifactorial including transplant mode (syngeneic associated with the lowest incidence, allogeneic associated with an incidence that parallels the severity of acute GVHD), the combined conditioning regimen, and the radiation dose, dose rate, and fractionation (121,132–139). Most current techniques compensate for added transmission through the measured lung volume and also deliver a dosage to the midplane of the lungs 10–15% lower than the dose to the “total body”; heterogeneity-corrected dose levels of ≤ 9 –9.5 Gy are suggested to reduce serious pulmonary complications when planning approximately 12 Gy TBI (120,132,133,135,136,139,140). Lung blocks should include the pulmonary volumes identified on AP:PA radiographs, typically excluding the upper mediastinum (i.e., thymus) from the lung shields. In lateral body techniques, the added width of the thorax in most children and adolescents compensates for the lung transmission. Tomotherapy has been used to deliver total marrow/total lymphoid irradiation, the helical techniques providing

targeted marrow/lymphoid doses while delivering 50–80% less dose to critical viscera (137,141).

Based on an initial testicular failure rate in 4 of 28 boys, Shank and colleagues at Memorial/Sloan–Kettering Cancer Center (142) recommended the addition of a testicular “boost” in TBI. The use of a 4 Gy testicular boost essentially eliminated testicular relapse. A subsequent French experience (with TBI and high-dose cytosine arabinoside–busulfan) used 12 Gy TBI in six fractions or 9–10 Gy as a single fraction with no testicular boost in two thirds of the boys treated; no testicular failures were recorded (120).

Children with isolated CNS relapse may benefit from CrI given immediately before the start of the conditioning regimen. CrI to 6–12 Gy in 4–8 fractions timed to be in close temporal proximity/continuity with TBI has resulted in essentially eliminating second relapse without transplant-related mortality in series reporting HSCT for isolated CNS relapse (116,117,120).

Dosage (Hematologic Malignancies)

The initial experience with TBI was based on a single fraction of 9–10 Gy (134,143,144). Modifications in TBI delivery were stimulated by the occurrence of interstitial pneumonitis. Initial studies indicated a relative sparing by reducing the dose rate below 10 cGy per minute; in parallel, a change to fractionated TBI was suggested (114,134,136,145–147). Subsequent trials have generally indicated improvement in the therapeutic ratio with fractionated delivery based on one or two fractions per day (104,112,135,148). The most commonly used schedules include 2 Gy administered twice daily to 10–12 Gy at an instantaneous dose rate of 5–10 cGy per minute (112,120,135,148). Recent reports of reduced-dose “traditional” TBI at 8 Gy in one fraction show engraftment and perhaps reduced toxicity (149); this differs from the low-intensity TBI regimens (2 Gy total in one fraction) in non-myeloablative regimens relying on graft-versus-leukemia effect with chimerism (101). Somewhat higher dosages have been used in study settings: 225 cGy once daily to 15.5 Gy or 1.75 Gy twice daily to 14 Gy (133,148). Alternative adult schedules deliver up to 12 Gy in 3–3.3 Gy fraction once daily (121,136). The range of fractionation regimens attests to the flexibility apparent at low-dose levels for TBI (i.e., 8–10 Gy single fraction or 10–12 Gy fractionated). Suggestions that more fractionated regimens are better tolerated in terms of acute pulmonary and late visceral effects are difficult to prove across institutions and trials; correlations between radiation parameters and lower rates of untoward renal effects, for example, identify both increased fractionation and instantaneous lower dose rate (134,150). Higher doses are typically used with matched unrelated donor BMT (151). There is some suggestion that dosages beyond 14 Gy are associated with greater risks of TBI-related toxicities (148,152).

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Supratentorial Brain Tumors

Larry E. Kun, Shannon MacDonald, and Nancy J. Tarbell

Twenty percent of all neoplasms in children arise in the central nervous system (CNS). The incidence of CNS tumors in children has increased over the past three decades (1). The relative frequency of brain tumors by site and histology is indicated in Table 3.1. The current World Health Organization (WHO) classification of CNS neoplasms is summarized in Table 3.2 (2).

Over half of pediatric CNS tumors arise in the supratentorial brain. Anatomically, the supratentorial cranial compartment (Fig. 3.1) includes the cerebral hemispheres (frontal, parietal, temporal, and occipital lobes), the diencephalon (hypothalamus, the optic chiasm, and the thalamic, caudate nucleus, putamen, and basal ganglion structures, the latter generally considered together as the thalamic region), the pineal region (pineal gland and posterior third ventricular region), and the sellar/suprasellar region. Tumors can be

Table 3.1

Common Brain Tumors in Children – Relative Incidence

Supratentorial tumors	50–55%
Astrocytoma	23%
Malignant gliomas (anaplastic astrocytoma, glioblastoma multiforme)	6%
Craniopharyngioma	6%
Embryonal tumors (PNET and others)	4%
Pineal region tumors/ intracranial GCTs	4%
Ependymoma	3%
Oligodendroglioma	2%
Other (meningioma, ganglioglioma, gangliocytoma, choroids plexus tumors, others)	2%
Infratentorial tumors	45–50%
Medulloblastoma	15%
Astrocytoma	15%
Brainstem glioma	10%
Ependymoma	6%
AT/RT	1%

PNET, primitive neuroectodermal tumor; GCTs, germ cell tumors; AT/RT, atypical teratoid/rhabdoid tumor.

From Refs. 2, 146, and 150, with permission.

Table 3.2

Histopathologic Classification of CNS Tumors—WHO Classification 2007

- Tumors of neuroepithelial tissue
 - Astrocytic tumors (astrocytoma, anaplastic astrocytoma, glioblastoma, pilocytic astrocytoma, pleomorphic xanthoastrocytoma, subependymal giant cell astrocytoma)
 - Oligodendroglial tumors (oligodendroglioma, anaplastic oligodendroglioma)
 - Ependymal tumors (ependymoma, anaplastic ependymoma, myxopapillary ependymoma)
 - Mixed gliomas (oligodendroglioma, others)
 - Choroids plexus tumors
 - Neuronal tumors (gangliocytoma, ganglioglioma, desmoplastic infantile neuroepithelioma, dysembryoplastic neuroepithelial tumor, central neurocytoma)
- Pineal parenchymal tumors (pineocytoma, pineoblastoma)
- Embryonal tumors
 - Medulloepithelioma
 - Neuroblastoma
 - Ependymblastoma
 - Primitive neuroectodermal tumors
 - Medulloblastoma
 - Cerebral (supratentorial), spinal PNET
- Tumors of meningotheial cells
 - Meningioma
 - Malignant meningioma
- Tumors of the uncertain histogenesis
 - Hemangioblastoma
- GCTs
 - Germinoma
 - Embryonal carcinoma
 - Endodermal sinus tumor
 - Choriocarcinoma
 - Teratoma
 - Mixed GCTs
- Tumors of the sellar region
 - Pituitary adenoma
 - Craniopharyngioma

PNET, primitive neuroectodermal tumor; GCTs, germ cell tumors.

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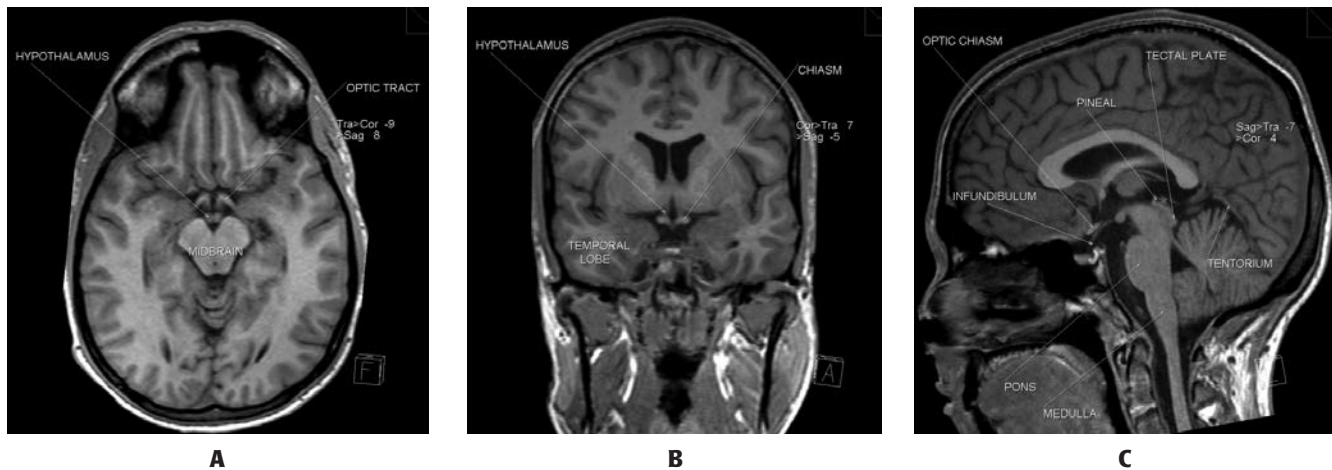


Figure 3.1 **A:** Axial MRI demonstrating key anatomic sites from the interorbital frontal lobes, through the superior suprasellar region (optic tracts, hypothalamus), midbrain, and superior cerebellar vermis (posterior to midbrain). **B:** Coronal MRI through central suprasellar location with posterior chiasm, hypothalamic nuclei, anterior aspect of third ventricle (between R and L hypothalamic nuclei), lateral ventricles (above third), and mid-temporal lobes. **C:** Sagittal MRI demonstrating supratentorial brain, tentorium and underlying cerebellum (with central fourth ventricle), brainstem (pons with medulla below and tegmentum of midbrain contiguously above), tectal plate (cerebral aqueduct delineates this in midline from anteroinferior tegmentum), pineal gland, and suprasellar structures (optic chiasm and infundibulum of pituitary-hypothalamic stalk).

categorized by anatomic region, correlating with clinical signs and specific histotypes: suprasellar lesions (including glial tumors of the optic chiasm and adjacent hypothalamic area, craniopharyngiomas, and germ cell tumors [GCTs]), central deep-seated lesions (gliomas of the thalamic region and tumors of the pineal region, including germ cell, embryonal, and glial neoplasms), and peripheral lesions (gliomas, ependymomas, and embryonal tumors of the cerebral hemispheres).

Advances in neuroimaging have improved the accuracy of diagnosis in CNS tumors. Introduction of perfusion, diffusion, and diffusion tensor imaging may add to diagnostic capabilities. In suprasellar and pineal region lesions, computed tomography (CT) is helpful to delineate calcification typically seen in craniopharyngiomas and malignant GCTs. Positron emission tomography (PET), single photon emission tomography (SPECT), magnetic resonance spectroscopy (MRS), and magnetoencephalography are of potential value in assessing tumor type or grade, and may be helpful in differentiating tumor progression from radiation-related changes (e.g., intralesional necrosis) (3–6).

Modern neurosurgical techniques have largely eliminated the need to consider multidisciplinary therapy without a histologic diagnosis (7). Central lesions within or around the third ventricle (suprasellar, thalamic, or pineal region tumors) can be biopsied endoscopically at the time of third ventriculostomy, often indicated to decompress the ventricular system in preference to a ventriculoperitoneal shunt at diagnosis. Histology may not be required for diagnosis of malignant GCTs (where elevated level of α -fetoprotein [AFP] or β -human chorionic gonadotropin [β -HCG] is diagnostic) and optic pathway tumors (OPTs) that involve the optic nerve alone or the chiasm in conjunction with adjacent optic pathway structures (8,9). For craniopharyngiomas, the imaging diagnosis can be confirmed by cyst aspiration documenting the presence of diagnostic squamous cells or cholesterol crystals

in the cyst fluid (9). Both diagnostic and therapeutic benefit may be realized by second-look surgery before initial postoperative therapy or following preirradiation chemotherapy.

ETIOLOGY

Although most brain tumors are sporadic, a number of pediatric brain tumor presentations are associated with recognized neurocutaneous or other genetic syndromes, as outlined in Table 3.3 (10).

Neurofibromatosis is a common congenital disorder associated with CNS tumors (11). Clinical criteria for type I neurofibromatosis (NF1) include six or more café au lait spots and peripheral neurofibromas among other characteristic features. NF1 is an autosomal dominant syndrome linked to a 17q11 chromosomal defect. Fully 15–20% of children with neurofibromatosis ultimately present with CNS neoplasms, usually gliomas of the optic pathways or low-grade tumors of the diencephalon, cerebral hemispheres, or posterior fossa (12). Low-grade gliomas associated with NF1 may be less aggressive than similar gliomas in the general population. As in sporadic cases, NF1 children with diffuse (infiltrating) astrocytomas (WHO grade II) do less well than those with the more common classical juvenile pilocytic astrocytomas (JPAs; WHO grade I) (13,14).

The indolent subependymal giant cell astrocytoma occurs in children with tuberous sclerosis, a hereditary disorder signified also by cutaneous acneiform lesions and hamartomatous angiofibromas in the skin, brain, heart, and kidneys, mental retardation, and renal insufficiency; CNS findings include hamartomatous periventricular lesions known as tubers. The disease is marked by the tuberous sclerosis complex gene 1 (*TSC1*), identified as a 9q34 mutation (15).

Childhood brain tumors (and sarcomas) are frequently noted in families with the Li–Fraumeni familial tumor syndrome; the entity is also associated with breast cancer, sarcomas,

Table 3.3
Genetic Syndromes Related to Pediatric CNS Tumors^a

Syndrome	Gene (Chromosome Location)	Related Histiotype
Neurofibromatosis, type 1	<i>NF1</i> (17q11)	Gliomas (1° JPA, optic pathway; cerebral, cerebellar, brainstem)
Neurofibromatosis, type 2	<i>NF2</i> (22q12)	Acoustic neuromas, meningiomas
Tuberous sclerosis	<i>TSC1</i> (9q34) <i>TSC2</i> (16p13)	Subependymal giant cell astrocytoma
Li–Fraumeni	<i>TP53</i> (17p13)	Medulloblastoma, astrocytoma
Turcot	<i>APC</i> (5q21) <i>hMCH1</i> (3p21.3) <i>hMSH2</i> (2p22-21) <i>PMS2</i> (7p22)	Medulloblastoma, high-grade glioma
Cowden	<i>PTEN</i> (10q23.3)	(Lhermitte–Duclos)
Retinoblastoma 1	<i>RB1</i> (13q14)	Pineoblastoma
Nevoid/Basal cell carcinoma (the Gorlin syndrome)	<i>PTCH1</i> , <i>SUFU</i> (9q31)	Medulloblastoma

^aMulvihill JJ. Clinical ecogenetics: cancer in families. *N Engl J Med*. 1985;312:1569–1570.

and brain tumors in adults, commonly occurring before the age of 35–40 (16). The syndrome is associated with germline *TP53* mutations and a high incidence of astrocytoma (low and high grades), gliosarcoma, medulloblastoma, and primitive neuroectodermal tumor (PNET). Those with the syndrome are also at high risk for secondary, treatment-related neoplasms (17).

Radiation-induced meningiomas have long been recognized. Data from the Israeli experience with low-dose irradiation for tinea capitis show a striking, dose-related incidence of meningiomas (and a relatively marginal increase in gliomas), largely apparent 30+ years postexposure. Reports indicate a disturbing incidence of secondary gliomas in certain pediatric settings, with recent focus on high-grade tumors among long-term survivors of childhood acute lymphoblastic leukemia (ALL) (18,19). The estimated risk is 1–3% after routine preventive cranial irradiation (CrI); a dose–response relationship has shown a minimal incidence after dosages less than 20 Gy and a risk approximating 10% ten or more years after cumulative dosages greater than 30 Gy (19). A unique experience at St. Jude Children’s Research Hospital found a 12% incidence of malignant secondary tumors 3–5 years posttherapy in a particular study who had received 18 Gy CrI and concurrent high-dose antimetabolite therapy (6-mercaptopurine); the incidence is now over 20% in the latter trial (20).

CLINICAL PRESENTATION

Supratentorial tumors generally present with localizing neurologic symptoms; symptoms and signs may develop over extended time intervals and are often protean. Seizures are the most common symptom in cerebral hemispheric lesions, especially with tumors arising in the temporal lobe. Lateralizing neurologic signs (motor and/or sensory) occur in thalamic region tumors, often associated with symptoms of increased intracranial pressure (i.e., headaches, vomiting). Suprasellar tumors typically occlude the foramen of Monro, also resulting in symptoms of elevated intracranial pressure. Visual signs (visual field deficits and/or decreased acuity) and endocrine

abnormalities (diminished growth hormone, cortisol or thyroid production; diabetes insipidus; delayed or precocious puberty) are often apparent with midline suprasellar lesions. Youngsters with suprasellar tumors may show features of the diencephalic syndrome (hyperactivity and asthenia, the latter despite normal or high food intake) (21). Pineal region tumors produce hydrocephalus by compressing the aqueduct of Sylvius; specific ocular signs (i.e., the Parinaud syndrome: decreased upward gaze, near-light dissociation of the pupillary response, convergence nystagmus) are classically noted (22).

LOW-GRADE SUPRATENTORIAL ASTROCYTOMAS

Low-grade astrocytomas are a diverse group of tumors that collectively represent the most common category of pediatric brain tumors (23). Management is variable and dependent on tumor location, patient age, presence of a genetic mutation, and, often, physician and parental preference. Outcomes are generally favorable; the goal of treatment is durable disease control or cure with preservation of function. The most frequent site of origin is in the cerebellum (see Chapter 4) followed by the deep midline diencephalon (thalamus, hypothalamus, optic chiasm and nerves, basal ganglia, and related structures) and the cerebral hemispheres. The most common locations for the hemispheric tumors are the frontal and temporal lobes (24–27). In contrast to adults who are most commonly diagnosed with high-grade astrocytomas, the majority of supratentorial tumors occurring in childhood are low-grade astrocytomas. Low-grade gliomas of the optic pathway and hypothalamus have distinct features and are discussed below as a separate group.

A subset of diffuse low-grade tumors extend across two or three lobes often with no obvious or dominant mass lesion; the diffuse pattern of involvement is classified as gliomatosis cerebri (28–30). Typical unifocal low-grade gliomas occasionally present with subarachnoid dissemination; the incidence is approximately 3%, most often seen in tumors located in the diencephalon (31,32).

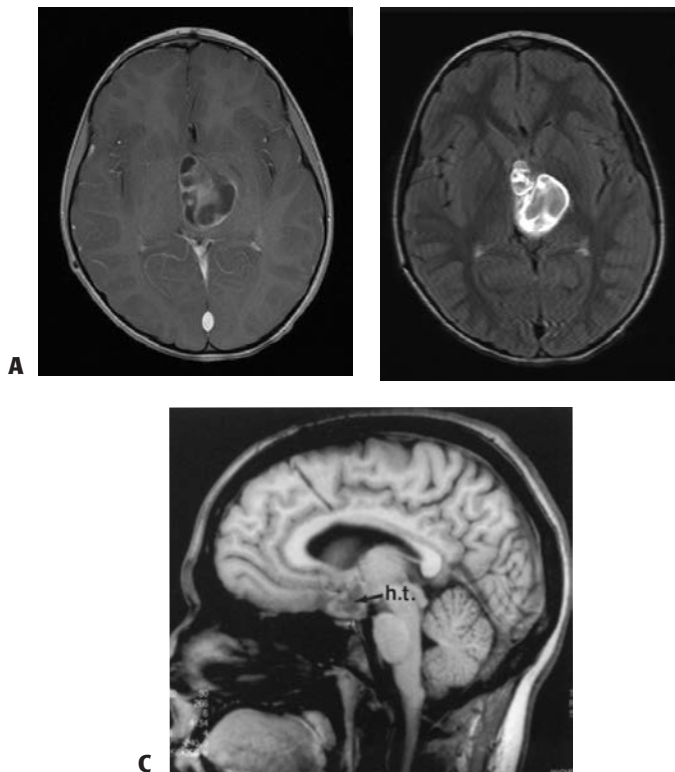


Figure 3.2 A: JPA of (L) thalamus, presenting in a 4-year-old boy—cystic and solid, largely enhancing tumor on T1-gadolinium MRI. B: JPA visualized on T2-FLAIR sequence post-contrast. Note even better tumor definition. C: Note leptomeningeal metastasis in hypothalamus/chiasmatic JPA, a finding largely at diagnosis in <10% of cases.

Diagnostic imaging generally reveals a lesion that is isointense on CT and T1 MRI sequences and hyperintense on T2 sequence (33). JPAs enhance briskly and diffusely, but most other low-grade tumors show little or no enhancement with gadolinium (33–35). Scattered calcifications may be present. Tumors may include small or dominant cysts; some degree of cyst formation is common in JPAs. MRI is the imaging modality of choice. Due to the variability of enhancement, T1 sequences may not provide the best demarcation of the tumor borders; post-gadolinium T2-FLAIR images are often preferred (Fig. 3.2B).

Histopathology of low-grade astrocytomas is characterized by low cellularity, little nuclear atypia, and few, if any,

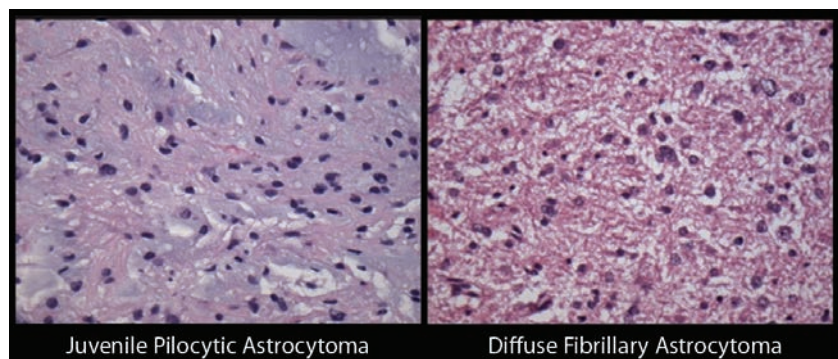
mitotic figures. Although the term “low grade” applies to all pediatric gliomas that are not anaplastic, the various histiotypes differ in the degree of infiltration, relative aggressiveness, and prognosis (36). JPAs and diffuse fibrillary astrocytomas comprise the majority of pediatric low-grade gliomas. Figure 3.3 depicts histological features of these two most commonly encountered low-grade astrocytomas. Less common low-grade astrocytomas include gemistocytic astrocytomas, pleomorphic xanthoastrocytomas, desmoplastic infantile astrocytomas, protoplasmic astrocytomas, and subependymal giant cell astrocytomas. These tumors are generally classified by the WHO histological criteria (2,37). The WHO system categorizes JPA as grade I and other differentiated astrocytomas including all diffuse astrocytomas, as grade II; anaplastic astrocytoma and glioblastoma multiforme are coded as grade III and IV, respectively (2,37). Broniscer et al. reported a cumulative rate of malignant transformation amongst pediatric grade II astrocytomas of 7% at 15 years post-diagnosis, a much lower frequency than has been reported in adults (38). JPAs almost uniformly retain low-grade characteristics even when uncontrolled or recurrent (38).

JPAs are characterized by elongated bipolar astrocytes organized in a parallel array of glial fibers, giving a hairlike or piloid appearance (39). The sparsely cellular tumors are signified by microcysts and Rosenthal fibers (amorphous eosinophilic material formed by plump, degenerating astrocytes). Macroscopically, visible cystic components often are present, sometimes with less prominent solid tumor components. The tumors may be circumscribed or may extend along white matter tracts, depending on the location (Fig. 3.4) (39). JPA is the most common tumor in the diencephalic region and comprises 25% of hemispheric astrocytomas (7,25). The tumor typically is nonaggressive, although multifocal presentation, rapid progression, and dissemination may occur (31,40–42).

Pilomyxoid tumors have recently been defined as a subset of low-grade gliomas, previously classified with pilocytic astrocytomas (43,44). Pilomyxoid tumors have a myxoid matrix with highly monomorphic piloid cells; they may demonstrate an arrangement resembling perivascular rosettes; they are usually solid with less prominent cystic components and lack Rosenthal fibers (45). These tumors are felt to be more aggressive than classical pilocytic astrocytomas and are categorized by the WHO as grade II, although little data yet confirm the clinical implications of this diagnosis (2,44).

Grade II astrocytomas are characterized by a greater degree of infiltration; the proliferation index may exceed

Figure 3.3 Histological features of the most common pediatric low-grade gliomas: JPA (L) and diffuse fibrillary astrocytoma (R). JPAs (WHO grade I) show biphasic architecture with more cellular areas that tend to have the Rosenthal fibers and loose areas with microcysts. Cells are elongated, bipolar, and have thin “hairlike” processes. Diffuse fibrillary astrocytomas (WHO grade II) consist of long, thin cells highlighted by a crisscrossing background of cytoplasmic glial filaments; nuclear atypia often apparent.



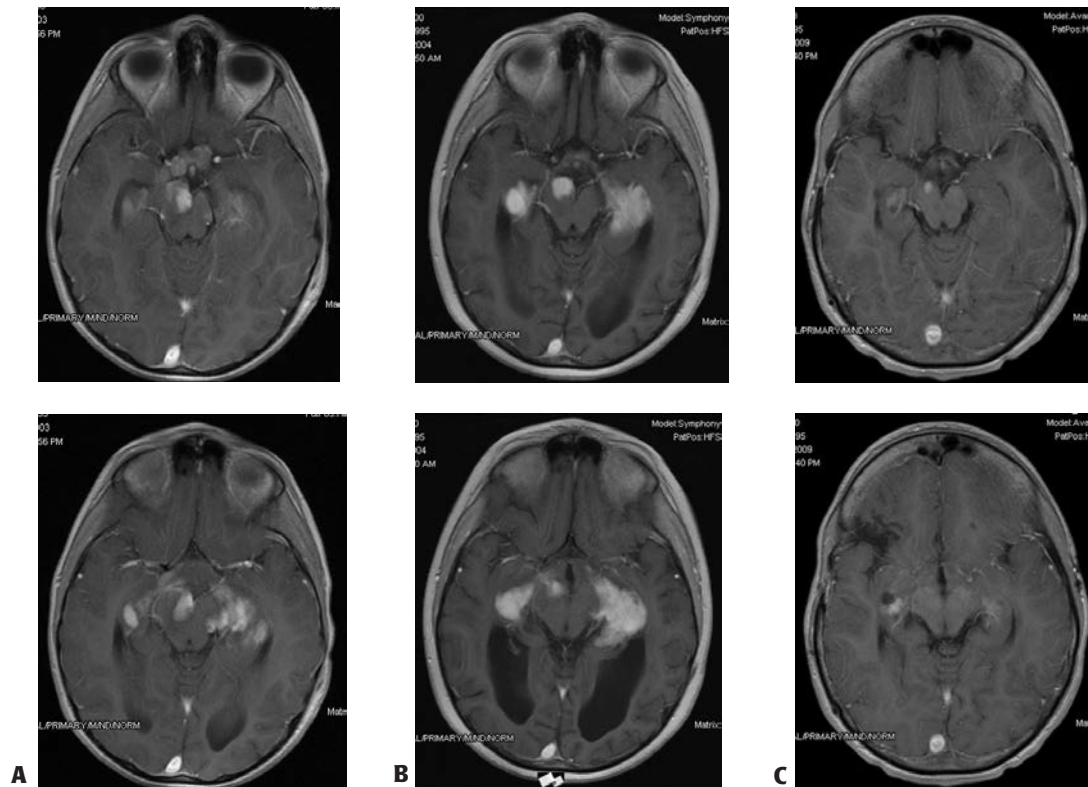


Figure 3.4 A: A 7-year-old boy with JPA of optic chiasm and optic tracts (without neurofibromatosis), involving and distorting chiasm (A, top) with spread along optic tracts (A, bottom). B: Increased tumor size, enhancement along optic tracts noted 7 months postradiation therapy (post-RT), attributed to transient posttherapy effects (B, top and bottom). C: Same levels with marked, spontaneous reduction in tumor volume compared to pre-irradiation or MRI 7 months post-RT (Figures B); note normal chiasm (C, top). Patient now 5.5 years post-RT, with intervening (R) middle cerebral infarct (C, bottom; same time as C, top).

that of the JPA, and a greater number of molecular aberrations are apparent. Diffuse fibrillary astrocytomas consist of long, thin cells highlighted by a crisscrossing background matrix of cytoplasmic glial filaments. Gemistocytic astrocytomas are less common, presenting as benign-appearing, often circumscribed lesions with a high rate of recurrence; these tumors often demonstrate malignant degeneration within several years after initial presentation (46). Protoplasmic astrocytomas are characterized by large, rounded astrocytes with abundant cytoplasm and a background largely devoid of fibrils (47). Grade II astrocytomas are more often associated with local recurrence and may present with malignant progression (38,48,49).

Pleomorphic xanthoastrocytomas present as superficial tumors in the cerebral hemispheres. Despite an aggressive histological appearance with cellular pleomorphism and numerous mitoses, the behavior of pleomorphic xanthoastrocytomas is quite benign; the tumor is classified as grade II. Long-term disease control usually is obtained through surgery alone; a proportion of cases do recur late and occasionally show malignant degeneration (50,51). A small percentage of these lesions show mitotic activity, areas of necrosis, and a high proliferative index at initial diagnosis and are designated as anaplastic pleomorphic xanthoastrocytoma. The latter may be somewhat more aggressive clinically (52,53).

Subependymal giant cell astrocytomas are a distinct subtype of sharply margined tumors that occur along the linings of the lateral ventricles (2). The lesions occur in the setting of tuberous sclerosis (v.s.); children often have seizures and show

significant developmental delays (54). Subependymal giant cell tumors are almost always managed with surgical resection alone.

Therapy Surgery

For low-grade gliomas amenable to complete surgical resection, surgery is generally the first and sole intervention providing excellent control of disease. Total resection is usually feasible for tumors arising in the cerebral hemispheres with reports indicating gross total resection (GTR) in 90% of cerebral hemispheric astrocytomas (25,26,55). Low recurrence rates are reported for both JPA and other astrocytomas after total resection (25,26,55–57). Data from the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) study of primary surgery in low-grade gliomas indicate 5-year progression-free survival in 92% of children after GTR, ranging from 95–100% for JPAs and gangliogliomas to 80% for grade II diffuse astrocytomas in this age group (58). Resection of tumors involving the dominant medial temporal lobe, motor strip region, or the Broca speech cortex may not be possible without inducing severe neurologic deficits. Partial resection may provide initial intervention for decompression and histopathologic diagnosis.

Low-grade gliomas of the diencephalon are technically challenging due to the deep location and eloquent area; however, contemporary series report successful resection for selected tumors in this region (59–66). Long-term disease control is typically achieved by total resection; occasional regression of diencephalic JPA after partial resection alone has

been reported (59,65,66). The CCG-POG study notes a progression-free survival after surgery alone of 50–60% for diencephalic tumors, much lower than for lesions originating in the cerebellum or cerebral hemispheres where GTR is more common (58).

Radiation Therapy

Radiation therapy is an established, effective treatment for low-grade gliomas, achieving tumor response and durable disease control in a significant proportion of pediatric cases (Fig. 3.2) (26,56,67–70). An analysis from Pollack et al. showed improved disease control at 10 years after irradiation following incomplete resection of cerebral hemispheric astrocytomas: 82% progression-free survival with irradiation versus 42% after surgery alone. The same study showed no significant benefit in overall survival (26). A recent phase II prospective study published by Merchant et al. demonstrated excellent event-free survival (87% and 74% at 5 and 10 years, respectively) and overall survival over 90% at 10 years for children treated with three-dimensional (3D) conformal irradiation to the MRI-defined tumor volume (71). These outcomes compared favorably to the literature and have been associated with excellent functional outcomes (72). The decreased volume of normal brain exposed to moderate or high radiation doses using conformal techniques with small margins may significantly decrease some of the serious radiation-induced side effects (72,73). Care must be taken to accurately delineate tumor volumes, addressing white matter tracts in defining the clinical tumor volume (CTV). Merchant et al. suggest a minimal margin (as small as 5 mm) may be adequate for well-demarcated tumors (71). Children's Oncology Group (COG) is currently examining outcomes with the use of a 5-mm anatomically limited CTV margin around the gross tumor volume (GTV) in a multi-institutional trial.

There are no contemporary data suggesting a benefit to postoperative irradiation for completely resected low-grade astrocytomas. For incompletely resected low-grade astrocytomas, early administration of irradiation may not benefit the patient (74). Current indications for radiation therapy after a near total resection (with imaging evidence of disease residual) include symptoms or signs that might improve with irradiation or postsurgical progression in a location not amenable to safe, definitive second resection. Other factors that are taken into consideration are histological subtype or biology (57,75). Chemotherapy may be advised prior to irradiation for young children or for patients with neurofibromatosis (NF1) or cognitive delay.

Reports from the large CCG-POG low-grade trial confirm previous institutional data suggesting that a significant proportion of incompletely resected astrocytomas remain indolent over 3–5 years; progression-free survival rate at 5 years is 55% after near total or subtotal resection (58). A decision to observe children with residual astrocytoma should involve all subspecialties (neurosurgery, radiation oncology, pediatric oncology) indicating the obligation for regular clinical follow-up and imaging that allows one to comfortably observe a child with the anticipation that treatment can be initiated upon documented tumor progression (55). Such an approach balances the recognized efficacy of radiation therapy with potential toxicities related, in part, to the anatomic location and volume of the tumor and the age of the patient (13,27). Inherent in such an approach is the commitment to intervene

appropriately with documented disease progression, including use of primary radiation therapy, additional surgery, or chemotherapy as indicated.

JPs predominate in hypothalamic and OPTs. Prolonged progression-free survival after irradiation alone for these tumors reflects both the indolent nature of tumors in this site and the efficacy of irradiation. Survival rates in excess of 80% at 10 years after irradiation are common for these tumors (9,73). In thalamic astrocytomas, pilocytic histology is less prevalent; 10-year survival results range from 33% to 60% after therapy (9,71,73,74,76).

Anatomically, diffuse low-grade gliomas are uncommon outside the brainstem in children. Gliomatosis cerebri or bithalamic astrocytomas may represent supratentorial counterparts of the more common infiltrating pontine astrocytomas (76,77). These tumors respond to radiation therapy both symptomatically and by imaging, although recurrence and progression often are apparent within a year (76,77).

Chemotherapy

Chemotherapy has been used with increasing frequency for low-grade gliomas as a strategy to delay or avoid radiation therapy; less data is available regarding chemotherapy response for progressive disease following irradiation. The use of initial chemotherapy for low-grade gliomas has been studied primarily in centrally located tumors that tend to occur in younger patients and are not amenable to resection. Chemotherapy can provide disease control for months to years, more often achieving stable disease or partial response than complete resolution; most tumors progress within 3–4 years, requiring radiation therapy at that time. The age below which chemotherapy is more appropriate is controversial and dependent on factors such as tumor size and location, presence of NF mutation, or developmental or neurocognitive delays. Packer et al. reported age to be the only significant prognostic factor, with 3-year progression-free survival rate of 74% for children ≤ 5 years old versus 39% for older children (78). In COG, the age of ≤ 10 years has been chosen for trial eligibility in studies evaluating chemotherapy as initial treatment (79). Individual centers have used thresholds of < 3 or < 5 years old.

Favorable control rates and relative absence of serious toxicity have established carboplatin and vincristine as the “standard” first-line chemotherapy for low-grade gliomas in younger children (78,80–82). Carboplatin hypersensitivity occurs over time, often limiting further administration of this regimen (83). Temozolomide, an alkylating agent with modest responsiveness in recurrent low-grade gliomas, is currently in trial with carboplatin/vincristine to try to prolong drug tolerance (84–87). The five-drug University of California at San Francisco (UCSF) regimen (6-thioguanine, procarbazine, dibromodulcitol, lomustine, and vincristine) has been reported to be similarly efficacious; a randomized trial comparing carboplatin/vincristine to this regimen has been completed in COG, suggesting equal or greater efficacy with the five-drug regimen (79,88). Bevacizumab in combination with irinotecan has been investigated for recurrent low-grade glioma with promising response rates for heavily pretreated patients (89). The decision to proceed with chemotherapy or irradiation relates to patient age and clinical presentation; consideration should involve consultation with and discussion among a multidisciplinary team reviewing

relative risks and benefits with the patient's family. Factors beyond age alone include symptoms and signs, potential for additional neurocognitive deficits, the likelihood of durable benefit from respective chemotherapeutic regimens, and the radiation volume required in weighing relative potential toxicities. Although not proven to be problematic, there is no confirmation that the response rate and durability of disease control following radiation therapy are independent of prior failure on chemotherapy.

Radiotherapeutic Management

Volume

Fusion of MRI with CT imaging is ideal to determine the extent of disease defining the GTV for treatment planning. T1 gadolinium-enhanced imaging may be ideal for JPA; for diffuse astrocytoma (grade II) and the less common low-grade neoplasms, T2-FLAIR or T2 sequences are most useful where the tumor rarely shows contrast enhancement throughout. The CTV may be defined as a 1-cm anatomic expansion; a prospective study at St. Jude indicated a dearth of marginal recurrences with a 1-cm anatomic expansion of the GTV to define the CTV (70,71). Smaller margins may provide adequate control; a 5-mm anatomic expansion is being examined in a prospective COG study. An additional 3–5 mm geometric expansion defines the planning target volume (PTV). The use of small margins requires a careful review of all neuroimaging with great attention to detail including all cystic and solid components of the tumor in the GTV. Similar guidelines appear to be appropriate for grade II (fibrillary) astrocytomas, recognizing that most such tumors in children have readily identifiable margins on imaging; expansion of the GTV by 1 cm has resulted in few marginal failures (70,90). Shrinking fields typically are not used in JPAs; when target volumes for infiltrating fibrillary astrocytomas are used, fields may be reduced to more narrowly encompass the obvious tumor after delivery of 50.4 Gy. For tumors with a cystic component, a CT or limited sequence MRI during radiation therapy may prove useful to evaluate changes in the cystic portion of the tumor during treatment. Diffuse low-grade gliomas can be associated with gliomatosis cerebri or bithalamic astrocytomas; both may be histologically WHO grade II, but the pattern of growth indicates a degree of aggressiveness and infiltration requiring large volume irradiation based on guidelines for malignant gliomas (76,77). For gliomatosis cerebri that is bilateral and involving much of the cerebral hemispheres, corpus callosum, and, sometimes, thalamic nuclei, it may be appropriate to include the whole brain, at least to a dosage level of 40–45 Gy before using a more imaging-defined “boost” volume (77,91).

Astrocytomas with multifocal presentations or subarachnoid seeding generally are treated with craniospinal irradiation (CSI), although the need to cover the entire neuraxis is controversial and unproven (31,40,41).

Dosage

There is little definitive dose-response data specific for pediatric astrocytomas. Shaw et al. showed an advantage with radiation therapy in JPA and other low-grade astrocytomas only at doses of greater than 53 Gy (91). It seems ironic that the adult low-grade glioma trials have established no clear benefit for dosage levels greater than 45 Gy (the European Organization for Research and Treatment of Cancer study showed no difference between 45 and 59.4 Gy; the North Central Cancer Treatment Group, Radiation Therapy Oncology Group, and

Eastern Cooperative Oncology Group study showed no difference between 50.4 and 64.8 Gy) (92,93). Pediatric national trials continue to use doses approaching the established tolerance of critical CNS structures (i.e., 50–54 Gy). The primary justification is the long-term disease control rates documented in studies of pediatric JPA and other low-grade astrocytomas. For children younger than 5 years, a delay in irradiation is appropriate as clinical signs permit, particularly with increasing data indicating the efficacy of chemotherapy in delaying irradiation for an average of 3–5 years. When radiation therapy is needed, a dose of 50–54 Gy with optimal conformality is standard—the same dose level recommended throughout the pediatric age range (70,71).

Technique

Ideal techniques achieve close conformation of the high-dose region to a well-defined local target volume. The 3D conformal or intensity-modulated photon irradiation or proton beam radiation therapy can achieve such conformality, with potential differences in sparing adjacent dose-limiting structures (e.g., optic chiasm, eye, and pituitary–hypothalamic region) and in intralesional homogeneity. Given the nature of low-grade gliomas and recognized dose-related toxicities, attention to dose volume histograms (DVH) and a 3D image-based radiation plan is critical in designing treatment techniques. Multiple fields, based on single-plane or non-coplanar techniques, may be used to achieve a dose distribution maximally conformed to the target volume (Fig. 3.5). The impact of low-dose irradiation on broader regions of the developing brain has not yet been fully explored; dose-volume modeling suggests correlations between low dose volumes and cognitive deficits (94). Early results suggest that 3D conformal techniques achieve greater sparing of neuropsychological function, for example, than past experience has shown for conventional therapies (95). The physical properties of protons allow for further reduction in the amount of brain exposed to low-dose irradiation (96,97) (Fig. 3.6). The greater conformality of 3D conformal radiation therapy, intensity-modulated radiotherapy (IMRT), and proton therapy are likely to be associated with less pronounced late toxicities as a result of diminished high-dose exposure of normal tissues (96,98–102).

The use of single-fraction radiosurgery for primary management of pediatric low-grade gliomas has been reported in several small institutional series (103,104). There are less data to understand the potential risks and benefits of this approach; however, in the rare instances where small lesions distant from critical structures can be targeted, especially in children with NF1 where subsequent development of additional CNS tumors is relatively common, data suggest reasonable efficacy and intermediate-term tolerance (103–105).

Results

Overall, outcomes for low-grade gliomas are quite favorable. Prognosis is related to age at diagnosis and degree of surgical resection; older children usually enjoy more favorable outcome. GTR is consistently linked to improved progression-free survival (26,58,106–110). Although low-grade gliomas are often considered one entity for the purposes of clinical trials and management, they represent diverse histotypes with variable prognoses as documented in series reporting detailed histopathologic analyses (36,111). Advances in pathology, particularly better molecular and genetic classification, should

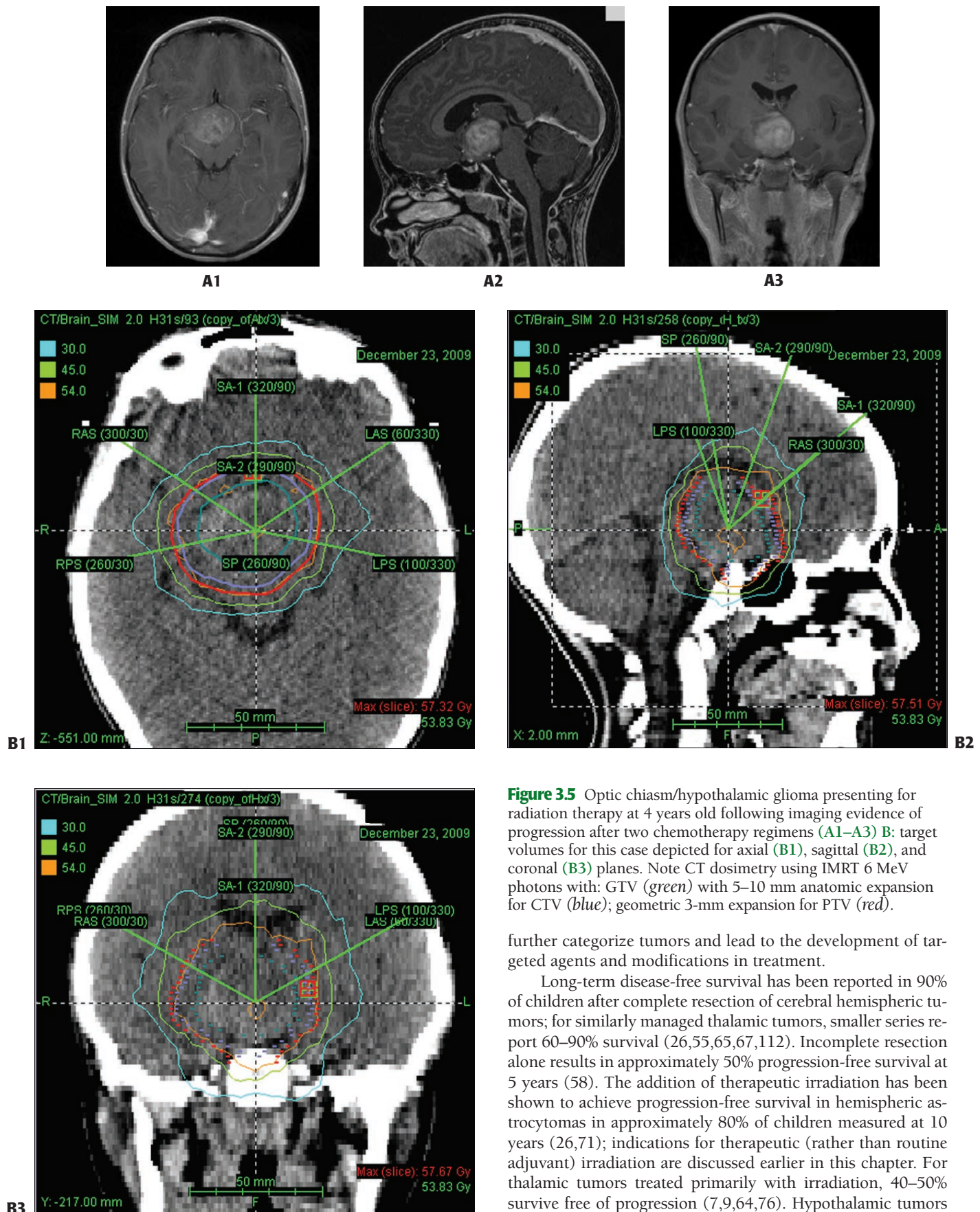


Figure 3.5 Optic chiasm/hypothalamic glioma presenting for radiation therapy at 4 years old following imaging evidence of progression after two chemotherapy regimens (A1–A3) B: target volumes for this case depicted for axial (B1), sagittal (B2), and coronal (B3) planes. Note CT dosimetry using IMRT 6 MeV photons with: GTV (green) with 5–10 mm anatomic expansion for CTV (blue); geometric 3-mm expansion for PTV (red).

further categorize tumors and lead to the development of targeted agents and modifications in treatment.

Long-term disease-free survival has been reported in 90% of children after complete resection of cerebral hemispheric tumors; for similarly managed thalamic tumors, smaller series report 60–90% survival (26,55,65,67,112). Incomplete resection alone results in approximately 50% progression-free survival at 5 years (58). The addition of therapeutic irradiation has been shown to achieve progression-free survival in hemispheric astrocytomas in approximately 80% of children measured at 10 years (26,71); indications for therapeutic (rather than routine adjuvant) irradiation are discussed earlier in this chapter. For thalamic tumors treated primarily with irradiation, 40–50% survive free of progression (7,9,64,76). Hypothalamic tumors have a favorable outcome after primary irradiation, with 10-year progression-free survival rates of 70–85%; current

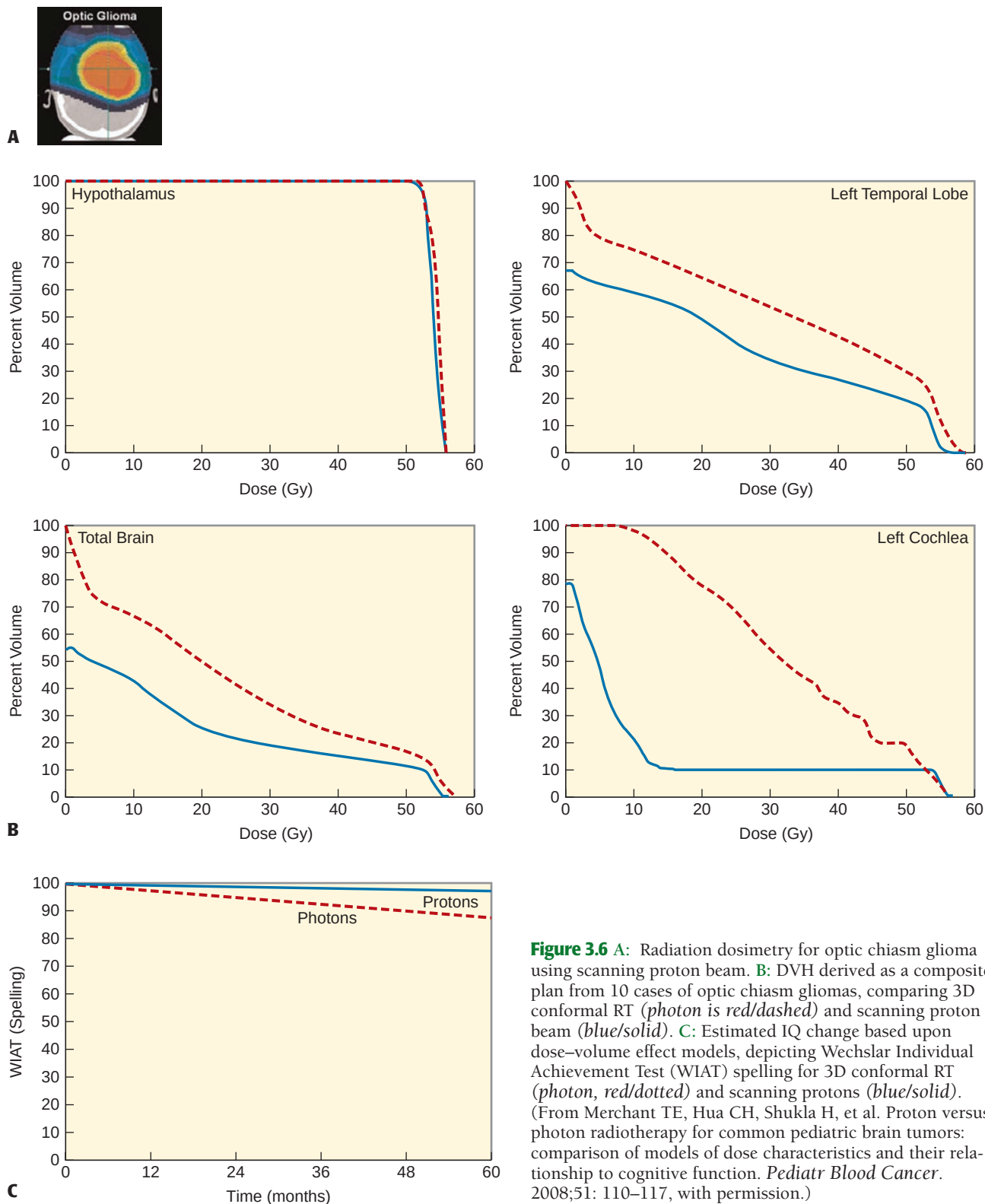


Figure 3.6 A: Radiation dosimetry for optic chiasm glioma using scanning proton beam. B: DVH derived as a composite plan from 10 cases of optic chiasm gliomas, comparing 3D conformal RT (photon is red/dashed) and scanning proton beam (blue/solid). C: Estimated IQ change based upon dose–volume effect models, depicting Wechsler Individual Achievement Test (WIAT) spelling for 3D conformal RT (photon, red/dotted) and scanning protons (blue/solid). (From Merchant TE, Hua CH, Shukla H, et al. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr Blood Cancer*. 2008;51: 110–117, with permission.)

literature typically groups these tumors with chiasmatic lesions as “hypothalamic/chiasmatic gliomas” as discussed below (7,9,68,113). Particularly when one is treating central (diencephalic) JPAs, it is noteworthy that tumor size may appear to increase approximately 6–12 months after irradiation, often by apparent intralesional necrosis or cyst formation; such changes typically remit over several months. The majority of

lesions respond by imaging criteria after radiation therapy (both by size and gradual loss of enhancement), but the median time to objective response is greater than 15 months (Fig. 3.4) (68,114). Low-grade gliomas involving both right and left thalamic regions (i.e., bithalamic tumors) have an aggressive course similar to that of the more diffuse gliomatosis cerebri or pontine gliomas (76).

OPTIC PATHWAY TUMORS

OPTs represent 5% of childhood brain tumors. OPTs may involve one or several anatomic sections of the optic system (optic nerves, optic chiasm, optic radiations) (Fig. 3.4) (13,68,115,116). They can be small and localized or extensive and infiltrative. Tumors involving the chiasm are often difficult to distinguish from tumors originating in the hypothalamus; hence, chiasmatic gliomas are commonly grouped with hypothalamic gliomas as one entity (113). OPTs occur predominantly in young children; 25% present before 18 months of age, and 50% present before 5 years (68,113,115,116). Up to 25% of childhood OPTs occur in children with NF1 (61,68,81). Conversely, of children with NF1, 10–20% are found to have OPTs on MRI; careful neuro-ophthalmological examination $\pm$ screening MRIs should be standard for patients with NF1 (61,68,81,113,117,118).

Clinical presentation is most often with diminished vision. In young children, increased intracranial pressure endocrinopathies and diencephalic syndrome may predominate. Histologically, more than 90% of OPTs are low-grade astrocytomas, most often JPAs (more than 65% of all cases) and grade II astrocytomas (25%), with infrequent gangliogliomas or hamartomas; malignant gliomas are uncommon (13,63,69,113,119).

The nature of OPTs has been debated. While acknowledging the sometimes indolent nature of OPTs, serial observations in major pediatric neuro-oncology clinics indicate progression in 75–85% of children, typically within 2 years of initial presentation (8,13,61,113,115,116). Tumors confined to the optic nerve(s) may behave in a more hamartomatous fashion. Children with NF1 have a more indolent course with lower rates of progression and longer latency intervals (113,118). Other signs of the neoplastic behavior of OPTs include extension to or invasion of the adjacent hypothalamus and posterior extension to the optic tracts (up to and including the lateral geniculate bodies) and optic radiations. Infrequently, optic chiasmatic and hypothalamic tumors demonstrate diffuse leptomeningeal disease (31,32,40–42). Mortality within 10 years of diagnosis is uncommon, although ultimate disease-related mortality has been documented in up to 40% of cases (9,13,68,115,120,121). Also to be noted is the rare but documented occurrence of spontaneous regression of OPTs (122,123).

Several series identify chiasmatic OPTs as optic pathway/hypothalamic gliomas, acknowledging the difficulty in identifying the origin of tumors that intimately involve both the chiasm and the hypothalamus (81,124). Although lesions extending to or originating in the hypothalamus may be somewhat more aggressive than lesions confined to the visual pathways, up to 50% of selected, asymptomatic children have been free of progression for 5 years or longer without therapeutic intervention. Preliminary data suggest adequate retrieval with secondary therapy at the time of progression during observation (13,113,121).

Therapy Surgery

Surgery has been the preferred treatment for unilateral tumors of the optic nerve (115,116,119). Observation may be selected, especially if there is residual vision associated with a lesion confined to the intraorbital optic nerve. Alvord and

Lofton (115) reported progression in 70% of children with untreated lesions within 6 years of diagnosis, although it was rarely associated with tumor-related mortality. Most series indicate more indolent, perhaps truly hamartomatous behavior in children with neurofibromatosis (119,121).

For lesions involving the optic chiasm, there are limited data suggesting a role for surgical resection. Decompression or limited resection may be successful in restoring vision (62,63,125). Series from the Hospital for Sick Children, Toronto, and New York University suggest a somewhat broader role for local excision in selected presentations. The latter authors indicate removal of lesions of partially infiltrating low-grade optic pathway astrocytomas with surprisingly little added visual compromise; approximately 50% of such cases have remained stable without further intervention for 3–5 years (60,63,119,125). Whether less aggressive surgery or observation would have achieved similar results relates to the selection of cases for surgery, a debate in the surgical community (8). Care should be taken to avoid visual compromise or other surgical complications as alternative therapies are quite successful.

Typical chiasmatic lesions that involve components of the visual pathways beyond the optic chiasm and hypothalamic region (i.e., with imaging extension to the optic nerves, optic tracts, or optic radiation) may be managed without biopsy confirmation. Most of these tumors are low-grade astrocytomas and most often can be managed based on the clinical and imaging diagnosis. Globular tumors that involve the chiasm and hypothalamus are best biopsied if this can be performed safely; a small percentage of these lesions may be GCTs, unusual types of low-grade neoplasms, or more aggressive malignant gliomas (62,69).

Radiation Therapy

Irradiation is indicated for significant visual or neurologic deficits at presentation or documented progression by clinical evaluation or neuroimaging after observation, surgery, or chemotherapy (13,61,78,81,82,115). Radiation therapy is highly effective for OPTs: 10-year progression-free survival rates exceed 80% (13,68,69,126). Although overall survival at 10 years is unaffected by the initial therapeutic approach (i.e., observation, resection, chemotherapy, or irradiation), progression-free survival rates at 5 and 10 years are substantially higher after radiation therapy (9,13,55). Serial imaging studies document significant tumor response in more than 50% of children after irradiation (69,113). Transient postirradiation tumor enlargement, often in the setting of central cystic degeneration, has been well documented (68). Close observation and medical management (i.e., steroids) rather than aggressive intervention for presumed tumor progression is advised, particularly for lesions that may appear to progress within 6–12 months after radiation (68). Visual improvement has been reported in 25–35% of children after irradiation (68,113,126). Visual deterioration is reported in 10–20% of children after irradiation, largely related to cystic degeneration (and consequent increased mass effect at the chiasm) or unrecognized elevated intracranial pressure (13,68,113,126). Vision should be monitored closely during the radiation course and in the months following completion.

Balancing the indications for radiation therapy and the timing requires judgment and, often, serial evaluations to determine the nature of the disease process. OPTs are associated

with unique late radiation-related sequelae. The young age at diagnosis, central location, and often extensive anatomic involvement challenge the ability to deliver adequate radiation therapy while preserving neurocognitive function; the problem is further accentuated in children with NF1, itself associated with cognitive delays (69,81,113,118). There is also concern about late vascular events: the incidence of occlusive vasculopathy at the circle of Willis in children with brain tumors is highest among those with OPTs, especially in younger children (69,81,127,128). Moyamoya syndrome is characterized by obliteration of the major vessels at the circle of Willis; incomplete brain perfusion is provided by collaterals and peripheral meningeal vessels. The syndrome has been noted after irradiation, perhaps related to cicatricial constriction of vessels tracking through chiasmal and hypothalamic gliomas. An incidence approaching 18% has been reported, especially noted among children less than 2–3 years and those with NF1 (69,127). A baseline MRA prior to irradiation to document vascular status is important, often revealing occult vascular compromise due to the tumor itself; the baseline is important to more easily detect changes after treatment. There is also a heightened concern regarding the risk of second malignancy in patients with NF1 (129,130). The Toronto group has uniquely reported a 10% incidence of second malignant neoplasms after irradiation for OPTs; of interest, a series from Children's Hospital of Los Angeles showed the same rate of anaplastic degeneration in JPA after surgery alone (112, 121,131).

Chemotherapy

Because of the radiation-associated morbidities in young children with OPT, Packer et al. (132) explored primary chemotherapy in children younger than 5 years. Initial experience with actinomycin D and vincristine resulted in stabilization in a majority of children and objective tumor reduction in approximately 25%. Although more than 60% of children needed irradiation by 5 years after diagnosis, the approach resulted in a substantial delay in radiation therapy, with a median time to progression of 3 years (132). Subsequent experience with an 18-month regimen of carboplatin and vincristine for low-grade gliomas including those of the hypothalamic region and OPTs has shown a significant rate of objective tumor reduction (reporting greater than 50% tumor reduction in one third of patients), early progression in only 10%, and 3-year progression-free survival that ranges from 75% for children younger than 5 years to 39% for those older than 5 years (78,81). Similar results have been reported with the UCSF five-drug regimen (88). Children with low-grade gliomas of this location are included on the recent and current COG studies discussed earlier in this chapter.

Early experience suggests favorable outcome with secondary irradiation after progression during or after chemotherapy; recent observations related to the timing of initiating radiation therapy suggest that long-term disease control and function are not diminished with prolonged preirradiation intervals (13,78,113). Toxicity with carboplatin and vincristine has been limited, and early data suggest continued intellectual development during chemotherapy (81). There is a balance between duration of disease control (clearly superior with radiation therapy) and less durable control with chemotherapy apparently without the serious morbidities associated with irradiation in the younger age

group (13,113,124). In current practice, most children below 5–10 years receive chemotherapy as the initial intervention, with some centers extending this to all prepubertal children. It is important not to avoid irradiation even in younger children when progressive visual loss is apparent despite chemotherapy.

Radiotherapeutic Management

Volume and Technique

The volume of disease can be quite variable for OPTs. The target volume includes only the radiographically involved aspects of the optic pathway. MRI has enhanced the ability to better define segments of the optic pathway that are involved. Tumors are often confined to the suprasellar region for lesions that are limited to the chiasm with or without hypothalamic involvement. Central lesions necessitate multifield, often noncoplanar arrangements to optimize 3D conformal approaches, limiting the dosage to the surrounding cerebral hemispheres and minimizing intralesional inhomogeneity of dose (71,100). Proton radiation therapy provides a dosimetric benefit for such tumors (101). Optic nerve involvement, most often in NF1, necessitates inclusion of the nerve to the posterior aspect of the globe in defining the target volume. For lesions extending along the optic tracts or beyond (occasionally to involve the optic radiation, toward or to the occipital lobes), it is key to discern where apparent neoplastic changes differ from edema (68,118).

Dosage

The extensive literature on radiation therapy for OPTs typically calls for dosage levels of 50–54 Gy, most often at 180 cGy per fraction (68,116,121,126). Reduction to 50 Gy at 150 cGy daily may be appropriate in children younger than 3 years (9,126).

OLIGODENDROGLIOMA

Oligodendrogliomas represent 1–2% of supratentorial tumors in children (133). The generally circumscribed tumors occur most often in the cerebral hemispheres. In adults, loss of chromosome 1p or 19q is noted in 50–80% of cases and is predictive of response to treatment (134,135). Specific data for pediatric oligodendrogliomas are limited but suggest that similar molecular findings are uncommon in adolescents and not apparent in children younger than 10 years (30,136,137). Treatment recommendations are based largely on adult experience with surgery and irradiation (133). Adults show excellent response to procarbazine, lomustine, and vincristine (PCV) or to temozolomide chemotherapy, particularly in anaplastic oligodendrogliomas with isochromosome 1p or p53 mutations (138–140). Given differences in biology, it is unclear whether chemosensitivity can be extrapolated to children.

Total surgical resection is the treatment of choice for accessible lesions. GTR has been documented in 20–25% of all cases, apparently more often in children and adolescents (133,141). The survival rate at 10 years after total excision is reported to be 60% in the Mayo Clinic series; of six children, five survived (91,141).

For incompletely resected oligodendrogliomas, a short-term benefit for radiation therapy has been documented. Shaw et al. (91) reported 5-year survival rate of 25% after subtotal resection, compared with 62% with the addition of

irradiation to doses greater than 50 Gy; by 10 years, the survival rates were 31% with irradiation and 25% without irradiation. Adjuvant irradiation typically is withheld for differentiated oligodendrogliomas in children, even with incomplete resection. Histologic grade has been cited as a prognostic indicator in oligodendrogliomas (91,142). Anaplastic oligodendrogliomas are managed similarly to other malignant supratentorial gliomas in children, although the outcome tends to be superior to those with anaplastic astrocytoma and glioblastoma (143,144).

Combined radiation therapy and PCV has been associated with excellent disease control in adults, specifically with anaplastic oligodendroglioma (145). More recently, response to Temodar has also been demonstrated in adults (134). Limited chemotherapy has been associated with sufficient tumor reduction to permit delayed GTR in tumors initially felt to be unresectable (146).

The “benign” nature of oligodendrogliomas is open to some question, with few reports documenting survival rates greater than 25% beyond 15 years (91). Long-term reports after contemporary surgery and irradiation are limited in the literature; given the added facility of stereotactic neurosurgery, one might anticipate improved outcome in the larger proportion of children with grossly resected lesions (91).

GANGLIOGLIOMA

Gangliogliomas are uncommon, biologically benign neoplasms comprised of neuronal and glial elements (ganglion cells and astrocytes, respectively) (2). The tumors occur primarily in children and young adults, with a median age approximating 25 years (149). Gangliogliomas present most often in the mesial aspect of the temporal lobes, with seizures as the dominant symptom (2,148,149). Pediatric tumors uncommonly present in the posterior fossa. The lesions are typically well circumscribed and surgically resectable (148–150). Gangliogliomas are classically coded as WHO grade I, well differentiated histologically with no atypia or anaplasia (2,149). Surgery alone is the standard initial intervention; 10-year disease-free survival has been reported in 97% of pediatric cases after surgery (147,149). Malignant transformation at progression or recurrence is rare; at most 10% of cases show nuclear atypia or anaplastic components (grade II or III, respectively) (150–152). Malignant degeneration to glioblastoma (grade IV) is decidedly uncommon in children and adolescents (151,152). Prolonged progression-free survival has been noted in small series with irradiation following incomplete resection or recurrence; the efficacy following malignant degeneration is less apparent (151–153).

RARE LOW-GRADE NEOPLASMS

Neurocytomas are clinically indolent tumors that present as intraventricular lesions, usually in the lateral ventricles with attachment to the midline septum pellucidum; most are diagnosed in adolescents and young adults. Neurocytomas are composed of small neuronal cells thought to represent a benign neoplasm derived from cells midway in the maturation process of neuronal differentiation (147,148). These tumors are genetically distinct from the oligodendrogliomas and dysembryoplastic neuroepithelial tumors (DNETs), with which they can be confused both clinically and histologically

(149). The lesion generally is resectable (150). Some consider hemispheric neurocytomas more likely to be DNETs; the lesions seem to necessitate only local excision (151). Prognosis has been related to the rate of proliferation (gauged by MIB-1) (150). These tumors respond to irradiation; small series have suggested improved outcome in cases with less than total resection when followed by radiation therapy (local target volume; dose >54 Gy in 30 fractions reported to be superior to lower doses) (147,152–154).

DNETs are biologically indolent, often large cerebral cortical tumors typically presenting with a long-standing seizure history (145,155). Symptoms typically arise in children younger than 12 years; the mean age at diagnosis is 14 years (156). The tumors may be considered quasi-hamartomatous, classically are well demarcated, and show no contrast on MRI; uncommonly, DNETs present as complex solid and cystic lesions with enhancement, calcification, and intralesional hemorrhage (2,156,157). These tumors may be followed, but surgery often is needed for seizure control; although they appear to be responsive to irradiation, there is no documented role for postoperative therapy (145,155,158).

MALIGNANT GLIOMAS

Supratentorial malignant gliomas represent approximately 6% of brain tumors in children. Histologic grading divides high-grade (or malignant) gliomas into anaplastic astrocytoma (WHO Grade III) and glioblastoma (WHO Grade IV) (2,159). Children have a higher proportion of anaplastic astrocytomas among the malignant gliomas and have arguably longer survival intervals (2,160,161). The tumors are biologically separate from the more common adult malignant gliomas (162,163). Adult *primary* malignant gliomas appear to arise de novo and are associated with amplification of the epidermal growth factor receptor (*EGFR*) gene and *PTEN*; less common *secondary* malignant gliomas evolve from low-grade tumors (primarily infiltrating astrocytomas, WHO grade II) and typically have *TP53* mutations (2,138). Overexpression of p53 and mutations in *TP53* have been noted in pediatric malignant glial tumors; *EGFR* is less commonly expressed (2,164,165).

Supratentorial malignant gliomas arise primarily as cerebral hemispheric tumors; 20–30% present centrally in the thalamus or basal ganglia (144,166). Imaging characteristics are similar to those in adults, with often poorly marginated, peripherally enhancing lesions on MRI or CT associated with surrounding white matter changes (edema); the enhancing components correlate with the cellular, vascularized periphery of the tumor complex (167). Adult studies have shown infiltration of the small, round anaplastic cells well into the perilesional low-density areas on CT or areas of abnormal signal on T2 MRI (2,159,168). The infiltrative characteristics of high-grade gliomas necessitate some caution in aggressive surgery and high-dose local radiation techniques; interest in functional imaging (e.g., PET) for both stereotactic surgical planning and radiation therapy reflects the acknowledged heterogeneity of the tumors and invasiveness beyond areas identified by anatomic imaging (169,170). Even with acknowledged infiltration at a distance from the “overt” tumor, clinical data shows both a direct relationship between the degree of resection and duration of tumor control as well as a pattern of failure that is overwhelmingly at the primary target volume even after high-dose focal radiation therapy (144,160,166,168,

171,172). Leptomeningeal dissemination had been reported in up to 15% of children at diagnosis; however, the large prospective CCG trial (CCG-945) showed disease beyond the primary site only anecdotally (160,168,173).

The diagnosis of high-grade glioma in children has often been challenging to the neuropathologist. Central review of pathology in the CCG-945 trial showed 36% of cases entered based on an institutional diagnosis of anaplastic astrocytomas or glioblastoma were felt to have a discordant diagnosis, primarily a low-grade glioma, based on the reviewers' interpretation (160,174). As might be anticipated, favorable results of combined modality studies are significantly less impressive when corrected for reviewed histopathology (160,174,175). In addition to confusion with pleomorphic xanthoastrocytoma and some of the benign embryonal tumors in younger children, the newly identified "glioneuronal tumor" may present with an apparently malignant phenotype despite sometimes benign natural history (176).

Therapy

Surgery

Surgical resection often has been limited in extent by the poorly circumscribed nature of the tumor and the attendant lack of aggressive neurosurgical intent. The large CCG series indicated that more than 90% resection (gross total and near total, by definition) was achieved in only 37% of cases: 49% of lesions arising in the superficial cerebral hemispheres, 45% of lesions arising in the cerebellum, and 8% of those arising in the central structures (diencephalons, midbrain) (172). GTR has been less common (approximately 25% of supratentorial cases in children) (144,160,166,172). There is a significant relationship between degree of resection and outcome. Five-year progression-free survival in the initially reported CCG-945 experience was 44% and 26% for anaplastic astrocytomas and glioblastoma, respectively, after more than 90% removal, compared with 22% and 4%, respectively, after less aggressive resection (172).

RADIATION THERAPY

Radiation therapy is a primary component of initial management of pediatric malignant gliomas. Adult studies have documented the impact of adequate radiation therapy on survival, although survival beyond 2 years occurs almost entirely among those with anaplastic astrocytoma rather than glioblastoma. Treatment has evolved to local irradiation, with margins reflecting the known pattern of microscopic extension and, increasingly, functional imaging to guide evolving therapeutic approaches. A series of dose-escalating trials have yet to demonstrate a convincing impact on disease control (170,171, 177–181). Current trials use 3D conformal radiation therapy or IMRT to dosage levels approximating 59–60 Gy, similar to those used in adults (74,171,181,182).

Chemotherapy

The large EORTC-NCIC prospective trial has convincingly shown the advantage of temozolomide in conjunction with surgery and irradiation in adult glioblastoma: 2-year survival rate increased from 11% to 27%, and 5-year survival rate, from 2% to 10% (183). The advantage of chemotherapy was apparent in all clinical settings (age, extent of resection, performance status; the impact of chemotherapy correlated most closely with the presence or absence of MGMT methylation)

(183). Unfortunately, the pediatric experience has not been as favorable with temozolomide: the rate of objective response in phase II trials with recurrent malignant gliomas has been quite disappointing, and prospective primary management phase II trials have shown no benefit in progression free survival (PFS) or overall survival (OS) (184,185). An early pediatric trial reported an apparent benefit when chemotherapy (vincristine, lomustine, and prednisone) was added after radiation therapy, with 5-year event free survival (EFS) approaching 45% with chemotherapy compared with 17% for those who received irradiation alone (175). Later follow-up of this study showed a significant number of low-grade tumors misinterpreted as malignant gliomas (186). The subsequent CCG-945 trial showed overall survival at 5 years in 21% of children with reviewed malignant gliomas treated on the same regimen (160). Interest in overcoming the theoretical blood–brain barrier and the potential advantage of dosage intensification have stimulated investigation of high-dose chemotherapy with autologous bone marrow rescue in childhood malignant gliomas (187–189). Attempts to utilize relatively high-dose therapy with G-CSF support (short of doses requiring peripheral stem cell support) in CCG resulted in 42% progression prior to irradiation and an additional 15% failing to complete 12 weeks of chemotherapy due to toxicities; over 20% of cases were unable to proceed to scheduled radiation therapy (186).

Current trials in COG and the Pediatric Brain Tumor Consortium (PBTC) focus on the addition of molecular targeting agents (a series of anti-angiogenic compounds targeting VEGF and related angiogenesis pathways as well as EGFR, PDGF, and mTOR inhibitors) administered concurrently or sequentially with irradiation (161,190,191).

Radiotherapeutic Management

Volume and Technique

The target volume is best defined by the enhancing lesion and surrounding low-density change using both pre- and postoperative MRI that includes gadolinium-enhanced T1 sequence and the larger region often identified only on T2 (and/or FLAIR). Detailed reviews of imaging and histologic extent in malignant gliomas and clinical patterns of failure have suggested that a 2-cm margin beyond the tumor/tumor bed and associated T2 (or FLAIR) define the initial CTV, with subsequent reduction to the residual enhancing tumor and/or tumor bed (on postoperative MRI) with 0.5–1 cm expansion define the "boost" CTV (177,180–182,192) (Fig. 3.7). Imaging guidelines reflect findings of histologic infiltration in the "surrounding edema" in most supratentorial malignant glioma cases (168,193). Most studies indicate that central failures (within the high-dose volume) yet predominate in these cases (179,192,194). There is recent evidence that functional imaging (11C-methionine PET or MET-PET) provides information regarding residual tumor that may alter postoperative targeting and that higher doses to more defined volumes may diminish central failures, with little ultimate impact on disease control (179–181). The use of image-guided radiation planning in pediatric malignant gliomas is important in sparing the normal brain. While 3D conformal irradiation has been the standard, IMRT may provide superior target conformity with better sparing of critical normal structures (e.g., optic chiasm and nerves, brainstem) and no significant increase in low-dose exposure to vital aspects of the normal brain (182,195).

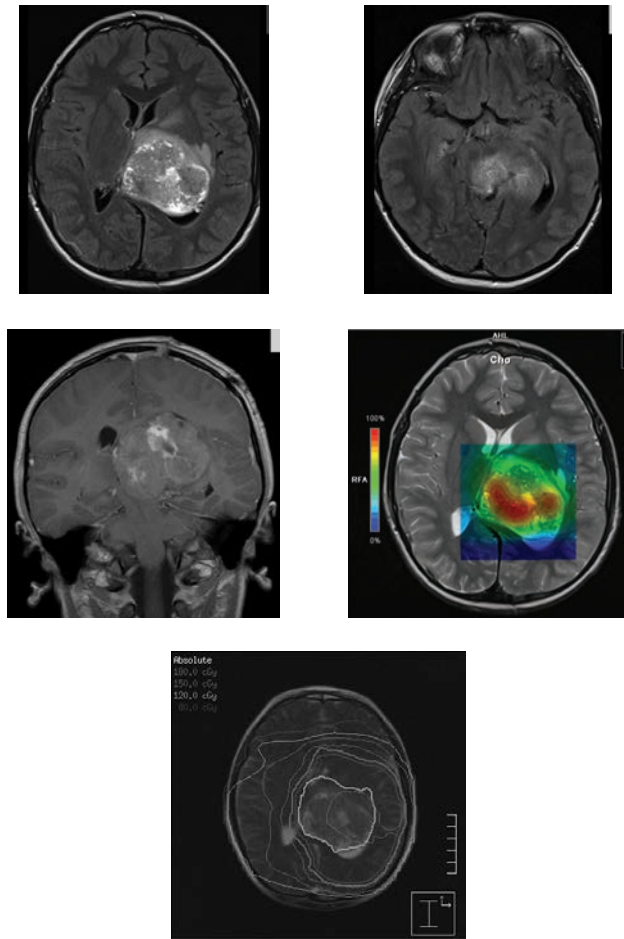


Figure 3.7 Glioblastoma multiforme presenting in an 8-year-old boy, involving (L) thalamus in a “nodular” pattern, status post minimal resection (A–C). **D:** MR spectroscopy map demonstrates quantitative ratio of choline:NAA. **E:** 3D conformal plan with GTV (green), 2-cm 3D anatomic expansion to CTV (blue), and 3-mm geometric expansion to PTV (red).

Dosage

The conventional dose–volume relationships in children have favored levels of 45–54 Gy to the initial CTV, with a total of 60 Gy to the “boost” volume as defined above based on adult guidelines (178,192). Higher-dose “boost” achieved through radiosurgical or brachytherapy techniques may provide some improvement in “central” disease control, but are often associated with postirradiation necrosis in as many as 50% of cases (194,196).

Results

Median survival times for pediatric malignant gliomas are 18–24 months in recent series (144,160,166,186). Event-free survival rate at 3–5 years is as high as 45% among the minority of patients in whom GTR is apparent, confirmed by postoperative neuroimaging and treated subsequently with both irradiation and chemotherapy (144,160,166, 172). For the 65–75% of childhood malignant gliomas with residual disease identifiable after surgery, the progression-free survival rate at 3–5 years is only 5–20%, slightly higher among the anaplastic astrocytomas than the glioblastomas (144, 160,172,174).

EMBRYONAL CNS TUMORS (PRIMITIVE NEUROECTODERMAL TUMORS OR sPNET AND PINEOBLASTOMA)

The WHO classification of embryonal CNS tumors clarifies earlier controversies regarding PNETs (2,197). Hart and Earle (198) described the supratentorial primitive neuroectodermal tumor (sPNET) in 1973 as an aggressive cerebral tumor occurring predominantly in young children and comprising 2–3% of pediatric CNS neoplasms. The tumor consists of undifferentiated neuroepithelial cells with areas of divergent differentiation toward glial, neuronal, and mesenchymal lines (2,197–199). In 1983, Rorke (200) introduced the PNET as a unifying concept, grouping together the “small round blue cell” CNS tumors, with or without specific differentiation but sharing common histologic and clinical features (e.g., tendency to seed along the CSF pathways and relative responsiveness to irradiation and chemotherapy). Recent biologic studies and gene profiling have demonstrated markers specific for medulloblastomas (e.g., isochromosome 17p), separating the classical posterior fossa embryonal tumor from the several sPNET “subtypes” (e.g., cerebral neuroblastoma, ependymoblastoma, medulloepithelioma, pineoblastoma) (201). Other gene findings correlate with specific sPNET subtypes (e.g., loss of chromosome 14q or 19q in sPNETs) (201). The atypical teratoid–rhabdoid tumor is a biologically and clinically unique embryonal tumor that is discussed in Chapter 4 with infant neoplasms. The clinical outcomes of the supratentorial embryonal tumors have been classically inferior to those of medulloblastoma; the different supratentorial entities may show varying survival rates dependent on subtype as well as age, disease extent, and therapy (2,197,202–206).

The supratentorial embryonal tumors occur more commonly in younger children, although the two most common subtypes, sPNET and pineoblastoma, also occur in adolescents and young adults. Embryonal tumors typically present as solid or partially cystic lesions (Fig. 3.8). Although sPNET and cerebral neuroblastoma may present as well-demarcated lesions, most embryonal tumors are generally invasive (197,198,207). Leptomeningeal dissemination is apparent at the time of diagnosis or at the time of initial tumor recurrence

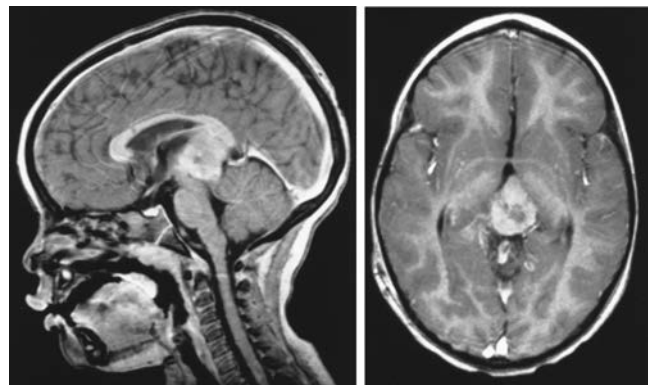


Figure 3.8 Classical pineoblastoma presenting in a 3-year-old child with large, complex solid, and cystic pineal tumor.

or progression in approximately one third of children (203,207); there is some controversy regarding the frequency of CSF failure in initially localized cerebral neuroblastoma, but most reports indicate CNS dissemination at a rate similar to that of the other embryonal tumor types (204,207,208).

The WHO classification outlines specific embryonal histotypes (2) (Table 3.2). Medulloepithelioma is the most primitive embryonal tumor, histologically showing features of primitive medullary epithelium and primitive tubular structures; focal differentiation toward glial, neuronal, or mesenchymal lines is often present (205). Primitive polar spongioblastoma is a rare cerebral tumor thought to be derived from migrating glial precursor cells and characterized by immature unipolar glial cells (209). Ependymoblastoma is a poorly differentiated embryonal tumor with ependymal differentiation marked by multilayered rosettes similar to those seen in retinoblastoma (Flexner–Wintersteiner rosettes) (2). The tumor is felt to be a specific embryonal neoplasm, different from the differentiated and anaplastic ependymomas (discussed in Chapter 4) that occur both in the posterior fossa and supratentorially (2,209). Cerebral neuroblastoma ranges histologically from an undifferentiated tumor similar to the extra-CNS childhood neuroblastoma, often including unilayered Homer–Wright rosettes, to lesions demonstrating ganglionic differentiation (207,209).

The tumor most often confused with medulloblastoma histologically and by contiguous anatomic location is the pineoblastoma. The tumor is believed to arise from pineal parenchymal cells, histologically signified by undifferentiated small round cells, usually including scattered Homer–Wright rosettes. The tumor may mimic retinoblastoma, including fleurettes and Flexner–Wintersteiner rosettes (210,211).

Therapy

The basic principle of surgical resection is often limited by disease site and extent. The sPNETs may be resectable in up to 50% of cases, especially when cystic (197,202–204, 212). Pineoblastomas are generally approached for stereotactic biopsy or limited resection (210,213,214).

Postoperative irradiation is indicated for the embryonal CNS tumors. Classic studies indicate disease control in fewer than 25% of cases with sPNET and pineoblastoma (197,215,216). A review of the SIOP/UKCCSG experience showed high rates of disease control with CSI for pineoblastomas with or without chemotherapy (214). The use of immediate postoperative irradiation and subsequent chemotherapy in CCG resulted in a 60% survival rate in children over 1.5–3 years with pineoblastomas (210). Overall results in other more recent series highlight interest in high-dose chemotherapy (e.g., high-dose methotrexate in the HIT regimens from the German studies or high-dose therapy with peripheral stem cell rescue) following irradiation (217–220).

Radiotherapeutic Management

Volume and Technique

CSI has been the standard for embryonal CNS tumors in children older than 3 years (203,208,210,214,218, 220–222). The technique for CSI is discussed in Chapter 4. For supratentorial embryonal tumors, the local boost is defined by the preoperative tumor volume, corrected for tissue shifts that occur with resection of often sizable lesions; in practice,

the preoperative volume is diminished to the tumor bed and residual neoplasm to identify the GTV. Anatomic expansion by 1–2 cm is utilized to define the CTV for all but the most circumscribed tumors; more diffuse tumors requiring a 2-cm expansion may be treated with subsequent reduction (at 45 Gy) to a more limited target volume with a 1-cm expansion for a final boost phase. As in other supratentorial lesions, the use of 3D conformal or intensity modulated irradiation offers a potential advantage in coverage and limits the dosage to adjacent critical brain volumes.

Dosage

The dosage of CSI is comparable to that used in medulloblastoma, with full neuraxis dosages of 35–36 Gy in children older than 3 years (203,210). Data from St. Jude suggest that reduced neuraxis irradiation (23.4 Gy) may be appropriate in localized sPNET with limited or no postoperative residual when combined with dose-intensive chemotherapy (218). The primary tumor volume is treated to a cumulative dose of 54 Gy with volume reduction at 45–50.4 Gy if necessary, as above (203,208,210,214,218, 220–222).

CRANIOPHARYNGIOMA

Craniopharyngiomas are benign tumors of epithelial origin believed to arise from remnants of the Rathke pouch in the suprasellar region. The typical adamantinomatous craniopharyngioma is a calcified, cystic tumor derived from embryonic cell rests of enamel organs located adjacent to the tuber cinereum along the pituitary stalk (29,223). The adamantinomatous craniopharyngioma seen in children and adolescents includes solid components and often large, complex cysts filled with fluid containing high lipid content and cholesterol granules, described as “crankcase oil.” Up to 10% may present as purely cystic lesions (224). The less common squamous cell craniopharyngioma occurs almost exclusively in adults; the latter type is rarely calcified and often presents as a solid lesion without cyst formation.

Craniopharyngiomas are well-circumscribed, encapsulated extra-axial lesions. The tumor has an interdigitating pattern of adhesion to adjacent neurologic structures, including the optic chiasm, major vessels at the circle of Willis, the tuber cinereum (along the pituitary stalk), and the hypothalamus (225). Infiltration into the tuber cinereum and the presence of small tumor islets in the adjacent hypothalamus document the potential for local invasiveness (223,226). Grading systems proposed for craniopharyngioma are based largely on the degree of hypothalamic involvement (e.g., none vs. abutting/displacing vs. involving/infiltrating, the latter marked by absence of the hypothalamus on imaging) (224).

Anatomically, 70–90% of childhood craniopharyngiomas involve the retrochiasmatic region, usually extending superiorly into the third ventricle and along the hypothalamus (Fig. 3.9) (224,227). The multicystic lesion may include cystic extension into the basal cisterns, even into the posterior fossa. In 10–30% of cases, the tumor presents in a prechiasmatic location between the optic nerves, pushing the chiasm posteriorly (224,228,229). Prechiasmatic tumors are more surgically accessible and less adherent to vital suprasellar structures (225,228).

Children present with visual disturbances (visual field deficits or impaired acuity) and symptoms of elevated intracranial pressure (headaches, nausea, vomiting). Endocrine

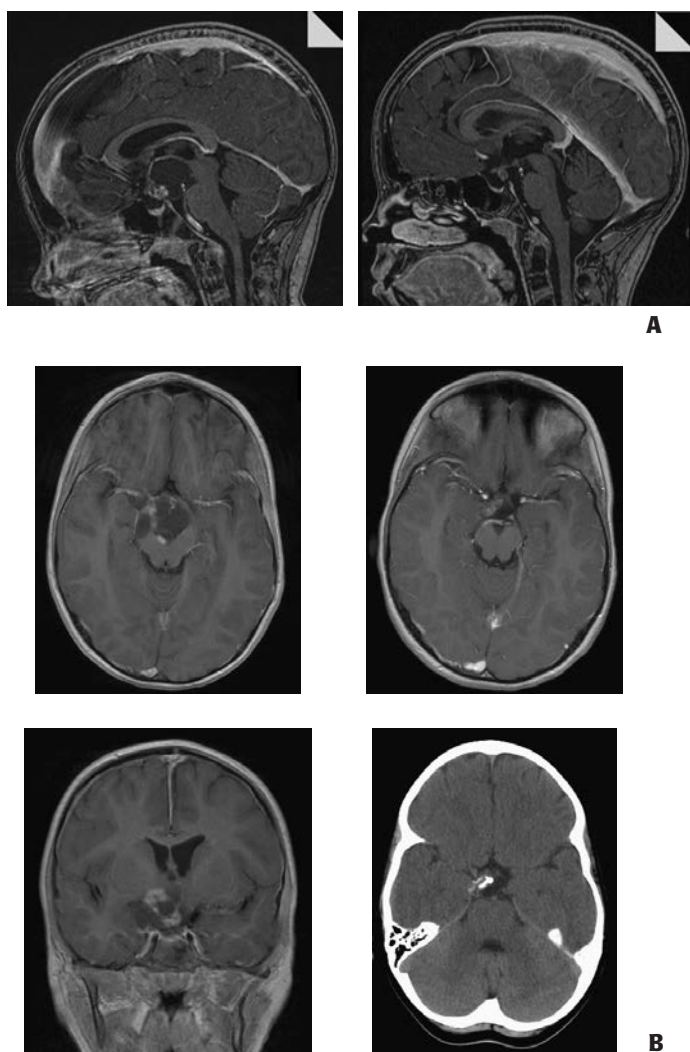


Figure 3.9 A (column on L) : Craniopharyngioma in a 5-year-old boy showing typical solid component in region of tuber cinereum (suprasellar cistern) and cystic components extending into the third ventricle/interpeduncular region and upper sella; T1-gadolinium imaging. **B (column on R):** 3.5 years following simple drainage of the superior cyst and 54 Gy per 30 fractions using 3D conformal RT. Small residual solid component off inferior tuber cinereum just posterior to optic chiasm shown in sagittal (top) and axial MRI (middle), largely calcified as noted in accompanying CT without contrast (bottom).

deficits at diagnosis are apparent in 50–90% of children studied, most often diminished growth hormone, but also diabetes insipidus (10–20% of cases preoperatively), and decreased gonadotropin, thyroid-stimulating hormone, or adrenocorticotrophic hormone (25% incidence) (230–233). Changes in personality and altered cognitive function have been noted in up to 50% of children at presentation (223,234–236).

Therapy

The treatment of craniopharyngiomas is one of the most controversial issues in pediatric neuro-oncology (224,225,237). Total resection is often curative in this technically “benign” neoplasm. Matson’s classic 1969 neurosurgical text described complete resection in 44 of 57 children preceding the modern era of the operating microscope; 10 of the 44 required more

than one surgical procedure to achieve GTR (238). Similar numbers were reported in Yasargil’s series published two decades ago (235). Numerous contemporary series reporting primary surgical intent in children note attempted total resection in 50–80% of cases (224,228,235,237–242). Postoperative imaging indicates residual calcification or obvious tumor in 15–50% of “totally resected” cases (224,228, 235,243). The rate of clinical recurrence even after imaging-confirmed total resection is 15–30%, linked to tumor volume and location (224,228,229,235,237,241,244). It is of interest that residual calcification alone, apparently representing minimal residual tumor, has been linked to the likelihood of subsequent recurrence (228,229,243).

Balanced against the low failure rate after aggressive surgery are risks of perioperative mortality (1–3%) and major postoperative morbidity (significant visual loss, vascular events, or added neurologic deficits in 10–20% of cases) (224,228,235,237,242). The skill and experience of the surgeon are important; tumor control and morbidity rates correlate with the number of cases performed annually (224,237). Extensive resection is associated with a 90% incidence of diabetes insipidus, a relatively difficult endocrine deficit to manage, and often marked hypothalamic obesity in $\geq 50\%$ of cases (224,228,231–233,239,244–246). Obesity is associated with uncontrollable appetite and correlated with a 15–20% incidence of severe behavioral problems (e.g., anger or aggressive behavior including rage or violence); independent of body mass index (BMI), behavioral and social problems are common, related to hypothalamic damage (224,233, 236,246, 247). Dissection is also associated with fusiform dilation of the internal carotid artery in up to 15% of cases (247).

Kramer and colleagues (248) first reported the efficacy of limited surgical decompression and primary irradiation for craniopharyngiomas from London’s Royal Marsden Hospital in 1961. An update indicated 15-year progression-free survival in all six children (249). The Royal Marsden Hospital later documented survival rates of 84% and 79% at 10 and 15 years, respectively, in patients treated between 1950 and 1981 by cyst aspiration or limited decompression followed by irradiation; for the 27 children treated with supervoltage, survival rates were 100%, 96%, and 96% at 5, 10, and 15 years, respectively (9,234,250). Kramer’s personal experience at Jefferson (Philadelphia) resulted in 80% 20-year disease control after limited surgery and irradiation (251).

The literature confirms long-term disease control in 80–90% of children with primary radiation therapy following relatively limited surgery. Most data reflect conventional radiation therapy, more recently representing image-based conformal techniques or fractionated stereotactic delivery (Table 3.4) (224,231,234,240,244,250–256). Early reports regarding proton beam therapy are just appearing (257, 258). Single-fraction radiosurgery has been used for postoperative residual when limited in size and anatomically positioned to allow avoidance of the chiasm and hypothalamus (259–261).

Acute reactions are rare during or after limited volume brain irradiation, while anticipated endocrine changes reflect initial tumor- or surgery-related damage to the hypothalamic region; later endocrinopathies are late radiation effects: growth hormone deficiency and less frequent accelerated or delayed sexual development; diminished thyroid-stimulating hormone or adrenocorticotrophic hormone secretion. Radiation-related

Table 3.4
Craniopharyngioma—Outcome in Children

Primary Therapy/Series	Interval	n	% Complete Resection	RT	PFS at 5 Years	PFS at 10 Years	PFS at 20 Years
Surgery							
JCRT, Boston (244) ^b	1970–1990	15	66% (op), 4/6 (NI)	0 ^a	52%	31%	
Hospital Sick Children, Toronto (228)	1975–1989	50	90% (op)	0 ^a	66%		
Great Ormond St. Hosp, London ^{gh}	1973–1994	29 (GTR)	66% (op), 49% (NI)	0 ^a (GTR only)	89%	78%	
Child Memorial Hosp, Chicago (267)	1983–1996	25	76% (op NI)	0 ^a	55%		
St. Jude (231) ^b	1984–1997	15	53% (NI)	0 ^a	73%		
Limited Surgery: Primary RT							
Royal Marsden, London (234)	1950–1986	77 (all)	<27%	56 Gy median (median 1.5 Gy/fx)	83%	79%	
Thomas Jefferson University (251)	1961–1981	12	8%	55.8 Gy mean (1.8–2 Gy/fx)	83%	81%	
JCRT, Boston (244) ^b	1970–1990	38		54.6 Gy median (1.8–2 Gy/fx)	92%	89%	
U. Pittsburgh (276)	1971–1992	24	4%	≥54 Gy (1.2–3.1 Gy/fx)	95%	89%	54%
St. Jude (231) ^b	1984–1997	15	0	55.8 Gy (1.8 Gy/fx) ^c	93%		
St. Jude ^f	1997–2003	28	0	54–55.8 Gy (1.8 Gy/fx) ^d	90% (3 yr)		
Royal Marsden (254)	1994–2003	19	<2	50 Gy	92% (1.51–1.67 Gy/fx) ^e		

op, neurosurgical assessment of degree of resection; NI, postoperative neuroimaging assessment; GTR, gross total resection.

^aWithout RT by primary intention; RT used for recurrent disease only.

^bComparative results of primary S and primary RT presented in table for JCRT (Harvard Joint Center for Radiation Therapy, Boston) and St. Jude Children's Research Hospital, Memphis.

^c¹³I/¹⁵P → external beam RT; 2 → ³²P (including the one failure within 5 years).

^dProspective 3D conformal RT approach (GTV + 1 cm = CTV).

^eProspective stereotactic RT (GTV = CTV); cohort = 19 children and 20 adults; data reported = all ages.

^fMerchant TE, Kiehna EN, Kun LE, et al. Phase II trial of conformal radiation therapy for pediatric patients with craniopharyngioma and correlation of surgical factors and radiation dosimetry with change in cognitive function. *J Neurosurg.* 2006;104:94–102.

^gDe Vile CJ, Grant DB, Kendall BE, et al. Management of childhood craniopharyngioma: can the morbidity of radical surgery be predicted? *J Neurosurg.* 1996;85:73–81.

diabetes insipidus is distinctly uncommon (224,232,233, 244,262). Comparative reports of neurocognitive and overall functional levels favor children treated by limited surgery and irradiation compared to those with aggressive total resection (224,231,233,240,244,250,256,262). Late vascular events are well documented in 10–20% of survivors, related to surgery and irradiation and ranging from localized vascular narrowing to moyamoya syndrome with occlusion of major vessels of the circle of Willis (251,263–265).

The option of incomplete resection and observation, delaying irradiation until later progression, is unattractive in most instances. Despite the low-grade histology of craniopharyngiomas, clinically detectable progression is apparent in 70% of incompletely removed tumors within 3 years (224,228,243). Second surgery is associated with less likelihood of GTR and higher surgical morbidity, reflected in lower quality of life (228,235,237,241,245,266). Results of delayed irradiation at the time of recurrent disease are reported to be

inferior to those achieved with planned postoperative irradiation (251,253). Children's Memorial Hospital (Chicago) noted an 88% relapse-free survival rate after irradiation administered only after the first or second recurrence (245,267).

Some patients have cyst enlargement that may not represent progressive tumor. A majority of children ultimately have stabilization and later regression of the cyst or need simple cyst aspiration for associated neurologic symptoms (249,254,268). In some instances, progressive but isolated cystic enlargement following surgery or more than 1–2 years following irradiation may be treated with intracystic irradiation using ^{32}P or ^{186}Re , pure beta emitters (269–273). Primary utilization of intracystic radioisotopes or bleomycin has been successful in selected settings, particularly in young children with largely cystic presentations (270,272,274). Vasogenic edema has been noted surrounding the tumor cyst after bleomycin instillation, raising questions regarding distribution of the intracystic agent (275).

Total resection alone or limited surgery with planned postoperative irradiation achieve excellent disease control. The controversy regarding primary treatment includes the balance of high rates of immediate postsurgical sequelae and recognized rates of late postirradiation sequelae (237,240, 253,267,276,277). Long debated among neurosurgeons and radiation oncologists, recent statements often converge on a judgmental approach reserving “radical” resection for cases with prechiasmatic or limited retrochiasmatic lesions (in particular, avoiding surgery likely to result in hypothalamic damage) while pursuing limited surgery and irradiation in most instances (224,237,277–281). Coordinated care is important as immediate decompression for increased intracranial pressure or marked visual compromise (e.g., stereotactic cyst aspiration or ventriculoperitoneal shunt) is required in 25–50% of presentations (224).

Radiotherapeutic Management

Volume and Technique

The volume of irradiation is limited to the well-margined tumor, including its cystic components. It is important to accurately map out the cystic areas; cystic extensions posteriorly or inferiorly may be obscured by the basal cisterns. With close margins and image-guided radiation planning and delivery, it may be fruitful to surgically decompress, or resect, cystic extensions to minimize the radiation volume, especially components growing superiorly within the third ventricle (256,280). Craniopharyngiomas often interdigitate or invade at the hypothalamic and chiasmatic regions; it is unusual to see invasion at other sites. Accordingly, one can define the GTV as the residual solid tumor and diminished cyst volume after surgical intervention. Definition should include both MRI (for soft tissue and cyst extent) and CT (for calcified residual tumor). The CTV has been defined as narrowly as the GTV itself in an experience from Heidelberg reporting preliminary results with fractionated stereotactic radiotherapy using CTV equal to GTV and an additional margin of 2 mm to identify the PTV (255). The recent prospective experience at St. Jude has been based on a GTV defined as the minimal postoperative residual (including the cyst wall), a CTV derived from a 1-cm 3D anatomic expansion of the GTV, and a PTV 3–5 mm geometrically expanding the

CTV (Fig. 3.10). Caution is warranted in documenting the sometimes significant re-expansion of cystic components during the 6-week course of irradiation, with cyst aspiration through indwelling Ommaya reservoirs or stereotactic access as necessary to maintain a limited target volume (256,282).

Stereotactic or 3D conformal techniques based on image-guided planning are the standard (256,283). These techniques decrease the volume of normal tissue irradiated and offer the promise of reduced neuropsychological sequelae of irradiation (255,256). Experience with proton beam therapy is early, with apparent improvement in dose conformality, particularly when comparing the volume of normal brain exposed to lower, but potentially meaningful, doses (257,258).

Single-fraction radiosurgery has been used largely in the context of minimal residual solid tumor components (i.e., after attempted complete resection with minimal residual in the sella or in areas of tumor not adherent to the chiasm or hypothalamus) or limited, localized recurrence (259–261). The target volume for such interventions is limited to residual solid tumor in most instances, typically smaller than 2 cm in diameter (260).

Intracavitary radionuclide insertion, in an effort to delay primary surgery or external irradiation (e.g., in children younger than 4–5 years) or to treat residual or recurrent cyst formation after definitive surgery or radiation therapy, is a valid approach for tumors that are largely cystic in centers with experience in this approach. A catheter is passed into the cyst at craniotomy or by stereotactic guidance. Based on the cyst volume, an appropriate dosage of isotope in diluent is instilled into the cavity. Most contemporary experience is with beta emitters such as ^{32}P , ^{186}Re , or ^{90}Yt , delivering a high dosage (i.e., 200 Gy) to the cyst wall (269,272,273).

Dosage

A radiation dose response has been documented at 54–55 Gy using 180-cGy fractions daily, noting apparent improvement with dose levels approximating 54 Gy compared to levels of <50 Gy (9,231,234,251,253,256). Data supporting dose levels above 55 Gy is less convincing (276). Late complications, including chiasmal injury, are increased with dosages greater than 60 Gy (9,234,251, 253,276).

Results

Long-term disease control rates for craniopharyngioma should be 80–90%, with a suggested plateau for disease-free and overall survival beyond 5 years. Such results are achievable among those selected for surgery who have successfully undergone GTR (228,229,235,237,241,243,244,277,279,281). Late recurrences and rare treatment-related mortality (largely neuroendocrine or vascular following surgery or irradiation, or postirradiation carcinogenesis) are reported well beyond 5–10 years (253). Most data suggest that postoperative irradiation is indicated with imaging evidence of residual disease (224,237, 245,251,253,256,267,277,279). Control rates after limited surgery and irradiation are equivalent to those of radical resection (9,224,231,234,240,251,252,256,276). Quality of life is particularly important in a tumor setting marked by significant potential neurologic deficits (vision, integrity of major cerebral vasculature), hypothalamic dysfunction, and neurocognitive compromise (225,231,233,236,253,276,283).

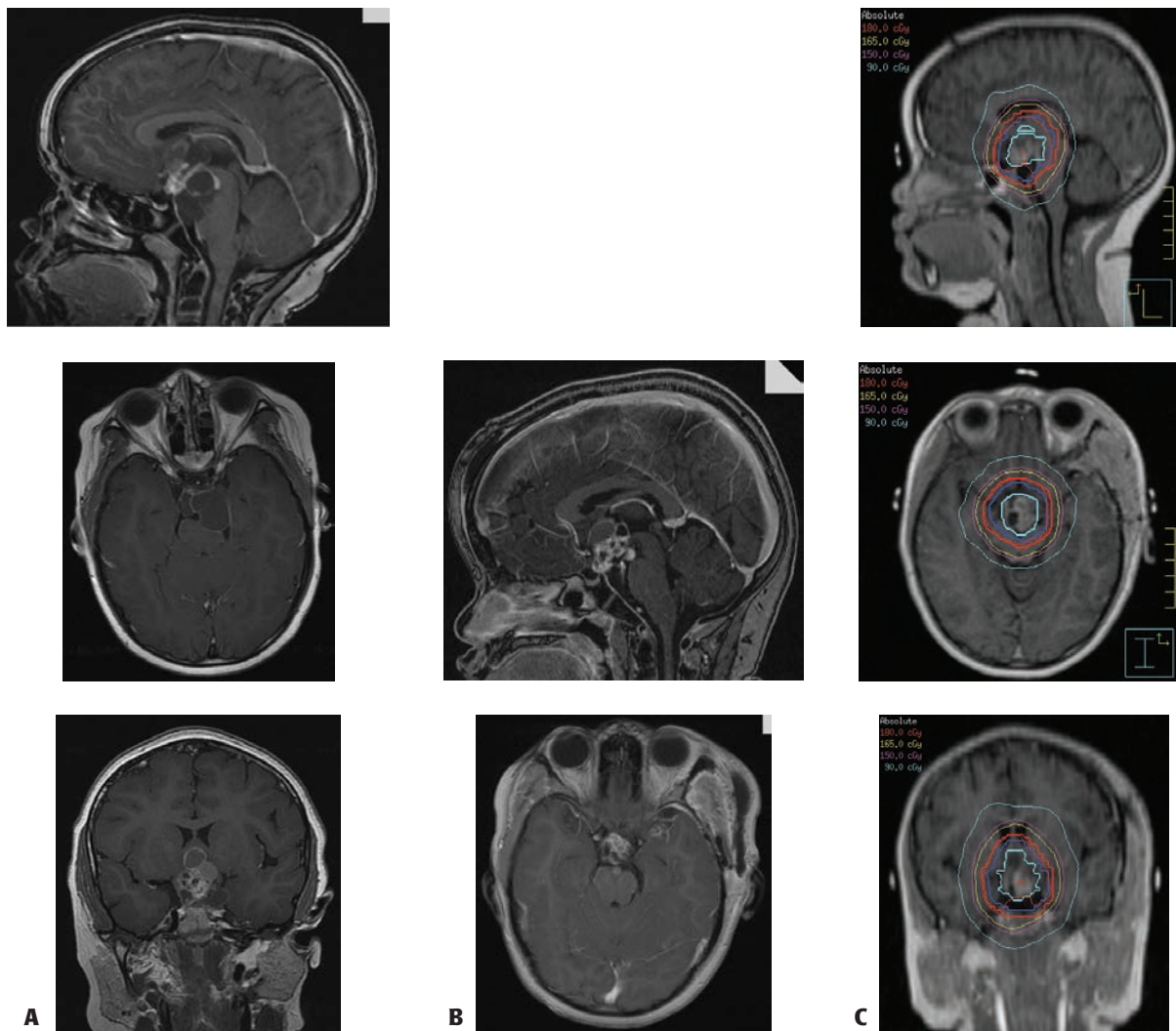


Figure 3.10 **A:** Craniopharyngioma with extensive cyst formation. Note extension to prepontine cistern and anterior third ventricle in three planes (a.1–a.3). **B:** Following craniotomy with microscopic resection of inferior/prepontine cyst and reduction of superior component within third ventricle (b.1, b.2). **C:** RT plan for 3D conformal treatment in three planes: GTV (heavy blue line) defined by postoperative reduction in prepontine component; CTV (lighter blue line) defined by 5–10 mm expansion of GTV, with 5-mm PTV (heavy red line). Daily fraction of 180 cGy delivered to PTV (c.1–c.3).

INTRACRANIAL GERM CELL TUMORS

Intracranial GCTs are rare in North America and Europe, representing fewer than 2–4% of pediatric CNS neoplasms; in Japan and Taiwan they are reported to represent up to 11% of childhood brain tumors (284,285). The full range of germ cell histotypes presents as primary CNS tumors: pure germinomas (60–70% of intracranial GCTs), “malignant” germ cell types (embryonal carcinomas, endodermal sinus tumors, and choriocarcinomas, collectively 15–20% of CNS GCTs), and teratomas (benign, immature, and malignant types, 15–20%) (2,22,286–288). Malignant teratomas are admixtures of benign teratomatous lesions with one or more malignant germ cell lines such as embryonal carcinoma, endodermal sinus tumor, or choriocarcinoma or with malignant elements of rhabdomyosarcoma, neuroblastoma, or epithelial carcinoma (29,39,287,289). GCTs are conventionally categorized into two

highly prognostic histological subgroups: pure germinomas and nongerminomatous (or “malignant”) germ cell tumors (NGGCTs). NGGCTs include GCTs with any malignant germ cell component and/or any tumor that secretes AFP or high levels of β -HCG (levels > 100–200 IU considered “high”). Some international trials have classified these tumors simply as “secreting” and “nonsecreting” based on the high likelihood of secretion from malignant germ cell components and lack thereof from pure germinomas (22,290). Pure germinomas carry a much more favorable prognosis, and therefore are generally treated less aggressively than NGGCTs.

CNS GCTs usually occur as midline third ventricular lesions. These tumors most often arise in the pineal region at the posterior third ventricle (50–60% of presentations) or from the infundibulum/pituitary stalk in the suprasellar region at the anterior recess of the third ventricle (30–35% of cases). Less common locations for primary intracranial GCTs



Figure 3.11 Midline multifocal germinoma involving suprasellar (anterior arrow) and pineal gland (posterior arrow) regions. This phenomenon is typically seen with pure germinomas in adolescent males.

include the basal ganglia or thalamic nuclei (22,286, 289,291,292). Involvement of multiple tumor sites around the third ventricle is common, most often the pineal and suprasellar regions concurrently; such tumors are referred to as “multiple midline germinomas” and appear to represent multicentric tumor development or subependymal infiltration around the ventricle rather than subarachnoid or CSF pathway metastasis (22,289,293,294). Up to 20% of intracranial germinomas present as multiple midline tumors, especially noted in adolescent males (Fig. 3.11). This phenomenon is much more frequently encountered with pure germinomas, but has been reported with NGGCTs (295). Leptomeningeal spread through the cerebrospinal axis may be seen, but is much less common.

Pineal germinomas occur with a higher prevalence in adolescent males. Suprasellar germinomas occur throughout the first two decades; there is no gender predilection for this location (22,289). Teratomas tend to occur in younger children, and other malignant histiotypes (e.g., embryonal carcinoma,

endodermal sinus tumor) generally present in older children, adolescents, and young adults.

GCTs are the most common tumors arising in the pineal region. A unique spectrum of neoplasms presents a broad differential diagnosis for tumors arising in the posterior third ventricular region (Table 3.5). Approximately 80% of the pineal region tumors in children and adolescents are GCTs (60–70%) or pineal parenchymal tumors (10–20%). In very young children, the most common tumor type is the pineoblastoma. Less common histiotypes include glial tumors (astrocytomas, ependymomas) and arachnoid cysts. Pineoblastomas are embryonal CNS tumors described earlier. Pineocytomas are “mature” parenchymal cell neoplasms, which are rare in children, clinically benign in adolescents but potentially malignant in younger children (296,297). The differential diagnosis for suprasellar tumors is also rather broad, including astrocytomas and craniopharyngiomas (together, more than 80% of lesions in this location) as well as GCTs.

Pineal GCTs present most often with increased intracranial pressure caused by compression of the adjacent Sylvian aqueduct. Ocular signs are classically noted as the Parinaud syndrome: a triad of decreased upward gaze, abnormal pupillary responses described as near-light dissociation (limited constriction to light but retained pupillary response to accommodation; otherwise known as the Argyll–Robertson pupil), and convergence nystagmus (22,298). Findings occur as a result of pressure from the pineal tumor on the superior colliculus of the tectum. In suprasellar GCTs, the classic triad of presenting symptoms is diabetes insipidus, precocious or delayed sexual development, and visual deficits (291,299). Diabetes insipidus or other symptoms of suprasellar disease in conjunction with an apparently isolated pineal tumor are virtually diagnostic of a multiple midline germinoma and should be treated as such (300–302). Conversely, care should be taken in evaluating the pineal region with suprasellar tumors (303).

Evaluation for GCT should include MRI of the brain with and without gadolinium with thin cuts (≤ 2.5 mm thickness, no skip) through the suprasellar and pineal regions. A screening MRI of the spine should be obtained with axial images through any regions suspicious for disease. Lumbar puncture with CSF cytology and CSF AFP and β -HCG should be obtained with

Table 3.5

Pineal Region Tumors—Relative Incidence

Tumor Type	Relative Frequency (%)	Characteristics
Germinoma	40–60	Predominantly adolescent males, (–) AFP; may have isolated (+) β -HCG (typically to <15 to 75 units)
Malignant GCTs: endodermal sinus tumor, choriocarcinoma, malignant teratoma, immature teratoma	20–25	(+ + +) AFP (+ + +) β -HCG; frequent intralesional hemorrhage often partly calcified; (+ +) AFP $\pm$ (+ +) β -HCG
Pineal parenchymal tumors: pineoblastoma, pineocytoma	14	Predominantly in young children
Glioma, astrocytoma, ependymoma	15	Uncommon in children/adolescents Adjacent to pineal gland; intra-axial tumors, typically low grade

caution, especially in children with large pineal tumors or potentially persistent increased intracranial pressure. Serum AFP and β -HCG should also be measured. AFP is usually present in serum and CSF in embryonal carcinoma, endodermal sinus tumor, or malignant teratoma (287,288). β -HCG is elevated in a subset of germinomas (10–20% of pure germinomas show levels above 10 IU, up to 70–100 IU; levels above 100–200 IU are found in germinomas with syncytiotrophoblastic giant cells); significant elevation (typically more than 1000 IU) is diagnostic of choriocarcinoma (22,287,288,290,304–306). If there is any detectable elevation of AFP above institutional norm (generally, serum >5 –10 ng/dL; CSF >2 –5 ng/dL), this is diagnostic of malignant germ cell histiotype; the tumor is classified as an NGGCT. β -HCG elevation may be seen in pure germinomas; the appropriate cut-off for categorization as a NGGCT is controversial. The COG ultimately recognized values >75 to 100 IU/L; this may be a conservative number (307–309). Additional baseline studies should include a full evaluation of hypothalamic and pituitary function, ophthalmological examination, and baseline neuropsychological testing.

Therapy

Treatment of CNS GCTs is controversial, from the decision to establish histology to the role of surgery, radiation parameters, and the role of chemotherapy. Although excellent disease control has been reported in series based on clinical and imaging diagnosis (i.e., without histological confirmation), specific radiation, chemotherapy, and surgical interventions are best guided by a histologic diagnosis (Table 3.6). At present, clinicians routinely recommend confirmation of pathology for all GCTs, regardless of location. When there is a significant elevation of tumor markers in serum or CSF (any clear elevation of AFP or marked elevation of β -HCG, typically more than 100–200 IU), clinicians may consider the diagnosis of an NGGCT without a biopsy. Similarly, a classical imaging presentation with β -HCG above normal but <100 IU is sometimes considered pathognomonic of germinomas. Others advocate for histological verification in all settings, as some studies indicate important prognostic implications based on histological subtypes (290,310).

Historically, the nonoperative approach for pineal region tumors had been to assume the relative dominance of germinoma, especially among adolescent males with pineal region tumors, and initiate local irradiation as a “histologic test.” Prompt tumor reduction (after 20–25 Gy) was interpreted to be diagnostic of germinoma, and subsequent therapy used modified radiation parameters based on institutional use of local, cranial, or craniospinal fields (311–313). If a tumor showed limited early response to the “test” dosage, then surgical intervention was entertained, or subsequent therapy (modified radiation parameters with chemotherapy) was based on the presumption of a benign (e.g., teratoma, glioma) or malignant (i.e., malignant germ cell histiotype) tumor (9,313). However, it is clear that tumors other than pure germinomas may show a prompt response to radiation therapy. In addition, major improvements in neurosurgical techniques over the past two to three decades have markedly decreased rates of morbidity and mortality. In modern practice, the “radiation dose test” is not a recommended approach.

Radiation therapy has long been the standard sole treatment or an essential element of treatment for pure

germinomas; it is an important component of multimodality therapy for NGGCTs (312,314–319). Intracranial pure germinomas are quite chemoresponsive; the use of combined chemotherapy and limited-volume and/or limited-dose irradiation has been an alternative approach in treating these tumors (314,320–325). The use of chemotherapy alone has been associated with unacceptable recurrence and mortality rates for GCTs (304,305). For NGGCTs, irradiation alone has achieved disease control in only 20–45% of tumors, and combined-modality therapy, also including chemotherapy and potential surgical resection, is standard (22,310, 313,323,326,327).

Surgery

The goal of surgical resection or biopsy is to provide accurate diagnosis, and in some cases, improve disease control. For patients with suspected GCT without elevation of tumor markers, biopsy is considered mandatory to confirm diagnosis of germinoma and to attempt to rule out malignant germ cell components. Contemporary surgical techniques permit stereotactic or open biopsy for both suprasellar and pineal region tumors with low rates of morbidity and mortality (321,328,329). Although it is clear that limited tissue sampling may lead to misdiagnosis for some patients, particularly in the setting of a mixed histology tumor, aggressive upfront resection is not advocated by the majority of institutions in Europe and North America as higher rates of morbidity and mortality have been encountered; delayed surgery for persistent disease after chemotherapy is preferred (330). However, more aggressive resection is advocated by some authors for therapeutic and prognostic implications and is routinely performed in Japan (290,310,331). In the past, there was some suggestion that surgery or biopsy predisposed the patient to a higher risk of subarachnoid dissemination; this has been refuted (313,328,332).

There is no known advantage to achieving a GTR for pure germinomas (333,334). However, a benefit of surgical resection for NGGCT has been suggested if yet somewhat controversial (321,323,326,335). Some series have shown a trend toward improved control with more aggressive resection for malignant histiotype. As stated above, others advocate initial chemotherapy with consideration of second-look surgery for tumors or components of tumors that do not respond. Often, teratoma components of these tumors do not respond to chemotherapy and may even grow during chemotherapy. For these cases, surgical resection is therapeutic and provides local control.

For patients with pineal region tumors that present with hydrocephalus, decompression of the ventricles is required, often urgently. The placement of a ventriculoperitoneal shunt or external ventricular drain can provide relief of hydrocephalus. Endoscopic third ventriculostomy (ETV) is a particularly attractive, alternative method of treating hydrocephalus by diverting CSF flow and obtaining a biopsy under direct visualization. This procedure is performed by inserting and guiding a ventriculoscope through the lateral and third ventricles and then carefully creating a hole in the thin membrane of the floor of the third ventricle and establishing flow between the third ventricle and the prepontine cistern (Fig. 3.12). ETV also allows for close inspection of the ventricular system and may be more sensitive than MRI for detection of metastatic deposits (336).

Table 3.6

Intracranial Germinoma—Outcome^a

Primary Therapy/Series	n	RT Volume/Dose	Chemotherapy Timing	Drugs	PFS at 5 Years	OS at 5 Years
Radiation Therapy						
JCRT, Boston (318)	40	CrI (15–44 Gy, median 32 Gy), local (median 52 Gy) SpI (n = 30, median = 25 Gy)	n = 4j	CDDP-based	97%	100%
Mayo Clinic ⁱ	32	CrI or CSI (median = 30 Gy), local (median = 48.5 Gy)	n = 5	CDDP/VP-16	70%	91%
Kyoto University (333)	38	local (n = 13)/36–50 Gy ^b CSI (n = 25) M + or selected/21–24 Gy CSI (primary as above)	0		95%	97%
MAKEI 83/86/89 ^c (330,354)	11	CSI (36 Gy), local (50 Gy)	0		100%	100%
	49	CSI (30 Gy), local (45 Gy)			89%	92%
St. Jude (353)	12	CSI (median = 25.5 Gy), local (median = 50.4 Gy)	0		100%	100%
M.D. Anderson ^e	12	CSI (24 Gy), primary T (50 Gy)			100%	83% at 10 years
	9	1° T + 2 cm 30.6 Gy	Pre-RT		59%	89% at 10 years
Seoul National University ^g	39	CSI (21 Gy), primary T 54 Gy (45 Gy with CR)			100%	
Yonsei Cancer Center, Seoul ^h	81	CSI or CrI (36 Gy, later 19.5 Gy) 1 T (59, later 39 Gy)	O		100%	96%
			O		69% (9/13)	
Chemotherapy → Reduced RT						
New York University (321)	11	Local/30 Gy, CSI (M+)	Pre-RT	Cyclo		91%
Hokkaido University (342)	15	Local (n = 11), (pre-RT volume)/24 Gy CSI (n = 2 M+)/24 Gy	Pre-RT × 4	CDDP/VP-16 (n = 6, localized) ifos/CDDP/VP-16 (n = 9, ↑-HCG, multifocal, or M+)	83% at 4 years	100%
SFOP ^d (343)	57	local (n = 51, pre-RT volume)/40 Gy local 30 Gy, CSI (M+)	Pre-RT × 2	CBCDA/VP-16/ifos	96 at 3 years	98% at 3 years
POG 9530 (337)	12	Primary tumor + 2 cm 30.6 Gy; if CR, 50.4 Gy if residual	VP-16–CDDP–CBCDA–vcr		95%	100%

(Continued)

Table 3.6

Intracranial Germinoma—Outcome^a (Continued)

Primary Therapy/Series	n	RT Volume/Dose	Chemotherapy Timing	Drugs	PFS at 5 Years	OS at 5 Years
Seoul National University ^g	42	1 T (50 Gy) (45 Gy with CR)	66 bleomycin VP-16-cyclo- vcr, or “8-in-1” ^f		80%	100% (93% at 10 years)

CrI, cranial irradiation; CDDP, cisplatin; CSI, craniospinal irradiation; ifos, ifosfamide; VP-16, etoposide; CBCDA, carboplatin; cyclo, cyclophosphamide; Spl, spinal irradiation.

^aOutcome in series of children and, in several, adults up to 30–40 years of age.

^bLocal tumor RT dose size-dependent.

^cGerman Society of Pediatric Oncology and Hematology studies.

^dFrench Society of Pediatric Oncology.

^eNguyen QN, Chang EL, Allen PK, et al. Focal and craniospinal irradiation for patients with intracranial germinoma and patterns of failure. *Cancer*. 2006;107:2228–2236.

^f“8-in-1” = vcr-CCNV-PC2-hydroxyurea-CDDP-cytosine arabinoside—cyclophosphamide.

^gEom KY, Kim IH, Park CI, et al. Upfront chemotherapy and involved-field radiotherapy results in more relapses than extended radiotherapy for intracranial germinomas: modification in radiotherapy volume might be needed. *Int J Radiat Oncol Biol Phys*. 2008;71:667–671.

^hCho J, Choi JU, Kim DS, et al. Low-dose craniospinal irradiation as a definitive treatment for intracranial germinoma. *Radiother Oncol*. 2009;91:75–79.

ⁱHaddock MG, Schild SE, Scheithauer BW, et al. Radiation therapy for histologically confirmed primary central nervous system germinoma. *Int J Radiat Oncol Biol Phys*. 1997;38:915–923.

^j4 of 41 patients received chemotherapy

Radiation Therapy

For pure germinomas, radiation therapy has been the major curative modality. Long-term disease control rates range from 80% to more than 90–95% with the use of irradiation alone (291,293,306,313,316,317,319,328,332,337). There is ongoing controversy regarding the appropriate radiation volume (local tumor with or without wider volumes that have included third ventricular, full ventricular, full cranial irradiation, or CSI) and dose (40–50 Gy for primary irradiation). Whether primary radiation therapy is the best course of treatment is often a complex decision based on tumor site and extent, the child's age, and the child's functional status at presentation,



Figure 3.12 Sagittal T1-gadolinium image showing third ventriculostomy defect. Endoscopic third ventriculostomy (ETV) alleviates hydrocephalus by creating flow from the ventricle to the preoptine space.

presenting a choice between irradiation alone or a combination of chemotherapy and reduced-dose, limited-volume irradiation (328,338). The recently closed COG trial, ACNS 0232, attempted to determine the better treatment; radiation alone or chemotherapy and response-based reduced volume and dose irradiation. Unfortunately, this trial closed due to poor accrual leaving this important question unanswered.

For NGGCTs, combined chemotherapy and irradiation is the standard, again with some uncertainty regarding the appropriate radiation volume (local, whole ventricle, whole brain, or craniospinal) (22,323,339). The use of stereotactic radiosurgery to boost local disease visible on imaging after and persistent after chemotherapy and fractionated radiation therapy is rational, but investigational for children with persistent NGGCT that cannot be safely removed by surgery (340,341).

Chemotherapy

Intracranial GCTs are chemosensitive, with excellent objective response rates documented for cyclophosphamide; carboplatin; cisplatin and etoposide; ifosfamide, carboplatin, and etoposide; and cisplatin, etoposide, and bleomycin (305,321–324). Objective response rates approach 100% for germinomas (305,321,324,342,343).

Several series using preirradiation chemotherapy and limited-volume, “response-adjusted” attenuation of radiation doses have shown excellent disease control rates. Initially explored in the United States by Allen with the use of cyclophosphamide and, later, platinating agents, this treatment has resulted in a large proportion of complete or substantial responses, with long-term disease control after local irradiation to reduced dose levels of 24–36 Gy (321–324,342,343). Carboplatin, most often in combination with etoposide, has replaced cisplatin for germinomas because the drug is associated

with fewer long-term sequelae (322,324,343). The major short-term morbidity has been difficulties handling fluid and electrolyte balance in children with suprasellar tumors, often associated with diabetes insipidus and/or salt-wasting syndromes. This has been associated with early mortality during chemotherapy (305). The aim of combined chemotherapy and irradiation has not been to improve disease control, but to potentially improve long-term functional outcomes by decreasing radiation doses and/or volumes (311,322,338,344). The recently abandoned Phase III COG study had randomized patients with local disease to whole ventricular radiation therapy followed by a boost to the primary tumor bed or preirradiation chemotherapy (two cycles of carboplatin and etoposide) followed by involved field, reduced dose irradiation if complete response (CR) was documented. If CR was not obtained, two cycles of cisplatin and cyclophosphamide were administered; radiation dose depended upon response at the completion of the additional chemotherapy. For patients with disseminated disease, CSI was required, doses dependent upon response to chemotherapy.

The use of chemotherapy alone for intracranial germinomas has been tested in the international protocols coordinated by Balmaceda and colleagues (305). This trial included pure germinomas and NGGCTs. The first drug regimen tested (carboplatin, etoposide, bleomycin, $\pm$ cyclophosphamide) achieved high initial response rates, but disease progression or recurrence occurred in 50% of patients (both pure germinomas and NGGCTs); unacceptable chemotherapy-related mortality approximated 10% (305). Failures occurred primarily in the primary site at the ventricular system, with $<5\%$ in the spine. Although Merchant et al. (345) reported systematic salvage following chemotherapy-alone failure with high-dose cyclophosphamide and CSI, the more aggressive combined-therapy regimen is excessive in a significant cohort of children who would enjoy favorable outcome with less intensive initial radiation therapy (311).

For NGGCTs, prognosis with irradiation alone is inadequate; overall long-term survival rates approximate 20–40%. The addition of platinum-based chemotherapy has markedly improved outcome, with short-term survival rates in excess of 70%. Chemotherapy has become a standard component of therapy for these tumors prior to irradiation (323,326,343). Chemotherapy on both the French Society of Pediatric Oncology (SFOP) and recently completed COG ACNS 0122 study used alternating cycles of carboplatin/etoposide and ifosfamide/etoposide (346). The regimen has been both efficacious and well tolerated.

High-dose chemotherapy with stem cell rescue has shown promise for relapsed GCTs (347). For the subgroup of patients who do not experience a CR to all other modalities of treatment, this approach has been considered and was recommended for patients who did not undergo CR to chemotherapy and could not safely undergo a second look surgery on ACNS 0122.

Radiotherapy Management Volume and Technique

There has been continuing debate regarding the need for large-volume irradiation (full cranial or CSI or, alternatively, the entire ventricular system) for localized GCTs, both pure germinomas and NGGCTs. The concept originated in the pre-

CT era when Sung and colleagues (299) showed a more than 10% risk of subarachnoid dissemination in pineal region GCTs; among biopsied suprasellar germinomas, neuraxis dissemination occurred in 43%. Several more recent studies have proposed limiting the radiation volume to the primary tumor alone, the third ventricle, the whole ventricular system, or the whole brain. When volumes are larger than the involved field (i.e., ventricles, whole brain), a higher dose is administered as a “boost” to the primary tumor (328,332,333,348,349).

Evidence of disease beyond the primary site is apparent in 10–20% of intracranial germinomas at diagnosis. Third ventricular disease occurs as multiple midline presentations, classically involving the pineal and suprasellar recesses but sometimes showing multiple subependymal nodules along the linings of the ventricle (third and, less often, lateral) (293,311,312,332,337,350). Overt spinal seeding is rarely demonstrable by imaging (312,337). CSF involvement has been documented in fewer than 15% of cases (299,313). A higher rate of positive CSF cytology has been reported in Japanese series, where Shibamoto et al. (351) described disease-free survival in all of the six children with positive CSF cytology after irradiation limited to the third ventricular volume (315).

A large proportion of clinical series reporting disease control rates higher than 90% in the past years have been based on low-dose CSI as a component of therapy (312,313, 323,328,344,352,353). Other series report nearly similar results following more limited radiation volumes (290,312,328, 332,333,348,354). The incidence of spinal failure, specifically, has been reported to be 0–10% after irradiation to cranial volumes only (290,312,316,317,332, 333,348,354). Radiation volumes limited to the local tumor bed without the ventricles have been associated with significant rates of intracranial or ventricular region relapse in recent series; somewhat older series report high rates of disease-free survival with varying volumes identified as “local” without further description (328,337,354–356).

In light of these data, there is recognition that CSI has a marginal benefit for pure germinomas treated solely by radiation therapy (311,328,338). The potential gain is controversial and must be weighed against the potential added toxicities of 24–25 Gy to the neuraxis. In considering the debate on therapeutic volume, some studies reporting functional outcome or quality of life among long-term survivors of CSI in childhood and adolescence have shown remarkably normal achievement (344,353). Perhaps the most concerning morbidities associated with low-dose CSI in this setting are secondary neoplasms and cardiac dysfunction, the latter difficult to quantify. The most common approach has now migrated toward treatment of the full ventricular system (the “large field” component) followed by a boost to the site(s) of initial disease.

All patients with metastatic disease at diagnosis require CSI: 24–30 Gy with irradiation alone or 21–24 Gy with combined chemotherapy and irradiation; local doses to the primary and large metastatic foci remain 45 Gy or 30 Gy, cumulative, the former for radiation alone and the latter, combined therapy.

Local radiation volumes have included the primary tumor only, using a 1- to 2-cm anatomic expansion to define the CTV, or broader fields encompassing at least the third ventricle. Image-guided therapies using multiple (often

noncoplanar) fields, stereotactic radiotherapy, or proton beam are dosimetrically superior in treating midline GCTs (341,342,350). Care should be taken to ensure that the local volume is encompassed by the larger initial ventricular target volume. For tumors with multiple midline involvement, the initial radiation volume should include the neuraxis or the entire ventricular system at a minimum (333,348,350). Whole ventricular radiation is a sizable volume; however, using modern techniques (3D conformal radiation, IMRT, or proton radiation therapy) one can spare a substantial amount of cortical tissue when compared with full cranial irradiation (259–261,269–271,357) (Fig. 3.13). This whole ventricular volume can be challenging to define and should be done carefully and often with the help of a neuroradiologist.

For NGGCTs there seems to be consensus that even in the setting of chemotherapy, high radiation doses are required. However, the appropriate volume is controversial. Studies using chemotherapy followed by CSI plus a boost to the primary site have yielded long-term survival rates of 67–74% (323,326). The recently closed Phase II COG study for NGGCT, ACNS 0122, delivered six cycles of alternating carboplatin/etoposide and ifosfamide/etoposide followed by CSI to a dose of 36 Gy and an involved field boost to deliver a total dose of 54 Gy to the tumor bed. Preliminary reports are quite favorable. Limited trials from Europe and Japan have documented excellent disease-free survival for chemotherapy followed by whole ventricular or local field irradiation for patients with NGGCT (358,359). Lack of response to chemotherapy has been found to be a poor prognostic factor for NGGCTs (305,359). Second-look surgery is considered for these patients. For those who cannot safely undergo a second surgical, prognosis is poor. Incorporation of a final stereotactic radiosurgical “boost” to the local tumor site may be appropriate for persistent, unresectable NGGCTs (340,341).

Dosage

Dose-response data for intracranial germinomas had classically been identified at 50 Gy despite the known radioresponsiveness of extracranial seminomas and germinomas (291,293,313,328,337). More recent analyses suggest that a dosage of 40–45 Gy is appropriate for pure germinomas (316,318,333,351). The elective dose to the neuraxis (i.e., for M0 disease) is 21–24 Gy; in patients with positive cytology, neuraxis levels of 24–30 Gy have been used successfully. Similarly, in patients receiving full cranial or ventricular volumes, the dose to the initial volume is 21–24 Gy (311,350,353,354). The primary area(s) of tumor involvement require a total dose of approximately 45 Gy.

In conjunction with chemotherapy, patients with pure germinoma receive radiation doses of approximately 30 Gy after complete or near CR, with doses in the range of 36 Gy for patients with partial or incomplete response (24,322,342,343,356). Patients with less than partial response receive full-dose irradiation (45 Gy). Successful salvage (for patients with progressive or recurrent disease during or after primary chemotherapy) has been reported with 30 Gy to the neuroaxis and 45–50 Gy to the local tumor region (345).

Patients with NGGCT receive chemotherapy first. Consolidative irradiation generally has been delivered in doses in excess of 50 Gy to the primary site of disease. The use of CSI is somewhat controversial, but is considered the standard treatment in North America. Local field radiation to a dose of

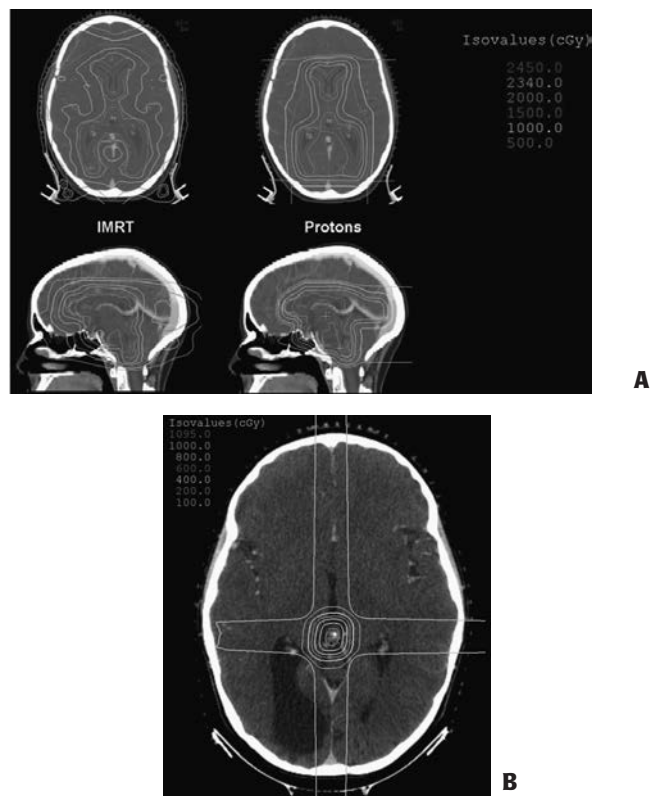


Figure 3.13 **A:** Axial and sagittal images of intensity-modulated photon radiation therapy (L) and proton therapy (R) plans for whole ventricular irradiation. Both techniques are highly conformal; care should be taken to accurately define the whole ventricular volume. **B:** Proton “stereotactic boost” to residual disease following chemotherapy and standard radiation therapy for NGGCT of the pineal gland.

54–59.4 Gy is the standard in many European countries; it was the standard treatment on the recently presented SFOP and SIOP studies (358). The next COG study for NGGCT plans to explore reduced volume irradiation (whole ventricle followed by boost) for patients with more favorable prognosis.

Results

Five-year disease-free survival rates of 90–95% is documented in pure germinomas treated with primary radiation therapy (291,313,315,316,318,328,333,337,350,351,353,354). Comparable results are reported with induction chemotherapy and more limited irradiation (321,322,324,342,343,358). It is important to recognize a 10% incidence of late failure (between 5 and 15 years) (293,337,350). Disease control with primary chemotherapy has been only about 50% (284). At present, there is no clear standard, and treatment choice is often based on tumor and patient characteristics and physician and/or parental biases.

For NGGCTs, survival after radiation alone is inadequate, and platinum-based chemotherapy is standard for all patients (22,313,321,352). Volume remains controversial, with the most recent standard in the United States being CSI followed by boost, but a future COG protocol under consideration plans for reduced volume irradiation (whole ventricle followed by boost) for selected patients. Malignant germ cell types that do

not respond completely to chemotherapy carry a worse prognosis, and continue to be a therapeutic challenge. The use of combined-modality therapy has been associated with long-term disease control rates of 50–67%, potentially improved with the addition of surgical resection or selected use of radio-surgical boost to the primary residual tumor (Fig. 3.4) (323,326,340,341,360,361). With further understanding of this disease and improvements in therapy, one would hope to bring the outcomes of malignant germ cell types closer to that of pure germinomas.

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Tumors of the Posterior Fossa and the Spinal Canal

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The posterior fossa occupies the lower half of the posterior cranial vault, bounded anteriorly by the clivus and posterior clinoid and inferiorly by the occipital bone and foramen magnum. Superiorly, the margin is defined by the tentorium cerebellae, that portion of the dura mater extending from the basisphenoid adjacent to the posterior clinoid, rising to cover the cerebellum, and extending posteriorly and inferiorly to insert at the level of the inion (the prominent midline outpouching of the occipital bone). The cerebellum and brainstem are located within the posterior fossa.

Nearly one half of all childhood brain tumors arise in the posterior fossa. The most common types are medulloblastoma, low-grade astrocytomas of the cerebellum, brainstem gliomas, and ependymomas (see Table 3.1) (1–3).

MEDULLOBLASTOMA

Medulloblastoma is a primitive cerebellar tumor of neuroectodermal origin. The tumor is the most common malignant brain tumor in children and adolescents, accounting for 20% of pediatric brain tumors or approximately 540 cases per year in the United States (1,3). Medulloblastoma was first identified in Bailey and Cushing's 1925 classification of central nervous system (CNS) tumors (4,5). The classic description defined medulloblastoma as a primitive (embryonal) tumor of the cerebellum, derived from putative undifferentiated progenitor medulloblasts located in the cerebellar external granular layer.

The World Health Organization (WHO) classification of CNS neoplasms identifies embryonal tumors as a subset of the neuroepithelial neoplasms that are particularly prominent among pediatric brain tumors (6). The current WHO classification is included in Table 3.2, separately identifying the three major categories of embryonal CNS tumors: (1) medulloblastoma and its subtypes; (2) CNS primitive neuroectodermal tumors (PNETs, including supratentorial PNETs, CNS neuroblastoma, CNS ganglioneuroblastoma, medulloepithelioma, and ependymoblastoma); and (3) atypical teratoid/rhabdoid tumors. Note that pineoblastoma, considered clinically as a type of PNET, is listed separately as a tumor of the pineal region (6).

The most common embryonal CNS tumor is medulloblastoma, by definition a malignant embryonal tumor arising in the cerebellum, with predominantly neuronal differentiation. The tumor is thought to arise from cerebellar stem cells in the superficial external germinal layer (giving rise to cerebellar granule cells) or the deep-seated subventricular

zone in the midline posterior medullary velum (generating cerebellar neuronal and glial cells) (7,8). DNA microarray gene expression patterns reported by Pomeroy et al. confirm the apparent derivation of medulloblastoma from the molecularly similar cerebellar granule cells, genetically distinct from supratentorial PNETs (9).

Histologically, medulloblastoma is a densely cellular neoplasm composed predominantly of undifferentiated small, round, blue cells. Differentiation may be toward neuronal or glial (astrocytic, oligodendroglial, and, less commonly, ependymal) lines in the more common “classic variant.” (6,10). Differentiation along mesenchymal lines (focal rhabdomyoblastic areas) define a variant called medulloblastoma (6,10). Approximately, 10% to 20% of medulloblastomas can be categorized as desmoplastic type, marked by relatively hypocellular areas of prominent nodularity in reticulin-free zones, occurring most often in the cerebellar hemispheres (6). Desmoplastic medulloblastoma is associated with mutations within the sonic hedgehog (SHH)–patched (PTCH) pathway and overexpression of IGF-2 (11–13). There is considerable excitement about the SHH pathway as a target for newly developing molecular-targeted therapies. Rodent models show the efficacy of cyclopamine in blocking the SHH pathway, resulting in dramatic shrinkage or prevention of the recombinant mouse medulloblastoma model (14,15). Anaplastic tumors are marked by nuclear pleomorphism and high mitotic rate; these tumors overlap with large cell medulloblastoma and are marked by chromosomal loss (17p-), *MYC* amplification, and poor prognosis (13, 16,17). Overexpression of *ERBB2* may also be related to anaplastic large cell tumors and is a similarly negative prognosticator (12).

The histologic grade of medulloblastoma has only recently been linked to prognosis. Extensive nodularity has been correlated with favorable outcome; desmoplastic variant is similarly a marker of more favorable diseases (13,18,19). The degree of anaplasia (and, particularly, the subset of large cell anaplastic tumors) has been associated with inferior survival rates (13,16,17,20). Tumors with extraneural metastasis, either at diagnosis or as a pattern of failure, are more often associated with markedly anaplastic histology (18,21).

From the clinical genetics standpoint, medulloblastoma is the CNS tumor most often associated with germline mutations and familial diseases (see Table 3.3). The most frequent association is between Gorlin syndrome (nevroid basal cell carcinoma syndrome [NBCCS]) and desmoplastic medulloblastoma, both related to the tumor suppressor gene *PTCH*

and the SHH receptor). In younger children, NBCCS is associated with extensive nodularity (19). NBCCS is characterized by somatic abnormalities (cutaneous nevi and palmar or plantar pits, odontogenic keratocysts of the jaw, bifid or fused ribs, falx calcifications) and development of numerous basal cell carcinomas, medulloblastoma, and rhabdomyosarcoma (12,19,22). In addition, mutations of the SHH-PTCH pathway are found in 10% to 20% of “sporadic” medulloblastoma (11,15). *TP53* mutations mark the Li-Fraumeni syndrome, associated with a small percentage of medulloblastoma.

Mutations of the *APC* gene define Turcot syndrome of colonic polyposis, also seen in conjunction with medulloblastoma (6). Mutations of the WNT pathway, developmentally linked to proliferation of stem cells in the subventricular zone, were first noted in children with Turcot syndrome. The pathway is activated in 5% to 10% of sporadic medulloblastomas with classic histopathology, manifest by accumulation of intranuclear β -catenin and associated with quite favorable prognosis; Wnt/Wg-active tumors are associated with isochromosome 16 (13,15,20, 23,24). *Notch2* overexpression has also been noted in medulloblastoma, interesting as hypoxia appears to promote neural stem cell proliferation through Notch (25).

Other molecular correlations important in understanding the current directions in medulloblastoma include TrkC expression (directly proportional to survival in one major study) and ErbB2 expression. The latter factor is biologically related to cerebellar granular cell proliferation, migration, and invasion; elevated levels of ErbB2 are associated with poor outcome. (12,25,26)

The median age at diagnosis is 5 to 6 years. Approximately 20% of medulloblastomas present in infants younger than 2 years and 10% occur in young adults. Boys are affected more often than girls. Presenting symptoms are those classically associated with posterior fossa lesions in children: symptoms related to elevated intracranial pressure (headaches

and vomiting, especially in the morning) and ataxia. Elevated intracranial pressure results from the tumor obstructing CSF flow through the sylvian aqueduct and the fourth ventricle.

Approximately 75% of medulloblastomas present in the midline cerebellar vermis. The tumor characteristically grows into and fills the fourth ventricle. Infiltration around the fourth ventricle is common, often involving the brachium pontis and extending onto the ventricular floor (i.e., the brain-stem). Nearly one in four tumors arises within the cerebellar hemispheres, more commonly with desmoplastic histology. On magnetic resonance imaging (MRI), medulloblastomas are well-defined, typically solid lesions with uniform or, less often, nonhomogeneous contrast enhancement. Correlation between MR spectroscopic findings and metastasis at diagnosis has been reported (9). By computed tomography (CT) scan, the tumor often is hyperdense, reflecting high cellularity.

Medulloblastoma is the classic CNS tumor associated with CSF seeding or metastasis. The standard of care requires postoperative staging, typically based on imaging of the brain to assess degree of resection and potential subarachnoid metastasis (ideally within 24 hours, but acceptable up to 72-hours postsurgery), spinal MRI (gadolinium-enhanced study approximately 10 to 14 days after surgery to assess potential overt metastasis), and lumbar CSF cytology (best obtained immediately after spinal imaging). Subarachnoid dissemination has been reported at diagnosis in 20% to 35% of children (27,28). A review of 106 consecutive cases staged at diagnosis showed leptomeningeal disease in 32%, noted on both spinal MRI and CSF cytology in 12%, positive CSF alone in 8%, and MRI alone in 11% (20,28). Neuraxis disease typically involves the spinal subarachnoid space; intracranial metastasis is less common, noted as isolated disease in the basal or suprasellar cisterns (Fig. 4.1) or diffusely in the subarachnoid space (29).

Since publication by a radiation oncologist, the Chang (30) staging system has been used for clinical staging in medulloblastoma. The system was developed in the pre-CT

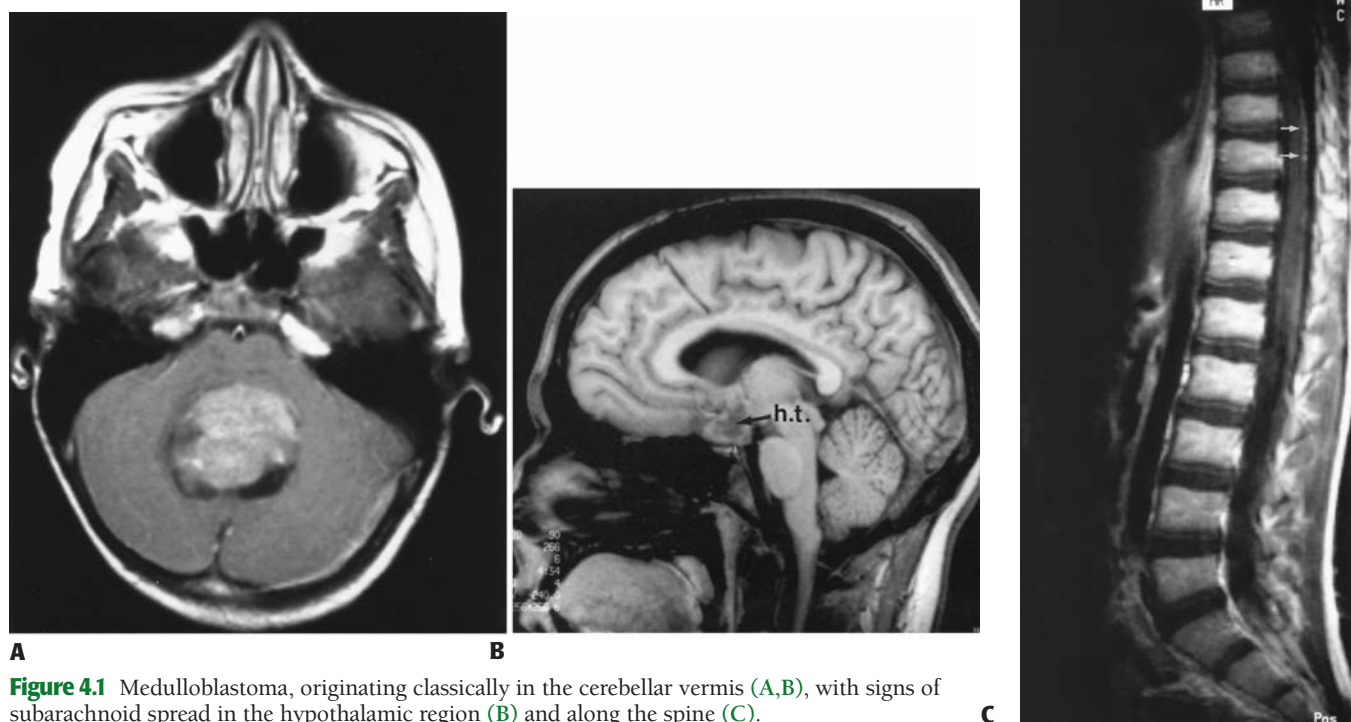


Table 4.1

Chang Staging for Medulloblastoma^a

T ₁	Tumor <3 cm in diameter	M ₀	No evidence of subarachnoid or hematogenous metastasis
T ₂	Tumor ≥3 cm in diameter	M ₁	Tumor cells found in cerebrospinal fluid
T _{3a}	Tumor >3 cm in diameter with extension	M ₂	Intracranial tumor beyond primary site (e.g., into the aqueduct of Sylvius and/or into the subarachnoid space or in the third or foramen of Luschka or lateral ventricles)
T _{3b} ^b	Tumor >3 cm in diameter with unequivocal extension into the brainstem	M ₃	Gross nodular seeding in spinal subarachnoid space
T ₄	Tumor >3 cm in diameter with extension up past the aqueduct of Sylvius and/or down past the foramen magnum (i.e., beyond the posterior fossa)	M ₄	Metastasis outside the cerebrospinal axis (esp. bone marrow, bone)

^aA pre-CT era system described by Chang (30), modified by J. Langston (*personal communication*, 1988).

^bT_{3b} is generally defined by *intraoperative* demonstration of tumor extension into the brainstem.

Note: T staging is of historical interest only, no longer used for clinical staging (33).

era and is based on the size and invasiveness of the primary tumor at surgery (“T stage”) and evidence of spread outside the posterior fossa (“M stage”) (Table 4.1). Progressive tumor size and invasion of the brainstem defined increasing local tumor burden and aggressive behavior, classified as T_{1–4}. With the advent of CT and MRI, it became apparent that imaging identification of brainstem invasion is not as reliable as surgical observation. There is no modern data to substantiate a role for T stage as an independent parameter predicting outcome or defining therapy (31,32). Comparisons in otherwise early medulloblastoma (defined as M₀ with complete or near total resection) and in series addressing advanced medulloblastoma have shown equivalent outcome among those with brainstem invasion (T_{3b}) and those without such (T_{1–3a}) (31,33).

M stage is based on subarachnoid metastasis, progressively coding abnormal CSF cytology (M₁) or imaging evidence of noncontiguous tumor in the cranium (M₂) or spine (M₃). Extraneural disease (most often confined to the bone marrow or bone) is present in fewer than 2% of cases at presentation, coded as M₄. M stage remains a highly significant prognostic factor; intensity of therapy in current protocols and outcome are strongly related to the presence or absence of metastatic disease (31,32,34,35).

Current clinical trials and standard management in North America define clinical risk categories for medulloblastoma as average risk (children older than 3 years with no metastatic disease after near total or total resection, with less than 1.5 cm² residual on early postoperative imaging) or high risk (overt metastatic disease based on CSF cytology or neuroimaging, or the presence of more than 1.5 cm² residual on early postoperative imaging; more recently, all children younger than 3 years of age typically have been classified as high risk based on outcome studies) (36). With appropriately aggressive surgical intent in most centers in the United States and Europe, more than 65% to 75% of children above 3 years of age are staged as average risk. Of the 25% to 35% staged as high risk, more than 85% present with metastatic disease at diagnosis: primarily M₃ (60%), but also M₁ (30%), and M₂ (10%); significant residual tumor at the primary site is present in >15% of cases (20,36,37).

Therapy

Surgery

Harvey Cushing’s (4) classic 1930 report of his experience with medulloblastoma demonstrated the inability of surgery alone to cure this tumor; only 1 of 61 patients survived 3 years after surgery with or without limited irradiation.

Maximal judicious surgical resection underlies most contemporary series (31,32). Gross total resection (i.e., no evidence of residual tumor seen at surgery and negative postoperative imaging) and near total resection (best defined as minimal residual: more than 90% resection estimated by the surgeon and less than 1.5 cm² residual on postoperative imaging) have resulted in superior outcome in comparison to subtotal (51% to 90% resection) or partial (11% to 50% removal) resection and biopsy only (less than 10% removal) (32). Data from the Children’s Cancer Group (CCG) indicate gross total or near total resection in approximately 90% of children (31,32). Survival appears to correlate more significantly with amount of tumor residual (i.e., the surgical result as documented on immediate postoperative imaging) than with the surgeon’s impression of degree of resection; data confirming the value of minimal residual disease are most apparent among children with M₀ disease (32,38). In an earlier CCG trial, 5-year event-free survival (EFS) was 78% for children with M₀ disease and less than 1.5 cm² residual, compared with 54% for those with larger residual volumes (31). For tumors adherent to or invading the brainstem, a report from St. Jude Children’s Research Hospital showed no advantage to pursuing gross total resection compared with near total removal, with none of the cases exhibiting more than 1.5 cm² residual; morbidity appeared to be greater with the more aggressive surgical approach (39). With maximal safe resection a principle of therapy, the impact of minimal residual (<1.5 cm²) is difficult to discern; key is the distinct advantage of treatment on an average-risk regimen whenever possible, assuming such is a “given” for M₀ disease (20,32,40–42).

Operative mortality has been reduced to 2% or less in pediatric neurosurgical centers. However, aggressive surgery may be associated with significant morbidity (32,43,44). The

Table 4.2

Medulloblastoma—Results of Postoperative Radiation Therapy (No Chemotherapy)

Series	Interval	No. Patients	Postoperative Therapy	5-Year PFS	5-Year OS	10-Year OS
Royal Marsden (44)	1950–1964	71	CrI (30–40r), Spl (25–30r), PF (45–50r)	—	40%	30%
Toronto (36)	1977–1987	72	CSI (35 Gy), PF (50–52.5 Gy)	64%	71%	63%
SIOP II (32)	1984–1989	40	CSI (35 Gy), PF (50 Gy)	60%	—	—
POG-CCG (31)	1986–1990	126	CSI (23.4 Gy), PF (54 Gy)	52%	63% n.s.	—
				$p = .08$		
			CSI (36 Gy), PF (54 Gy)	67%	80%	—
M-SFOP 98 (50)	1998–2001	48	CSI (36 Gy/36 fx)	75%	78%	—

CSI, Craniospinal irradiation; CrI, cranial irradiation; Spl, spinal irradiation; r, converted to rad; Gy, Gray; PFS, progression-free survival; OS, overall survival; M-SFOP, French Society for Pediatric Oncology, Medulloblastoma; PF, posterior fossa; fx, fraction.

posterior fossa syndrome has been described in 15% to 25% of children after posterior fossa craniotomy (21,45). The syndrome is signified by difficulty swallowing, truncal ataxia, mutism, and, less often, respiratory failure; recent imaging data suggest the etiology may be a cerebellocerebral diaschisis (45). Symptoms and signs typically are noted after a 12- to 24-hour period of initially uneventful postoperative recovery. Disabling neurologic signs often improve dramatically, sometimes over many months after surgery. It is important to maintain an aggressive, curative approach (including radiation therapy) in children with this syndrome, anticipating significant neurologic recovery, which may not be apparent early in the course of irradiation.

The routine use of ventriculoperitoneal shunts to reduce intracranial pressure before posterior fossa craniotomy resulted in significant improvement in operative morbidity and mortality, when introduced 40 years ago. Children with ventriculoperitoneal shunts typically become shunt dependent. Shunt failure or infection may complicate long-term survival, necessitating revision or replacement in nearly 25% of children measured 5 years after insertion. In many academic pediatric neurosurgical centers, it is a standard procedure to place a ventricular drain (ventriculostomy), as needed, at the time of surgery. The surgeon often can document reestablishment of CSF flow after fourth ventricular tumor resection. Later shunt insertion may be needed in 20% to 25% of children (32,46,47). A delayed shunt insertion approach provides physiologic CSF dynamics for the majority of children, avoiding potential late events related to an indwelling ventriculoperitoneal shunt.

Radiation Therapy

The efficacy of radiation therapy in medulloblastoma was reported within a decade of Cushing's initial description of the tumor. Cutler et al. (48) reported the radiation responsiveness of medulloblastoma and the value of preventive irradiation of the entire neuraxis based on Cushing's clinical series. The seminal report documenting cure of medulloblastoma with craniospinal irradiation (CSI) was published by Bloom et al. in 1969 (49), documenting 32% survival at 5 years and 25% disease-free survival at 10 years. Numerous reports have subsequently confirmed increasing rates of disease control with modern radiation techniques; at standard CSI dose levels, radiation therapy alone

achieves durable disease control in 65% to 75% of patients with average-risk disease (Table 4.2) (33,50). Modifications of radiation volume, dosage, and fractionation have been explored. The outcome following postoperative irradiation alone in average-risk medulloblastoma using conventional radiation parameters (Pediatric Oncology Group [POG]-CCG trial, one arm of which used CSI to 36 Gy, posterior fossa boost to 54 Gy resulting in 65% 7-year EFS in a large cohort evaluated largely by CT myelography rather than spinal MRI scans) has been used as a basis for nonrandomized comparisons in establishing current standards for combined modality therapy in North America. The result is systematic reduction in CSI dosage (to 23.4 Gy; *vi.*) with well-documented efficacy now in average-risk disease when combined with contemporary cis-platinum-based chemotherapy (20,51–53). Agreement on combined chemoradiation is based on disease control rates that appear to be superior to those achieved with irradiation alone for both average-risk and high-risk presentations, a randomized European trial demonstrating improved outcome with chemoradiation compared to contemporary radiation therapy alone, and several studies suggesting improvement in the risk:benefit ratio based on dose–volume modeling and evolving clinical data (52,54–58).

Chemotherapy

Phase II trials have documented the chemoresponsiveness of medulloblastoma to alkylating agents (cyclophosphamide, CCNU[lomustine]), platinum compounds (cisplatin, carboplatin), etoposide (administered orally or intravenously), antimetabolites (methotrexate), and camptothecins (topotecan) (59–62).

The sentinel trial documenting the efficacy of adjuvant chemotherapy was reported by CCG, combining the attenuated CSI dose in average-risk patients that had just shown only 55% EFS at 5 years in the POG-CCG trial referenced in the prior section with concurrent vincristine and postirradiation cis-platinum, vincristine, and CCNU; the 79% progression-free survival (PFS) at 5 years confirmed earlier institutional experience to show among the best disease control rates then documented in this disease (33,34,51). The International Society for Pediatric Oncology (SIOP)/United Kingdom Children's Cancer Study Group (UKCCSG) PNET-3 trial showed improved EFS with limited preirradiation chemotherapy and full-dose irradiation versus equivalent irradiation alone: 78% EFS at 5 years

with preirradiation vincristine, etoposide, carboplatin, and cyclophosphamide compared to 65% with irradiation alone (54). A large randomized trial assessing reduced-dose CSI followed by cisplatin and vincristine with “standard” CCNU versus cyclophosphamide confirmed overall EFS more than 80% with no difference in disease control on either chemotherapy arm; early analysis suggests a larger number of secondary neoplasms may be apparent in the cyclophosphamide arm (53). St. Jude reported a sizable prospective trial using postirradiation “compressed” cyclophosphamide, vincristine, and cisplatin; 83% EFS was obtained without sometimes toxic vincristine during irradiation and with a marked reduction in ototoxicity attending postirradiation cisplatin when the latter was given with amifostine (20,63). The standard of care for children with average-risk medulloblastoma throughout North America has been accepted as reduced-dose CSI (23.4 Gy) followed by chemotherapy including an alkylating agent, vincristine, and cisplatin (Table 4.3).

For patients with high-risk disease, studies through the 1990s typically showed 5-year EFS at the 40% to 50% level following full-dose irradiation and chemotherapy (41,42). St. Jude’s SJMB96 study has shown 70% 5-year EFS following the same compressed chemotherapy noted above, preceded by full-dose CSI (20). Randomized trials have shown somewhat conflicting results regarding the sequence of postoperative therapy: POG showed >60% 5-year EFS in high-risk medulloblastoma regardless of postoperative/preirradiation chemotherapy (cyclophosphamide, vincristine, cisplatin) or the opposite sequence, both using full-dose CSI (64). The German HIT’91 trial showed superior results with postoperative irradiation followed by CCNU/vincristine/cisplatin compared to postoperative ifosfamide/etoposide/high-dose methotrexate/cisplatin cytosine arabinoside followed by irradiation: 83% 5-year EFS compared to 53%, respectively for M_0 patients; no difference was noted in the M_{2-3} cohort, both at <40% EFS (42). CCG 9931 documented a 17% PD rate during a prolonged, 5-month preirradiation regimen, again showing only 43% EFS in high-risk disease (58). Similar trials have noted that outcome in average-risk patients receiving preirradiation chemotherapy correlates with response to chemotherapy; in the Milan trial, those with CR/PR to preirradiation chemotherapy enjoyed 94% PFS compared to 61% if only SD or PD attended chemotherapy (65). Several studies note the time to initiating irradiation is conversely related to disease control (41,47).

For disease recurrent after radiation therapy (with or without chemotherapy), numerous studies demonstrate chemotherapy responsiveness to single agents, multiagent combinations, and high-dose therapy with hematologic stem cell rescue. Except in the infant setting, best defined as “radiation therapy naïve,” durable secondary disease control following initial CSI has only rarely been achieved despite aggressive, high-dose chemotherapy and further irradiation (66–70). Local irradiation can provide further control at the primary site (71). Trials of intrathecal chemotherapy in this setting are of interest, but to date with only limited phases I and II data (72).

Radiotherapeutic Management

Volume

Medulloblastoma is the seminal tumor identified with subarachnoid dissemination. The need for full CSI has been recognized for more than five decades. In reviewing serial treat-

ment regimens in Sweden, Landberg et al. (73) noted serial improvements in survival rates with increasing radiation volume: 5% 10-year survival after limited posterior fossa irradiation, 15% after irradiation to the posterior fossa and spinal canal, and 53% after CSI. Reported failures in the subfrontal region additionally indicate the need to completely encompass the cranial and spinal subarachnoid spaces; such failures clearly represent inadequate dosage to the subfrontal area, a potential site of geographic miss even in the era of 3D, imaging-based treatment planning (74–77). Other parameters key to appropriate CSI encompassing the entire subarachnoid volume are discussed below (see Techniques, p. 61–64).

Prospective trials preceding the current decade have been based on the standard use of boost irradiation to the entire posterior fossa. Use of 3D conformal radiation therapy (3D CRT) to the entire posterior fossa provided some reduction in cochlear dose, important in children receiving cisplatin and at-risk for both chemotherapy- and radiation-related ototoxicity (Table 4.4) (57,63,78–81). The use of 3D CRT targeting only the tumor bed has been shown to be equivalent to treatment encompassing the entire posterior fossa, with in-field or posterior fossa recurrences at or below the 5% level even with more limited boost volumes (40,52,57,82). Initial experience with a 2 cm anatomically defined clinical target volume (CTV) expansion of the gross tumor volume (GTV) (postoperative tumor bed) showed few if any posterior fossa failures outside the targeted volume (78,83,84). The St. Jude SJMB96 trial confirmed local disease control in 95% of cases with the 2-cm CTV; the recent M-SFOP 98 and current COG trials are testing a 1.5-cm CTV expansion, while a previous study from the University of Washington and the current SJMB03 study have studied a 1 cm anatomically defined expansion to identify the CTV (40,52,82).

Detailed reviews of actual dosimetry and dose modeling, including 3D CRT, intensity-modulated radiation therapy (IMRT), and proton beam radiation therapy demonstrate significant dose reduction to the cochlea and upper cervical spinal cord with tumor bed targeting and 3D-planned therapy; more narrowly defining the target volume and more conformal treatment offer the potential to significantly spare the medial temporal lobes (and, potentially, the hippocampus, both volumes related to cognitive function) in addition to anterior cranial structures (optic chiasm, hypothalamus) (52,57,85).

Although the earlier literature had suggested a predominance of posterior fossa failures in medulloblastoma despite surgery and relatively high-dose irradiation to the entire posterior fossa using broad 2D techniques, more recent studies consistently indicate a shift in the pattern of failure toward diffuse leptomeningeal recurrences; failures limited to the posterior fossa occur in less than 5% to 10% of patients (33,51,78,83,84,86,87). Together with the several trials reporting outcome after local boost to the tumor bed, recent experience supports a major prospective trial of image-guided irradiation to limited tumor bed boost volumes, as planned for 2004 in COG.

Dosage

Medulloblastoma is a radiosensitive tumor. In vitro studies by Fertil and Malaise (88) demonstrated a favorable surviving fraction in vitro at 2 Gy (28%), comparable to most other

Table 4.3

Major Medulloblastomas Studies Reporting Outcome with Postoperative Irradiation Combined with Chemotherapy

Study	Schema ^a	n	RFS	5-Yr	EFS	OS	P of F
SFOP ⁴⁶ '91-'98 std risk	S → (8-in-1) × 2 → (CBCDA/VP-16) × 2 → RT 25 Gy CSI 55 Gy PF	136	65% 54%			74% M(+) – 20	PF-4 PF and M(+) – 23 51% Spine (+) /53% brain(+)
SIOP PNET 3 ⁵⁴ '92-'00 M ₀ -M ₁	S → (CBCDA/cyclo-vcr/VP-16) → RT _{same} vs. S → RT ₃₅ Gy CSI 55 Gy PF	217 → 179 eval		67% all pts		71% all pts	PF-13 PF and M(+) – 23 64% PF(+)
SIOP/UK CCSG ⁴¹ SIOP PNET 3 '92-'00 M ₂ -M ₃	S → (VCR/VP-16/CBCDA-vcr/VP-16/cyclo) → RT ₃₅ Gy CSI 55 Gy PF 40-55 Gy MET sites	68 → 61 eval		74% RT + CRx 60% RT alone 65% RT alone	p = .036 77% RT + CRx p = .09	65% RT alone	M(+) – 16 68% M(+)
HIT 91 ⁴² '91-'97 all stages	S → RT ₃₅ Gy CSI → (vcr/CCNU/cisplatin) 55 Gy PF vs S → (ifos/VP-16/CBCDA-MTX _{high-dose} - cisplatin/Ara-C) → RT _{same}	280 → 187 eval	M ₀ (n = 114) M ₁ (n = 33)	65% ₁₀ years 54%		73% ₁₀ years 53% M(+) – 54% 63%	PF-12% PF and M(+) – 24% M(+) – 63%
CCG 9931 ⁵⁸ high-risk	S → (CDPP/VP-16/cyclo-vcr-CBCDA/VP-16) residual(n = 16) → RT ₄₀ Gy/40 fx ^c CSI 72 Gy/72 PF	85 eval (MB)	M ₀ >1.5 cm ² M(+)(n = 69)	50% 36%		N/A 49%	N/A
SJMB96 ²⁰ '96-'03	S → RT _{23.4} Gy CSI, 55.8 Gy 1°T/av risk 36-39 1° Gy 55.8 Gy 1°T/high risk	134	av risk (n = 86) high risk (n = 48)	83% 70%		85% 70%	15% PD pre-RT PF-3 ^c PF and M(+) – 1 M(+) – 9
POG/CCG 9961 ⁵³ '96-'00	S → RT _{23.4} Gy CSI 55.8 Gy PF (cisplatin/CCNU/vcr) vs (cisplatin/cyclo-vcr)	422 → 379 eval	82% (CCNU) 80% (cyclo)			87%	PF-20 (32%) PF and M(+) – 16 (25%) M(+) – 25 (40%)

Abbreviations: std = standard; CBCDA = carboplatinum, CDDP = cis-platinum, cyclo = cyclophosphamide; CCNU = lomustine; VCR = vincristine, VP-16 = etoposide; CSI = craniospinal irradiation; PF = posterior fossa; 1°T = tumor bed.

^a – RT = conventional fractionation (1 fx/day) at 1.6-1.8 Gy/fx except as noted

^b – stages M₀, M₁, M_{2/3} combined

^c – hyperfractionated RT = 1.0 Gy twice daily

Table 4.4

Medulloblastoma—Radiation Therapy (Data Reporting Reduced Tumor/Target Volume Techniques)

Series	Interval	N	RT	Chemotherapy	EFS	OS	PF Failure
MSKCC (84)	1994–2002	32 ^a	CSI (23.4–36 Gy) TBed (CTV = GTV + 1–2 cm; PTV = CTV + 0.5 cm; 55.8–59.4 Gy)	cisplatin; vcr; CCNU or cyclo	84% at 5 years	85% at 5 years	0% at 5 years 14% at 10 years
U. Washington (14)	1994–2001	33 ^b	CSI (23.4 Gy) TBed (CTV = GTV 2 → 1 cm; PTV = CTV 0.5 cm)	cisplatin; CCNV or cyclo; vcr	86% at 5 years	87% at 5 years	67% at 5 years
SJCRH + collaborators (52,20)	1996–2002	86 ^b	CSI (23.4 Gy) PF (36 Gy) TBed (CTV = GTV + 2 cm; PTV = CTV + 0.5 cm, 55.8 Gy)	cisplatin; cyclo; vcr	83% at 5 years	85% at 5 years	5% at 5 years
M-SFOP 98 (82)	1998–2001	48 ^b	CSI (36 Gy at 100 cGy b.i.d) TBed (68 Gy at 100 cGy b.i.d)	No	81% at 3 years	89% at 3 years	10% overall

^aStandard risk = 27, high risk = 5^bStandard risk = all

CSI, craniospinal irradiation; TBed, Tumor Bed; PF, posterior fossa; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; CDDP, cis-platinum; vcr, vincristine; cyclo, cyclophosphamide.

embryonal pediatric tumors and notably different from the clinically less responsive malignant gliomas. Earlier data indicated a correlation between dosage to the primary tumor site and the outcome; local disease control and survival were consistently related to posterior fossa dosages of ≥ 50 to 55 Gy using conventional fractionation at 160 to 180 cGy per fraction (46,86,89). The use of limited volume boost to 59.4 Gy for patients with imaging evidence of residual disease at the primary site has been reported, with no clear evidence that escalation beyond 55 Gy is fruitful (78,84).

Recent trials support the use of 23.4 Gy (at 180 cGy/fraction) to the neuraxis for average-risk presentations when combined with effective chemotherapy as discussed above. Largely in response to age-related concerns regarding neurocognitive changes, a small pilot study of 18-Gy CSI for 10 children younger than 10 years was undertaken at the Children's Hospital of Philadelphia and at the University of Pennsylvania. Disease control in seven of ten children was initially reported with apparently only minor neuropsychologic deficits (90). Subsequent reports suggest failures following the 18-Gy level may be more apparent with time (91). The current COG average-risk medulloblastoma protocol randomizes children with average-risk disease between 3- and 8-years-old to 23.4-Gy CSI or 18-Gy CSI, prospectively addressing the potential efficacy and relative toxicities of further reduction in CSI dosage.

For patients with high-risk disease, particularly those with overt metastasis (including M1 in most studies in addition to M₂₋₃), 36 Gy to the neuraxis remains the standard. Several studies have used 39.6 to 40 Gy for cases with significant bulk disease through the intracranial and spinal meninges (20).

Trials of hyperfractionated CSI include neuraxis dosages of 30 to 48.4 Gy at 100 to 110 cGy per fraction twice daily, with an interfraction interval greater than 6 hours; cumulative dosages for the posterior fossa have been 66 to 72 Gy with similar fractionation (58,82,92,93). Long-term results of the French M-SFOP 98 trial showed 75% 6-year PFS in average-

risk medulloblastoma after hyperfractionated CSI (36 Gy in 36 fractions) with tumor bed boost (cumulative dosage, 68 Gy in 68 fractions); the goal with equivalent total CSI dose for average-risk disease treated with irradiation alone was to reduce toxicity while preserving equivalent disease control (50,82). A concurrent Milan study used preirradiation chemotherapy and hyperfractionated accelerated radiation therapy for M+ disease, with 1.36 Gy b.i.d. to 31.2 to 39 Gy (depending on age and response to chemotherapy), with 1.5 Gy b.i.d. to the posterior fossa to cumulative levels of 59 to 60 Gy; at investigator's option, cases with overt primary residual or progressive tumor received additional treatment to a reduced target volume to 9 Gy; preliminary reports seem favorable albeit without details regarding long-term toxicities to date (65). The potential value of altered fractionation has yet to be demonstrated.

Technique

The goal of achieving uniform dosage throughout the subarachnoid space, encompassing the entire intracranial vault and spinal canal, is one of the more technically demanding aspects of radiation oncology. Several techniques are appropriate for CSI administration (94). The fundamental is the use of opposed lateral fields including the cranium and upper cervical spinal canal, matching a posterior spinal field including the full spinal subarachnoid space or, in larger children, the upper one half of the spinal canal (with a separate, matched lower posterior spinal field) (Figs. 4.2 and 4.3).

It is important to establish immobilization and reproducibility of setup. Prone positioning is preferable because it allows greater immobilization and better extension of the chin (minimizing potential bone growth changes caused by the exit of the posterior spinal field) and simplifies technical maneuvers at the critical junction between the lateral cranio-cervical fields and the posterior spinal field(s). Immobilization can be achieved through a customized plaster cast, use of the Alpha Cradle system, or a vacuum bag (discussed in Chapter 22). CT simulation for CSI provides

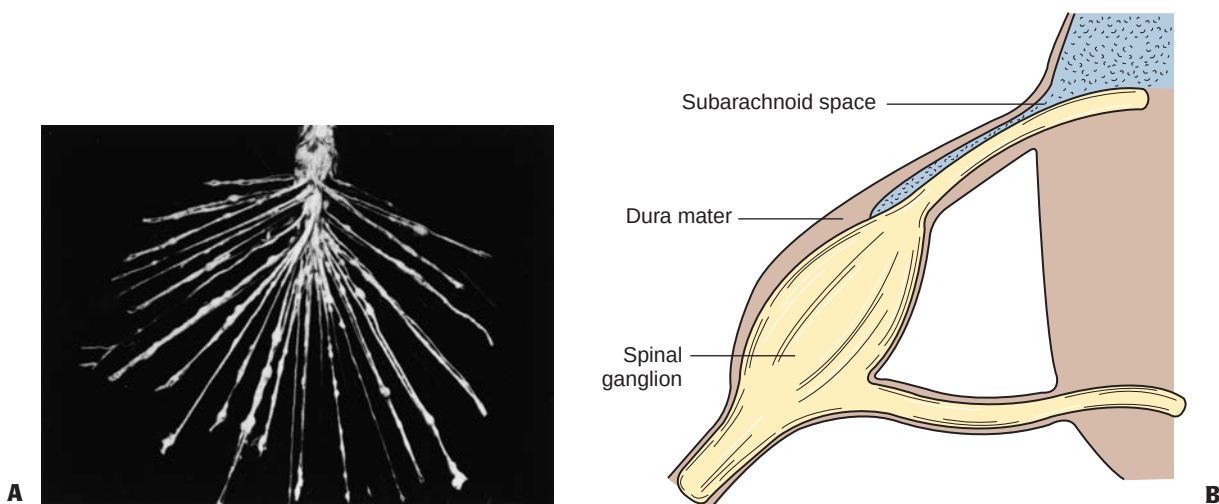


Figure 4.2 Consideration of spinal volume for craniospinal irradiation. **A:** Nerve root seeding in medulloblastoma; this figure first appeared in the *Bulletin of the Los Angeles Neurological Society* (8:1–10, 1943), representing advanced, diffuse leptomeningeal seeding. **B:** Typical anatomy of the nerve roots demonstrating the extension of the subarachnoid space laterally along the nerve root to a location in the neural foramen.

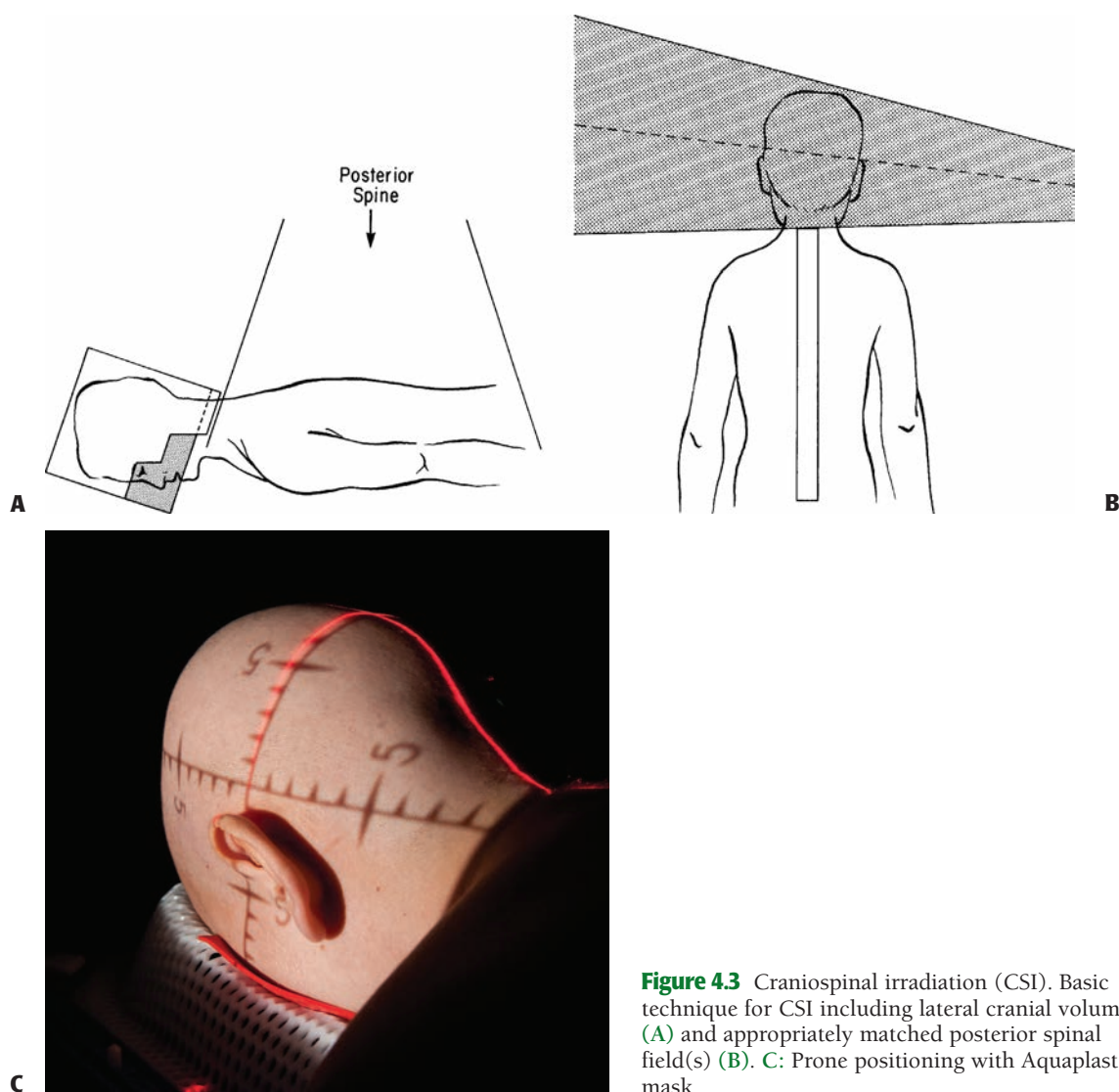


Figure 4.3 Craniospinal irradiation (CSI). Basic technique for CSI including lateral cranial volume (A) and appropriately matched posterior spinal field(s) (B). **C:** Prone positioning with Aquaplast mask.

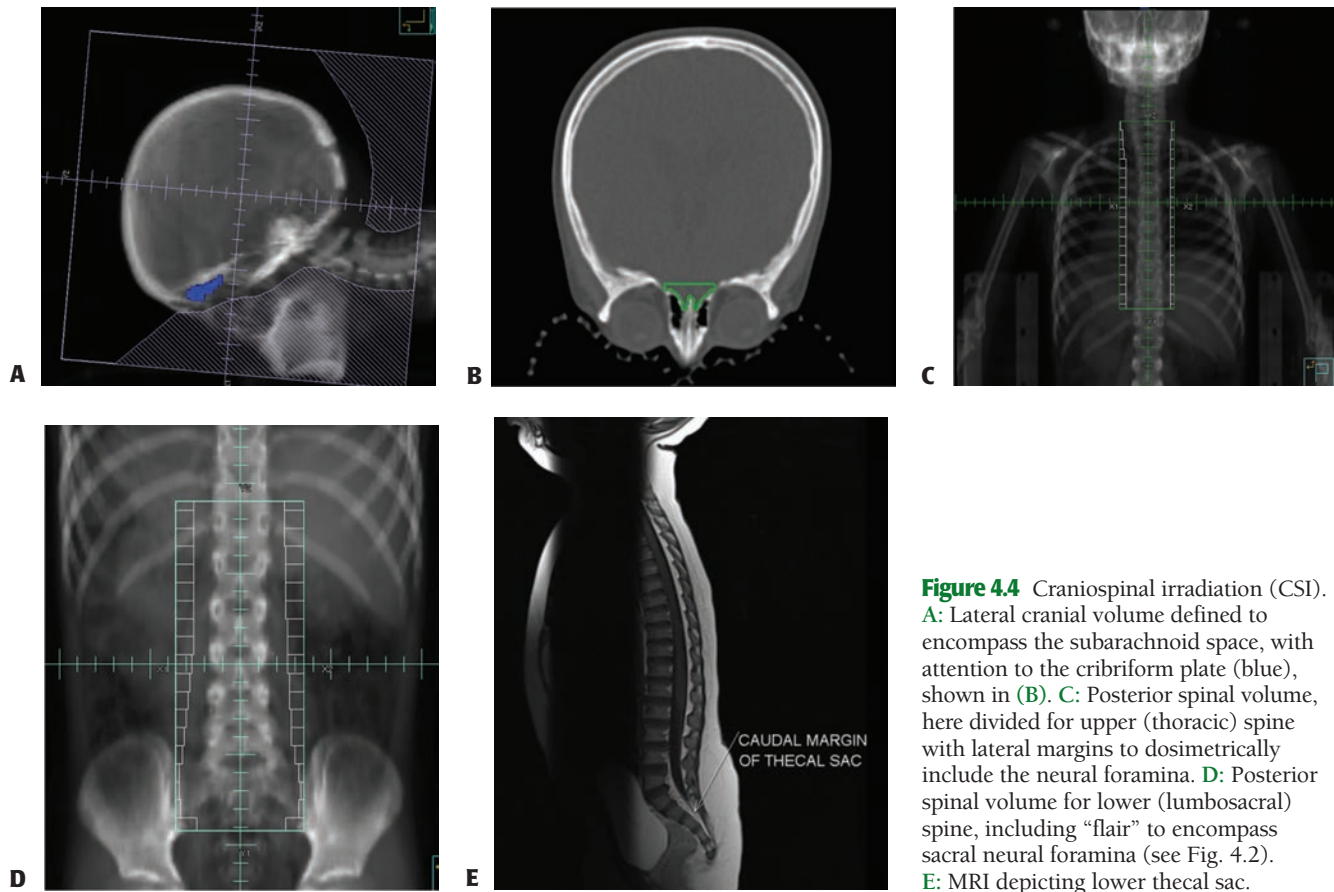


Figure 4.4 Craniospinal irradiation (CSI).

A: Lateral cranial volume defined to encompass the subarachnoid space, with attention to the cribriform plate (blue), shown in **(B)**. **C:** Posterior spinal volume, here divided for upper (thoracic) spine with lateral margins to dosimetrically include the neural foramina. **D:** Posterior spinal volume for lower (lumbosacral) spine, including “flair” to encompass sacral neural foramina (see Fig. 4.2). **E:** MRI depicting lower thecal sac.

both accuracy and flexibility in aligning fields and junction zones (95). Supine positioning may occasionally be medically necessary; detailed attention to the junction area is needed when one adapts the more familiar prone geometry to supine CSI use (96–98).

CT simulation provides axial and sagittal anatomy to enable one to accurately outline the key anatomic sites and plan junction areas (95). Key areas, already discussed, include attention to the cribriform plate—outlining that structure on axial images greatly facilitates accurate identification of target volumes at the “tight” interface of the cribriform plate and the eyes (76) (Fig. 4.4). Other critical anatomic sites important in designing full cranial volumes include the middle cranial fossa and a sufficient margin about the calvarium to be certain to achieve full-dose levels within. In younger children, the margin above the eye may be extremely close but should permit coverage of the subfrontal area as a first priority, minimizing dosage to the eye and, in particular, the optic lens. For older children, the pneumatized frontal sinuses allow sufficient margin to obviate concern for the cribriform anatomy (Fig. 4.4). The literature supports the use of customized blocking rather than the multileaf collimator (MLC) to ensure adequate subfrontal coverage while minimizing dosage to the eye (99); new MLC technology with ≤ 5 -mm leaf size over larger fields may permit MLC blocking in the near future.

Defining the lower border of the spinal field should always be based on the lowest level of the thecal sac as determined by MRI, typically at or below S2 (Figs. 4.4E and 4.5) (100,101). The width of the spinal field should be sufficient

to dosimetrically encompass the full width of the spinal canal to the dorsal nerve roots laterally. Adequate lateral coverage at the lower sacral margin is appropriate to cover the sacral foramina (Fig. 4.2) (101). Several institutions have reported the relative advantage in using intensity-modulated photon irradiation or, more recently, proton beam approaches (Fig. 4.5) (102,103). Proton spinal irradiation significantly spares the underlying heart, breasts, and soft tissues; long-term follow-up is not available as yet documenting late effects (102,104–106). Homogeneity in planning and delivering CSI with protons is challenging; introduction of scanning beam

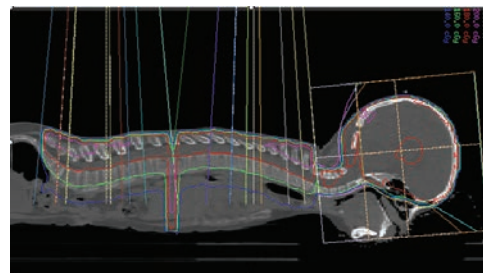


Figure 4.5 Craniospinal irradiation (3). Use of multiple “IMRT minibeam” compensates for diameters in lateral cranial volumes and depths in posterior spinal volumes to provide relatively homogeneous dose distribution for photon CSI. Note lateral dosimetric projection confirms adequacy of lower thecal sac coverage (see Fig. 4.4A).

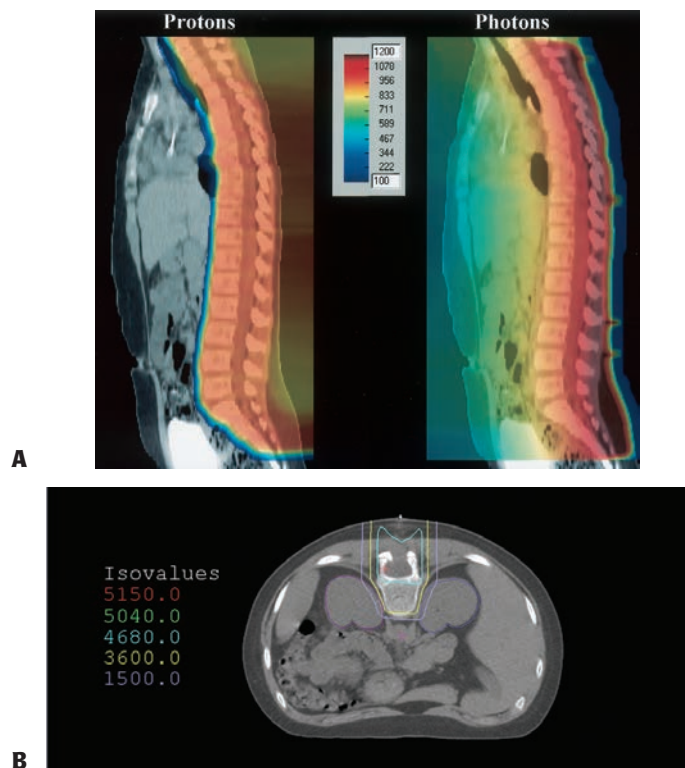


Figure 4.6 Spinal irradiation. **A:** Comparison of dosimetry with single PA field, PBRT versus photon. **B:** PBRT dosimetry closely conforming to spinal canal and vertebral body (to ensure relatively “normal” growth).

technology seems to provide more optimal dosimetry (Fig. 4.6) (107).

The brain and upper cervical spine are treated with lateral fields. The collimators for the lateral fields are angled to match the divergence of the posterior spinal field (Fig. 4.3). The cranial fields must accommodate serial decreases in length to feather the junction zone; discrete readjustments of the junction by 5 to 10 mm/week are typical, if there is some literature regarding daily modulation of the junction (108). A table angle generally is used to correct for caudal divergence of the craniocervical fields (Fig. 4.3). Although detailed analysis shows only minimal inhomogeneity if a correcting table angle is not used (94), full 3D attention at the junction

zone permits more confident abutting of the lateral craniocervical and posterior spinal fields. Even with the ideal craniocervical match using asymmetric jaws, it is important to feather all junctional zones, shifting the anatomic junction site by at least 5 mm every 8 to 9 Gy, effectively once a week (109). Helical tomotherapy has been used, with excellent handling of the complex, full neuraxis (110).

The cranial fields include the entire intracranial subarachnoid space. The most difficult area is at the level of the cribriform plate, where there is often little margin to allow one to block the eyes and dosimetrically encompass the critical subfrontal cribriform site (76). Even with 3D proton therapy, oblique beam configurations are required to reduce incidental lens dose (111). For CSI, there are both dosimetrically modeled data and direct clinical measures to document the relative advantage of the classic Cerrubend delivered by parallel-opposed or obliqued lateral fields. Current boost techniques typically include either (1) 3D CRT or IMRT to encompass the posterior fossa, or (2) using similar techniques to encompass the tumor bed alone, using anatomically corrected 3D expansion by 1 to 2 cm to define the CTV (40,52,57,82, 84,112). With photon irradiation, the differences between IMRT or 3D CRT and conventionally planned 2D therapy are impressive in relatively sparing the cochlea, temporal lobes, and brainstem (11,40,52,57). The current COG trial in average-risk medulloblastoma randomizes all cohorts between 3D-based therapy to the posterior fossa or to the tumor bed (using a 1.5-cm anatomic expansion → CTV and a 3- to 5-mm geometric expansion → PTV (COG: ACNS0331). In nonprotocol settings, there is now sufficient information to suggest the adequacy of boost volumes confined to the tumor bed (52,57,82,84). This sophisticated approach entails analyzing the initial tumor extent based upon pre-operative MRI (or CT) and identifying margins of the posterior fossa or the post-operatively reconfigured posterior fossa tumor bed using CT and, ideally, fused pre-operative MR imaging. (Fig. 4.7 demonstrates boost confined to the tumor bed). The goal of image-guided irradiation and narrow margins in targeting the tumor bed is to diminish the dosage to the cochlea (especially important with combined irradiation and cisplatin), the temporal lobes, and the hypothalamic–pituitary region (Fig. 4.7). Several reports document the theoretical advantage of proton beam therapy for the “boost” volume, based on significant further reduction in normal tissue doses to the key anatomic regions noted: cochlea, temporal lobes, and pituitary–hypothalamic region (11,104,113).

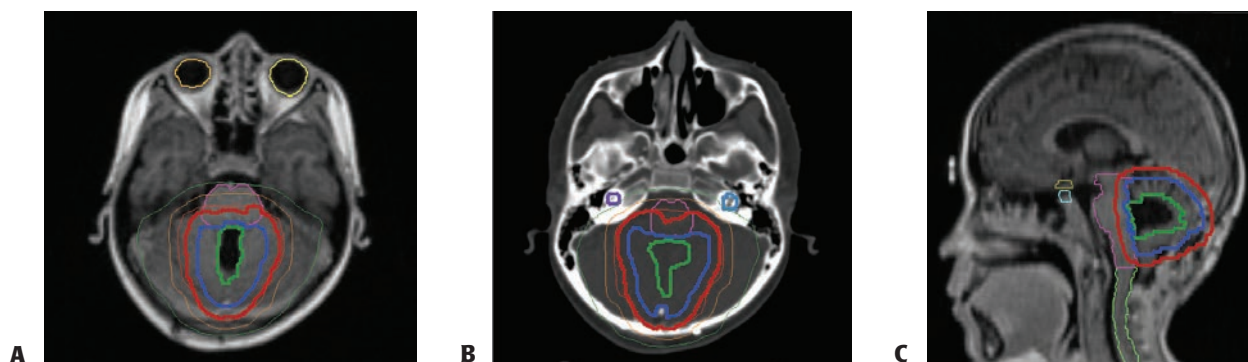


Figure 4.7 Tumor bed boost for resected medulloblastoma. GTV = tumor bed (green) with 1-cm anatomic 3D expansion to provide protocol-specified (SJMB03) CTV (blue) and further 3-mm geometric expansion to establish PTV (red). Shown are transverse planes (A = MRI, B = CT at level of cochlea, shown in blue) and sagittal plane (C = MRI in midline showing spinal cord, brainstem, chiasm in yellow, and pituitary in green).

The quality of radiation therapy has been correlated with improved outcome, based on both volume adequacy (in several but not all prospective cooperative group reviews) and duration of therapy (with several reports indicating inferior disease control when the interval to complete irradiation exceeds 45 days) (46,54,86,114–116).

Delivery

CSI results in predictable, if quantitatively variable, acute changes in the peripheral blood counts. Monitoring for neutropenia or thrombocytopenia, most often noted during or after the third week of CSI without preceding chemotherapy, is critically important. Traditionally, CSI is interrupted if absolute neutrophil count falls below 1000 cells per milliliter, especially if the child is febrile. When necessary to permit completion of neuraxis irradiation, granulocyte colony-stimulating factor may be used to correct neutropenia; thrombocytopenia may necessitate platelet transfusion (117). Irradiation is initiated with CSI. If blood counts necessitate delaying or interrupting CSI, initiation of posterior fossa irradiation will provide continuity and limit unnecessary interruption in irradiation at the primary site. One should return to CSI as soon as hematologic status permits. With preirradiation chemotherapy regimens, further delaying the start of radiation therapy can negatively impact the outcome (41, 47,54).

Nausea and vomiting are generally more pronounced in older children. Use of antiemetics is important in preventing “anticipatory” vomiting, which may be more difficult to control. Ondansetron usually is successful. Rarely, corticosteroids may be necessary at low dosage levels, particularly early in the postoperative period. Nutritional support during CSI is mandatory as children often go from completion of irradiation to adjuvant chemotherapy.

Results

Long-term disease-free survival after surgery and irradiation should now approach the 70% level overall (Table 4.2). Factors associated with more favorable outcome include age greater than 3 years, localized presentations (i.e., M_0), and tumors amenable to near total or total resection. The more effective combinations of radiation therapy and chemotherapy for children older than 3 years show long-term disease control in 80% of those with average-risk disease, and 60% to 70% of those with high-risk medulloblastoma (Table 4.3) (20,50,53,65). The impact of histology, biologic findings, and genetic analyses is increasingly important, as summarized above. Investigations to additionally improve the outcome seek improvement in disease control and reduction in functional limitations attendant to therapy.

EMBRYONAL AND MALIGNANT GLIAL TUMORS IN INFANTS AND YOUNG CHILDREN

Children younger than 3 years account for 15% to 25% of pediatric CNS neoplasms (1,118,119). Symptoms in this age group usually include enlarged head, lethargy, and vomiting. Tumors are predominantly supratentorial; in comparison to older children, infant tumors are more often malignant and may be more frequently metastatic at diagnosis (120). The most common tumor types include astroglial tumors (primarily low grade;

among infants <1-year-old, up to 25% are high-grade malignant gliomas), the embryonal neoplasms (medulloblastoma and the supratentorial embryonal tumors, including PNETs and pineoblastomas), and ependymomas (121–123). Atypical teratoid/rhabdoid tumors (AT/RTs) occur predominantly in this age group (6,124,125). A significant proportion of intracranial teratomas and choroid plexus tumors present in young children below 12 to 18 months of age (119,122). Infantile desmoplastic neuroepithelial tumors (desmoplastic infantile gangliogliomas and astrocytomas) also arise predominantly in the very young. These lesions often are quite large, are peripherally located, and appear aggressive histologically, but typically display rather “benign,” low-grade behavior, rarely recurring after primary resection (6,126,127).

Survival rates for the embryonal brain tumors presenting in children younger than 3 to 4 years are lower than for older children (122,123,128,129). Tumor type, pattern of growth, and the therapeutic ratio for both surgery and radiation therapy are unfavorable when compared to older children (32,130,131). Operative morbidity and mortality rates are higher in infants than in older children; after radiation therapy, cognitive dysfunction, somatic alterations, endocrine deficits, and neurotoxicity are more pronounced than in older children (55,56,122,132).

For malignant gliomas, there is actually suggestion that outcome exceeds that of older children and adults, based on apparent differences in biology and disease response to chemotherapy (133–136).

Therapy

For embryonal tumors with long-established chemosensitivity (particularly medulloblastoma, but also supratentorial PNETs), a number of trials between 1985 and 2000 explored the use of prolonged primary postoperative chemotherapy using delayed, diminished, or no irradiation (depending on the goals and philosophy of the group or institution) (Table 4.5). Several large series documented a high rate of chemoresponsiveness to a “standard” four-drug regimen (including cyclophosphamide, cisplatin, vincristine, etoposide) or to systemic methotrexate; durable disease control without irradiation was limited to 25% to 35% of cases in most trials, typically in those with localized disease amenable to complete resection at diagnosis (120,122,123,132,137–143).

Two different directions have proven more successful, at least in selected settings, over the past 10 to 15 years. Successive trials from the German POG tested progressively more intense systemic and intrathecal methotrexate with an alternating drug program incorporating the agents noted above. While overall PFS in the HIT SKK 87 trial (1987 to 1993) was 53% in the favorable resected, M_0 cohort (with identical overall survival [OS]), the study showed youngsters with desmoplastic medulloblastoma enjoyed nearly 90% PFS. The SKK 92 study (1992 to 1997) intensified methotrexate and noted overall 5-year PFS of 58%; among the resected M_0 group, 5-year PFS was 82% (with 14 of 17 survivors treated with surgery and chemotherapy only, absent irradiation which was used only for residual/progressive disease during chemotherapy). Once again, the results with desmoplastic histology were exceptional: 85% PFS (95% OS) compared to 34% PFS (41% OS) in those with classic medulloblastoma (142,144).

The second direction was suggested by Khalifa and the French group (SFOP), where primary chemotherapy showed

Table 4.5
Malignant Infant Brain Tumors—Outcome in Selected Prospective Primary Management Trials

Histiotype	Series	Interval	n (age <3 y.o. or as stated)	Surgery	Chemotherapy	RT	EFS at 5 Years	OS at 5 Years	OS w/o RT (%)
Medulloblastoma	POG 8633 (120,123)	1986–1990	62 (<3 y.o.)	All	vcr-cyc-cisplatin-VP-16 ^a	PD > 18 mo (CSI 30–36 Gy+PF (CSI 24 50–54 Gy) consolidation Gy + PF 45–50 Gy)	32%	40%	
	Institut Gustav Roussy + collaborators (159)	1988–1994, salvage CRV-RT	13 (<4 y.o.)	GTR ₁ M ₀ All, s/p PD (33% 2nd GTR) on infant chemotherapy	Same cyc-melphalan HSCR ^b	Same PF (50–55 Gy)		69%	
	CCG 9921 (139)	1993–1997	92	All	vcr-cyc/ifos-cisplatin/CBCDA-VP-16	With residual or M+, local (50–50 4 Gy) or CSI (> 18 m.o. with M+ or PD, 18–30.6 Gy)—<10% received RT before PD	32%	43%	(65%)
	BBSFOP (140)	1990–2002	38 79	GTR ₁ M ₀ All	CBCDA-PCZ-VP-16-cisplatin-vcr-cyc	0	41%	54%	(40%)
	GPOH HIT SKK 92 (144)	1992–1997	43	All	(Busulfan-, thiotepa) HSCR MTX-cyc-vcr-CBCDA-VP-16-IT-MTX	Not defined; 50% surviving children received RT	21%	55%	
	Head Start I, II (141)	1991–2002	17 21	GTR ₁ M ₀ All, M ₀	cyc-VP-16-cisplatin-vcr-(CBCDA-thiotepa-VP-16), HSCR	PD only; CS _{123,4-36} Gy, PF ₅₄ Gy	29%	61%	
	SJCRH CNS-13 (138)	1992–1996	20	All	cyc-CBCDA-VP-16	M+, or PD; CS ₁₂₇₋₄₈ Gy, PF ₄₈₋₆₆ Gy	58%	93%	(67%)
	POG 8633 (120,123,190)	1986–1990	48	48% GTR	As in vcr-cyc-cisplatin-VP-16 above	PD > 18 mo (local 50–54 Gy) consoli-dation (45–50 Gy)	82%	70%	(74%)
	SFOP (186)	1990–1998	73 (<5 y.o.)	60% GTR	CBCDA ^c -procarbazine cisplatin-VP-16; vcr-cyc	PD (local 50 Gy)	52%	52% at 4 years	
	SJCRH CNS-13 (138)	1992–1996	21	All	See above	PD only PF ₄₈₋₅₄ Gy	33%	62%	(33%)
Ependymoma <3 y.o.	CCG 9921 (139)	1993–1997	74	All	See above	See above	32%	59%	(45%)
	UKCCSG/SIOP CNS9204 (191)	1992–2003	80	All, M ₀	CBCDA-vcr-MTX-cyc-cisplatin	PD, local ₅₀ Gy	42%	65%	(42%)
	SJCRH RT-1 (211)	1997-2003	78	All, M ₀	>30% had pre-RT chemo-therapy (off protocol)	All CTV = GTV _{Tbed} + 1 cm; PTV = CTV + 3–5 mm	79%	90%	(0)

^avcr (vincristine)-cyc (cyclophosphamide); VP-16 (etoposide), CDDP (cis-platinum). ; CBCDA, carboplatin; ifos, ifosfamide; MTX, methotrexate, systemic; IT-MTX intrathecal methotrexate.

^bHSCR (hematologic stem cell rescue).

^cCBCDA (carboplatin).

only 29% PFS at 5 years even among the most favorable, resected M_0 cohort. Notable was the OS rate of 73%, reflecting excellent “salvage” therapy with high-dose chemotherapy, busulfan–thiotepa, and local irradiation; among 39 patients treated, 5-year postsecondary treatment survival was 77% for those with M_0 disease initially and at failure (140,145). Although the St. Jude group had also documented excellent salvage with CSI alone, the functional consequences of more limited irradiation in this age group seem “axiomatic” (132,138). Both POG and the Pediatric Brain Tumor Consortium (PBTC) initiated trials in the late 1990s testing chemotherapy (including intrathecal mafosfamide, an activated form of cyclophosphamide, in the PBTC study) with planned, localized irradiation after the initial 4 months of chemotherapy. Results are yet in analysis, recognizing that among the M_0 group that proceeded to consolidative local irradiation on PBTC 001, 5-year PFS is 85% and OS, 95% (Kun L, Blaney S. 2009, Personal Communication).

All infant trials to date have shown poor outcome for the 20% of patients presenting with neuraxis dissemination, OS rates rarely exceeding 10% to 25% (139,140, 142,144). Although CSI is curative in a significant proportion of such children, the consequences of CSI at effective dose levels are not considered acceptable (132). Alternative use of aggressive, high-dose chemotherapy alone has been fraught with otherwise unseen toxicity (including toxic deaths) and EFS for favorable (M_0 , resected) presentations approximating 50%; outcome in the M_+ cohort has been essentially zero (141).

Separate from medulloblastoma is the immature, highly aggressive AT/RT (6,146). AT/RTs occur predominantly in young children, presenting in the posterior fossa; those occurring in children older than 3 years are more often supratentorial lesions (129,146,147). The lesions are histologically distinctive, and diagnosis by light microscopy and immunohistochemistry (especially documenting positive epithelial membrane antigen and vimentin) is often definitive. The tumor is associated with monosomy of chromosome 22, a finding in common with extraneural primary rhabdoid tumors (148). Genetically, the tumor is associated with loss of the tumor suppressor gene *hSNF5/INI1* in more than 75% of cases; absence of *INI1* by FISH is diagnostic (129,147,149). Tumor that histologically might be called infant medulloblastoma or other embryonal diagnoses with documented loss of *INI1* is considered AT/RT and should be handled as such. Up to 15% to 25% of cases show leptomeningeal dissemination at diagnosis (149,150). Although AT/RTs often respond to chemotherapy (especially carboplatin-containing regimens), the disease course has been marked by rapid recurrence and neuraxis dissemination (146,147). There is an increasing evidence that the outcome is related to postoperative irradiation; recent trials incorporate early local irradiation for children as young as 12 to 18 months old, ideally limiting postoperative chemotherapy to 4 to 6 weeks (125,129,147, 151). For children older than 3 years of age, use of postoperative CSI followed by chemotherapy has resulted in 78% 2-year EFS compared to 11% for younger children in whom irradiation was delayed or avoided (129).

Surgery

As in older children, complete resection is often the primary predictor of disease control; for infant medulloblastoma, the differences in outcome strongly favor attempted GTR in

every major series regardless of the type and intensity of postoperative management (120,122,123,139–141,144). In the initial Baby POG study, OS for medulloblastoma was 40%, compared with 60% for the one third of children who had undergone GTR and 69% for those with GTR and localized disease (120). In the latest published GHOP trial, PFS among all M_0 cases falls from 82% to 50% based on the absence or presence of residual tumor postsurgery, respectively (144).

Delayed definitive surgery has been utilized for sizable medulloblastomas or supratentorial PNETs in this age group. After initial chemotherapy, tumors may be reduced in size and vascularity, resulting in more successful tumor resection (123,138).

Choroid plexus tumors are often malignant carcinomas in this age group. The tumors typically arise in the lateral ventricles; histology can be uncertain in predicting benign or malignant behavior, with carcinomas marked largely by brain invasiveness and atypia. Complete resection alone appears to be adequate therapy, with few recurrent tumors following imaging-confirmed removal even without added chemotherapy or irradiation (152–154).

Radiation Therapy

Evolving combinations of systematic or selected consolidative irradiation, “standard” irradiation for disease progression, or multimodality salvage regimens incorporating low- or high-dose radiation therapy have resulted in radiation therapy as a component of therapy for nearly half of all surviving children in this admittedly “vulnerable” age group (120,132,138,140,141,145). Important in the context of current strategies is identification of those cases most likely to benefit from local irradiation, with consensus developing toward noting those with classic (nondesmoplastic) histology and localized medulloblastoma or those with incompletely resected M_0 desmoplastic medulloblastoma. Using “early” planned irradiation, typically within the first 4 months of postoperative chemotherapy, is key to avoiding the scenario of requiring more aggressive irradiation (volume and dose) and chemotherapy (dose) for those who progress during or after more prolonged chemotherapy. In AT/RT, even earlier initiation of radiation therapy (4 to 8 weeks) is key to improving outcome, as noted above.

Although salvage CSI (at therapeutic dosage levels of 30 to 36 Gy using 180-cGy daily fractions) has been successful in controlling more than 40% of recurrent medulloblastomas (in fact, equally effective in M_0 and M_+ cases in earlier St. Jude data), the ultimate 40% to 60% disease control was balanced by a median IQ of only 62 at 7 years (132). The latter finding has dampened enthusiasm for salvage CSI, at least at dosage levels greater than 24 Gy, in this age group.

Chemotherapy

The initial van Eys study of primary mechlorethamine (nitrogen mustard), vincristine, procarbazine, and prednisone (MOPP) chemotherapy at M.D. Anderson Cancer Center showed long-term survival in 8 of 11 infants with medulloblastoma; 6 had not received radiation therapy (155).

Duffner et al. (123) reported the first POG trial with initial postoperative chemotherapy in 1993. The regimen included cycles of cyclophosphamide with vincristine and cisplatin with etoposide; response rates varied between

medulloblastoma (48% partial and complete response rate among those with imaging residual) and malignant gliomas (60%) (123). PFS and OS rates, respectively, at 5 years were 32% and 40% for medulloblastoma, 43% and 50% for malignant gliomas, and 0% and 0% for pineoblastomas; overall 5-year survival was 27% for supratentorial PNETs (120). As in subsequent infant trials, failures beyond 2 years have been uncommon except with ependymomas (122,132,137,138,141).

Most of the subsequent infant studies have used variations of the four-drug regimens noted in the first POG trial; more intensive regimens have shown benefit in specific subsets of infant malignant tumors (139,156). The Head Start series of dose-intensive chemotherapy have evolved to similar four-drug induction with second surgery for residual local tumor, followed by myeloablative doses of thiopeta, etoposide, and carboplatin. In the selected M_0 resected medulloblastoma cohort, EFS at 5 years was 52%; OS of 70% those requiring irradiation for disease progression; toxicity has remained a problem with this approach (141). The French experience with high-dose chemotherapy has been quoted above, reporting excellent disease control with busulfan–thiopeta and local irradiation for children with progressive disease following conventional chemotherapy alone (143).

Radiotherapeutic Management

Volume and Technique

Recently completed studies in COG and PBTC have sought to confirm the role for local irradiation in “high-risk” infant medulloblastoma, a group increasingly defined as those with localized disease (M_0) following incomplete resection (“R1” in the developing terminology for this setting) or with classical (i.e., not desmoplastic) histology M_0 disease following complete resection (“R0”: imaging-confirmed GTR) or R1 (157). Data are just evolving in these trials (v.s.), but suggests excellent overall disease control with the addition of posterior fossa irradiation for the M_0 medulloblastoma cohort (Kun L, Blaney S. 2009, Personal Communication). Given data in older children restricting “boost” volumes to the tumor bed, there is recent interest in testing only tumor bed irradiation in the infant or young children trials. Current infant studies in COG incorporate local tumor bed volume for AT/RT and allow elective local tumor bed irradiation in high-risk medulloblastoma (ACNS0333, ACNS0334); a similar trial in PBTC requires local irradiation as well in the M_0 setting (PBTC 026). Guidelines for radiation volume in the ongoing clinical trials parallel to those noted above for medulloblastoma and in Chapter 3 for supratentorial PNETs. The GTV is defined as the tumor bed and residual tumor following initial resection, ideally requiring fusion of preoperative MRI and the planning set of CT and MRI imaging (Fig. 4.7). Changes in tumor residual may be apparent after induction chemotherapy or, selectively, where second surgery has preceded irradiation; in such instances, changes in areas of the normal brain that were contiguous with the primary tumor need to be traced through sequential preoperative and intervening image sets to the time of simulation. In the infant population, the current trials define the CTV as a 1-cm anatomic expansion of the GTV and require an additional 3 to 5 mm or greater geometric expansion to identify the PTV, depending on immobilization and repositioning in a cohort requiring daily sedation/anesthesia for proper radiation therapy.

While most utilize 3D conformal irradiation in this setting, use of IMRT may be helpful in further diminishing dose to the critical medial temporal lobe–hippocampus region (important with regard to intellectual development), the cochlea, and the pituitary–hypothalamic regions. With IMRT, it is important to account for inhomogeneity and avoid overdosage to the upper cervical spine or any of the above structures, both with posterior fossa and supratentorial lesions. The potential advantage for proton beam irradiation may be best realized in the setting of infant tumors, reflecting optimal dosimetry with respect to both intralesional homogeneity and further sparing of critical normal structures (85,103–106).

The use of CSI in this age group has been discouraged based on the functional outcomes of earlier experience with primary irradiation and the retrieval studies; it seems clear that conventional dosages to the neuraxis (30 to 36 Gy) result in unacceptable functional consequences in children younger than 3 years of age (122,132). In cases with neuraxis dissemination either for consolidation or retrieval, patients with complete or near complete response to chemotherapy have received on-study CSI at the 18- to 23.4-Gy level. Efficacy is not yet demonstrated for this intervention, recommended in AT/RTs, for example, for children older than 12 to 18 months of age (100,138, 139,158).

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Dosage

For infant embryonal CNS tumors, response-adjusted irradiation is a component of most open trials in North America. Most regimens use 45 to 50 Gy to the planning target volume (PTV) for children up to 18 to 24 months of age and 54 Gy for those beyond 18 to 24 months old. Note that the French series that combined high-dose chemotherapy and local posterior fossa consolidation for progressive medulloblastoma used only 36-Gy total dosage to the posterior fossa (145,158). Although dose:response data are unavailable, AT/RTs are treated with similar dose regimens, the ongoing COG trial calling for a reduced CTV at 45 to 50 Gy with an additional 5.4 Gy to a reduced CTV2 derived from a 5-mm anatomic expansion of the GTV. The indications for CSI in this age group are discussed above. When used for consolidation in a protocol setting following complete response to chemotherapy, an age-adjusted regimen of 18- to 23.4-Gy CSI has been recommended.

Results

The most positive results in more recent infant medulloblastoma studies show OS rates approaching 45% to 65%, notably more positive for those with M_0 presentations, desmoplastic histology, and initial complete resection (Table 4.5) (138–140,144). Pineoblastomas and AT/RTs in this age group have done poorly, with few survivors beyond 1 year (120,123,137,159,160).

EPENDYMOMAS (INFANTS, CHILDREN, AND ADOLESCENTS)

Intracranial ependymomas represent 5% to 8% of intracranial neoplasms in children. More than 90% of pediatric ependymomas occur as intracranial tumors; primary spinal cord tumors

are relatively uncommon in children, where ependymomas represent 25% of primary spinal tumors. Two-thirds ependymomas in children present as posterior fossa lesions, arising along the linings of the fourth ventricle or at the cerebellopontine angle (CPA). Tumors originate from the ventricular floor as midline neoplasms, where attachment is commonly noted at the level of the obex (the caudal most aspect of the fourth ventricle along the posterior surface of the medulla, where the fourth ventricle ends and the central spinal canal begins). It is quite common for such tumors to grow into the foramina of Luschka (on either side of the brainstem) toward and to the CPA (161–164). Presentation in the CPA is noted less commonly, occurring particularly in very young children (165). Fourth ventricular tumors also extend caudally beyond foramen magnum and into the upper cervical spine; extension is either from caudal growth from foramen of Luschka or, more commonly, through the foramen of Magendie and then posteriorly from the cervicomedullary junction caudally (166). Growth below the foramen magnum marks nearly 50% of fourth ventricular lesions (Fig. 4.8) (161,162,164). Supratentorial ependymomas account for one third of childhood presentations, occurring predominantly as extraventricular cerebral hemispheric tumors; growth is commonly adjacent to the third or lateral ventricular regions (166,167).

Ependymomas consist histologically of polygonal cells with large vesicular nuclei and cytoplasmic granules. Characteristic are ependymal rosettes, formed by tumor cells oriented radially around a central lumen; cells also have a tendency to orient themselves around blood vessels, forming perivascular pseudorosettes (6,168). Molecular genetic analyses highlight the origin of ependymomas from populations of neural progenitor cells that are genetically distinct in the supratentorial, posterior fossa, and spinal regions—anatomically related patterns of gene expression and regions of chromosomal loss or gain mark the three sites independently (169).

There has been much debate over the clinical significance of the histologic classification or grading of ependymomas in the past (6,168). The WHO classification now defines ependymomas as grade 1 (subependymomas or myxopapillary spinal ependymomas), grade 2 (“classical ependymomas,” including cellular, papillary, clear cell, and tancytic types), and grade 3 (anaplastic) (6,168). Subependymomas are benign neoplasms most often arising beneath the fourth ventricular wall, but also similarly adjacent to the lateral ventricles. Myxopapillary tumors are “often indolent” lesions occurring primarily in young adults, specifically in the region of the cauda equina. Cellular tumors occur in extraventricular regions with a relatively low mitotic rate. Papillary ependymomas present along the ventricular surfaces. Clear cell tumors mimic oligodendrogliomas histologically, occurring primarily as supratentorial lesions; there is a suggestion that this variant is somewhat aggressive. Tancytic tumors grow as fascicles, usually within the spinal cord. Anaplastic ependymomas are marked by high mitotic rate, microvascular proliferation, and pseudopalisading necrosis (6,168). Ependymoblastoma are extremely rare, highly malignant primitive embryonal tumors occurring in infants as supratentorial lesions with features of an ependymal neoplasm; they are not considered in the classification of ependymomas, but rather as embryonal tumors (v.s.).

There have been conflicting reports regarding the correlation between tumor grade (ependymoma vs. anaplastic ependymoma) and survival. Three of the most prominent neuropathologists in the 1980s reported no correlation between anaplasia or grade and clinical behavior (170–172). More recent series identify histology as one of the dominant features related to disease control after aggressive surgery and irradiation (168,173,174). Merchant et al. (174) reviewed the St. Jude historical experience, noting 3-year PFS of 84% among the 70% of children with differentiated ependymomas and 28% for the 30% of cases with anaplastic features. Late

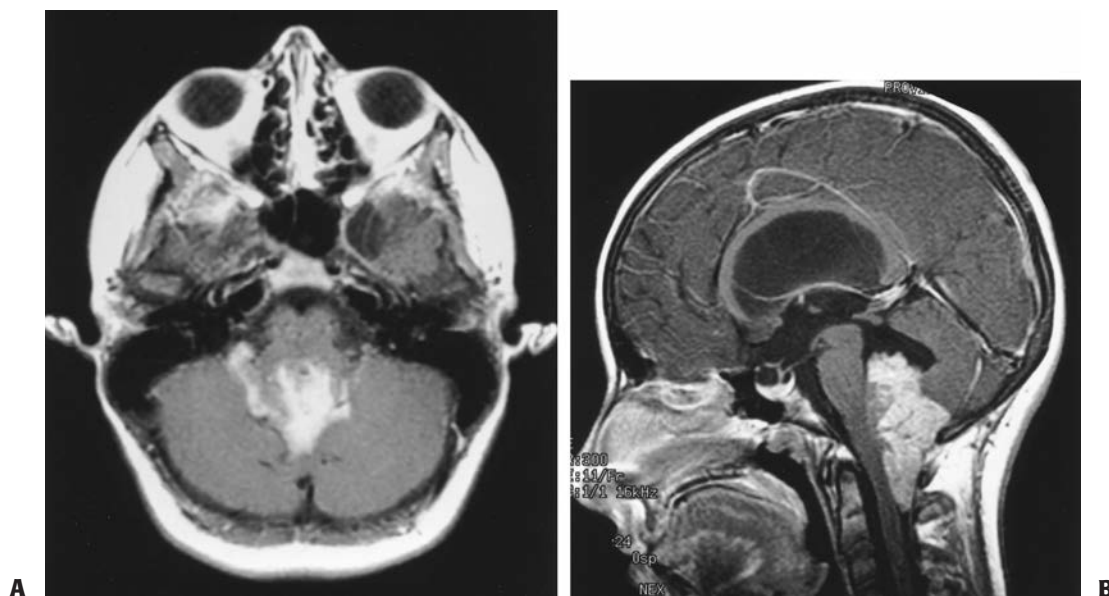


Figure 4.8 Posterior fossa ependymoma, typically extending from the region of the fourth ventricle, through the right foramen of Luschka (A) and caudally beyond the cerebellopontine angle along the cervicomedullary junction to a level below the foramen magnum (B).

follow-up of Merchant's expanded series confirms the impact of tumor grade on outcome (175). Multi-institutional reviews reflecting independent experience at 11 major US centers and that within the former POG document histopathology as a significant factor, with higher rates of 5-year EFS associated with differentiated histology but no statistical difference in OS for those with anaplastic tumors; the latter report includes a review of 1444 cases in the English literature between 1900 and 2005 substantiating such findings (176,177). Earlier data suggested a correlation between anaplasia and the frequency of neuraxis dissemination, particularly among fourth ventricular lesions (121). Merchant's recent report detailing the largest prospective trial similarly documents a significant correlation between anaplastic histology and a higher rate of distant failure (175).

The biology of ependymomas has been of considerable interest. Demonstration that tumors from different CNS sites show distinct patterns of gene expression and regions of chromosomal gain or loss parallels the excitement of documenting gene expression patterns that recapitulate those noted in radial glia cells in the same anatomic locations (163,169,178). Chromosomal abnormalities are present in approximately 50% of tumors, most commonly loss of the long arm of chromosome 22 (associated with loss of the tumor suppressor gene for neurofibromatosis type 2) or 6 or gain in chromosome 1q (179). *P16^{INK4}* A is absent in >90% of tumor cells from supratentorial lesions, but rarely altered in fourth ventricular or spinal lesions; trisomy 19 is similarly related only to the supratentorial lesions (169,180). Alterations in the Wnt/ β -catenin signaling pathway have been related to tumorigenesis in anaplastic ependymomas (181). The p53 pathway appears to be intact in ependymomas, although p53 induced G1 growth arrest is apparent in ependymomas, potentially implicated in radiation resistance (182). The tumors show expression of the ErbB receptors (25).

Ependymomas are somewhat more common in boys, although young children show equal sex distribution or even a slight female predominance. The median age at diagnosis is 4 to 5 years; one third occur in children younger than 3 years, with typically inferior likelihood of disease control (161, 162,176,183). Ependymomas represent a somewhat higher proportion of CNS tumors in infants and young children (119).

Symptoms usually are nonspecific and related to fourth ventricular obstruction with headaches, vomiting, and ataxia. Children with disease involving the CPA often show torticollis or cranial nerve signs (including unilateral hearing loss and facial weakness) (165). MRI often shows a nonhomogeneously enhancing lesion, diagnostic when there is characteristic involvement through the foramen of Luschka EP4. The patterns of extension in and around the cervicomedullary region are noted above (166,184). CT often shows stippled calcification.

Therapy

Surgery

Extent of resection is the dominant factor influencing outcome (161,162,165,174,176,183,185,186). Fourth ventricular lesions usually are adherent along the brainstem, especially at the level of the obex, where surgical damage can result in significant cardiorespiratory compromise. Total or near total re-

section has classically been realized in 50% to 75% of cases (161,162,174,183–186). Current image-guided neurosurgical techniques and recognition of the importance of gross total resection have allowed major referral centers to achieve gross total resection in 80% to 90% of instances, sometimes requiring a second procedure to complete surgery before adjuvant irradiation (164,165, 167,175). Even in very young children, complete or near complete resection is often feasible prior to initiating further therapy. The relationship between extent of resection (or degree of residual on postoperative MRI) and disease control has been apparent for several decades, with EFS averaging 50% to 75% after gross total resection compared with 30% to 45% with incomplete removal (Table 4.6) (162,165,167,174,176,183,184). With optimal postoperative radiation therapy in the prospective St. Jude trial, degree of resection is the single most significant correlate with outcome: 7-year EFS falls from 77% after GTR to 34% with near total or subtotal resection (166). Even in cases with metastatic disease at diagnosis, the impact of GTR on both 5-year EFS and OS is impressive, with 35% and 59% reported in a retrospective multi-institutional review (187).

Total resection is associated with a low but acknowledged rate of operative mortality (2.5% or less) and morbidity (10% to 25% incidence of new neurologic deficits postoperatively) (186). Postoperative cranial nerve deficits are common, including components of the posterior fossa syndrome (e.g., significant difficulties with speech, swallowing, and balance) (44,161,162,165,186). The proximity of vital centers makes gross total resection in the fourth ventricle rather challenging, particularly for those arising in or extending to the CPA (165,186,188). Total resection of supratentorial ependymomas is more readily achieved (167,188). The St. Jude experience with gross total resection in 96% of tumors originating in the CPA is marked by a 30% major complication rate, including need for tracheostomy (almost always transient, with removal between 3 and 12 months postsurgery), gastrostomy feeding tube (similarly), or major cranial nerve palsies (165). The rationale, continued improvement in neurologic function over time, and overall functional status of often young children has encouraged the neurosurgical team to continue aggressive resection for primary presentations, second surgery before irradiation, or for local recurrence (164,175). In young children with moderate disease residual, the option of initial chemotherapy with delayed surgery prior to irradiation has been noted for some time and is still under exploration (v.i.) (189,190).

Radiation Therapy

Radiation therapy has been a routine component of therapy for ependymomas since the 1950s. The favorable results summarized above following gross total resection are based on the addition of postoperative irradiation in almost all the instances (161,162,165,183,184,186). Earlier, two classic retrospective series confirmed the contribution of radiation therapy: (1) Pollack et al. (183) recorded overall 5-year survival of 45% with surgery and irradiation, compared with 13% with surgery alone, while (2) Rousseau et al. (184) noted 63% survival at 5 years after irradiation and 23% without. Although there are limited data from Epstein's New York University experience suggesting disease control for differentiated supratentorial ependymomas following surgery alone, there are very little data documenting favorable disease control rates

Table 4.6
Ependymoma—Outcome Following Surgery and Irradiation

Series	Interval	n	Site	Surgery	RT	EFS at 5 Years	OS at 5 Years
Institut Gustave Roussy, Paris (181)	1975–1989, <16 y.o.	65	All	48% GTR	Local (n = 28) with CrI or CSI (n = 37)	45% $p < 0.001$ 0	63% $p < 0.003$ 23%
Children's Hospital, Pittsburgh (184)	1975–1993	10	All	62% GTR	Local (n = 11) with CSI (n = 16)	59% $p = 0.03$ 13%	67% n.s. 38%
Hopital Necker-Enfants Malades, Paris (163)	1980–1998, <15 y.o.	44	All	73% GTR	Local (n = 25) with CSI or SPI (n = 19)	64% $p < 0.002$ 26%	80% $p < 0.04$ 69%
St. Jude RT-1 (211)	1997–2007, 1–22 y.o.	153	All	82% GTR	TBed (CTV = GTV + 1 cm, 54–59.4 Gy) (received BBSFOP ^a chemotherapy)	72%	84%

^aBBSFOP chemotherapy, carboplatin–procarbazine; etoposide–cisplatin; vincristine–cyclophosphamide.

GTR, gross total resection.

absent irradiation for posterior fossa presentations, patients with anaplastic histology, or those with any degree of residual disease (188). The prospective Italian Association for Pediatric Hematology and Oncology protocol reports inferior outcome when irradiation is deferred following surgery alone, with both inferior disease control and greater morbidity attendant to requisite second surgery (191).

The excellent results with complete resection and postoperative irradiation, even in children as young as 12 to 18 months of age, are best demonstrated by Merchant's series from St. Jude, where assiduously contoured target volumes for 3D CRT to relatively high-dose levels resulted in 74% EFS at 5 years, with 87% local tumor control and 85% OS; the rate of local failure is 16% at 7 years (Table 4.6) (175). The series shows little decrement in outcome at 7 years, recognizing that longer term data reporting results from Children's Hospital of Philadelphia (CHOP), University of Pennsylvania; and Washington University, St. Louis, both show a 10% or greater decline in EFS and OS between 5 and 10 years postirradiation (192,193). The coordination of aggressive surgical resection and prompt postoperative irradiation, even in the younger age cohort, resulted in an excellent rate of tumor control and survival with noted but relatively low rates of acute and subacute morbidities from surgery and radiation therapy; prospective data suggest relatively limited functional morbidities to date (194–196). Disease control rates (both EFS and OS) and local tumor control are equivalent in cohorts younger than 3 years or ≥ 3 years in the St. Jude data, based largely on surgery and irradiation (175). The recently completed COG trial (ACNS0121) studied children more than 12 months of age with postoperative irradiation for those with complete or near total resection except supratentorial differentiated ependymomas, the latter to be observed after confirmed GTR; children with significant local residual had the option of initial chemotherapy followed by second-look surgery prior to irradiation. The study, based largely on the St. Jude radiation parameters, will undergo its first analysis in 2010.

There is a modest literature regarding retreatment for ependymomas recurrent following prior surgery and irradiation, with or without chemotherapy. Resection and full-dose local reirradiation to 50 to 54 Gy resulted in secondary disease control for 10 of 13 children following local recurrence at St. Jude; among 12 children with metastatic recurrence retreated with CSI, the 4-year secondary EFS was 53% (prior therapy had included only local irradiation) (197). Tolerance has been surprisingly good, as reported in more eclectic series with stereotactic radiosurgery used for reirradiation in children and adults (197,198).

Chemotherapy

Ependymomas are only modestly chemosensitive tumors, with objective responses most apparent after exposure to cisplatin and oral etoposide (162,164,189,199,200). The only prospective, randomized trial that tested adjuvant chemotherapy (CCNU, vincristine, prednisone) after surgery and irradiation was completed by CCG in the early 1980's and tested adjuvant (201). The trial was small, but there was no suggestion of improved disease control with chemotherapy; a subsequent randomized trial of adjuvant CCNU/vincristine/prednisone versus the “8-in-1” regimen showed no improvement in either arm of the trial; the group concluded that local tumor control was the dominant issue, inadequately addressed systemically (199). Needle reported a limited-institution pilot study in children 3- to 14-years-old where moderately aggressive carboplatin/vincristine alternating with ifosfamide/etoposide resulted in a 74% 5-year PFS rate, noting half the cohort had incomplete resection; the data reflect a combination intentionally derived from infant protocols, and it is in the latter setting that further assessment of dose-intensive chemotherapy is ongoing (202).

Gilbertson's documentation of ERBB2 and ERBB4 coexpression in $>75\%$ of ependymomas specimens has prompted studies in the PBTC testing lapatinib, a molecular targeting agent active in preclinical models against ERBB expressing

xenografts (203). Preliminary reports have not been encouraging with this approach, but trials of molecular agents are ongoing.

Infant studies may be interpreted positively in documenting that approximately 20% to 25% of children with ependymomas can be controlled with surgery and chemotherapy, absent radiation therapy; the more recent UKCCSG/SIOP study alone shows radiation-free EFS at 5 years of 42% (185,189,190,204). The CCG 9921 experience resulted in postoperative, postchemotherapy 5-year EFS of 32% with OS of 59% (139). The multidrug regimens have included the traditional four-drug combination (cisplatin, etoposide, vincristine, and cyclophosphamide) or, more recently, the UKCCSG/SIOP dose-intensive regime including sequential carboplatin and vincristine, high-dose methotrexate and vincristine, cyclophosphamide, and cisplatin (189,190). The St. Jude experience with a carboplatin-based regimen showed 33% 5-year PFS and 62% OS in a series utilizing postchemotherapy irradiation with any imaging evidence of residual (138). The impact of irradiation on disease control in young children had early been suggested in the first POG infant brain tumor study: children 2- to 3-years-old received irradiation after 1 year of chemotherapy, and those younger than 2-years-old were scheduled to receive irradiation after 2 years of chemotherapy. Long-term disease control was significantly higher in the older cohort, interpreted as likely to be related to earlier irradiation (189). Part of the rationale for continuing primary chemotherapy in this age group is the potential ability for postchemotherapy (including postprogression) surgery and irradiation to achieve ultimate disease control: the overall 5-year survival in the SFOP series was 59% despite the 22% rate of PFS (185). Timmermann et al. concluded that the 27% EFS at 3 years following HIT SKK 87 and 92 chemotherapy (highly high-dose methotrexate based, both systemic and intrathecal) is inadequate, resulting in local failures in 75% of cases prior to irradiation and an early OS rate (at 3 years) of 56% (205).

Radiotherapeutic Management

Volume

Target volumes for postoperative irradiation have evolved from whole brain to posterior fossa to outlining the local tumor bed only over the past two decades, from full posterior fossa therapy to local tumor bed volumes and consideration of high-dose volumes restricted to residual tumor sites (121,161,162,174,184,206,207). Posterior fossa ependymomas tend to adhere to the floor of the fourth ventricle and to cranial nerves and vessels rather than invading the brainstem or adjacent normal brain, suggesting that limited margins may be appropriate for this tumor. Recurrence patterns are predominantly local, within the high-dose volume; detailed patterns of failure analyses show 50% to 70% of failures confined to the primary site, an additional 10% to 20% involving the primary site and the neuraxis, and 10% to 40% involving the neuraxis alone (161,183,184,192,193,206–209). As local control rates improve, recently noted at more than 85% at 5 to 7 years with aggressive surgery and optimal radiation therapy, the percentage of failures involving the neuraxis or limited to the neuraxis has increased (175,186). For the 85% to 90% of children presenting with localized ependymomas, current recommendations for the GTV include the tumor bed and residual tumor based on both pre- and postoperative im-

aging. Optimal planning requires fusion of MRI studies to the planning CT, carefully assessing common patterns of disease extension (foramina of Luschka, circumferentially around the brainstem to encase the basilar artery, into foramen of Magendie and beyond foramen magnum to the upper spinal canal (164,166,175). The GTV is expanded anatomically by 1 cm to form the CTV, curtailed at fixed anatomic borders; a final 3D geometric expansion of 3 to 10 mm provides the PTV (174,210) (Fig. 4.9).

The incidence of neuraxis dissemination at diagnosis varies between 7% and 15% in the recent literature (162,192,211,212). Bloom et al. (220) initially reported a high frequency of seeding among high-grade posterior fossa ependymomas, recommending CSI for such presentations (213). Late follow-up of Bloom's Royal Marsden experience reported neuraxis dissemination in only 2 of 33 children with local posterior fossa tumor control, also noting no difference between children who had received CSI and those treated with only local volumes (213). Although varying significantly among recent reports, the prospective St. Jude series noted a 12% rate of failure limited to the neuraxis (i.e., with primary tumor control), notably related to histology: 5% for differentiated ependymomas versus 17% for anaplastic tumors, data that remarkably reproduced Bloom's earlier experience (121,175,207,212,213). Except for patients with neuraxis dissemination at diagnosis, no ongoing trial incorporates CSI as primary management.

Dosage

It has been difficult to define a dose-response relationship in ependymomas, largely reflecting differences in the proportion of completely resected cases and other factors (age, histology) that impact local tumor control. Data from CHOP suggest improved disease control with doses of >54 Gy (192). The excellent local control noted in Merchant's series was based largely on 59.4 Gy, although the infant cohort younger than 18 months in that series received only 54 Gy; no statistical difference was noted in tumor control related to dose. Awaiting the larger, multi-institutional COG trial, one is tempted to recommend 59/4 Gy, noting that the technique should spare the chiasm and upper spinal cord dose beyond the 54-Gy level (164,175,186). There have been trials of hyperfractionated delivery, with doses of 60 to 66 Gy delivered as 100 cGy twice daily through the SFOP; although readily tolerated, no advantage in outcome measures was apparent (214).

Technique

The standard of practice now entails use of 3D CRT or IMRT to target the tumor bed with a CTV expansion of 1 to 1.5 cm and a PTV expanded by an additional 5 to 7 mm, depending on the immobilization techniques and experience of the treating institution (Fig. 4.9). Comparative dosimetry reveals advantages in normal tissue sparing at the cochlea and in the nearby optic chiasm and upper spinal cord with IMRT (164,209). Further conformality with sparing of critical adjacent regions of the brain is noted with intensity-modulated proton beam irradiation (PBRT), for which there is preliminary experience with 17 children treated at the Massachusetts General Hospital (MGH) facility between 2000 and 2006 (215). The potential advantage of PBRT is apparent in considerable dose sparing; prospective clinical data are anticipated as the experience matures at MGH and begins at other PBRT

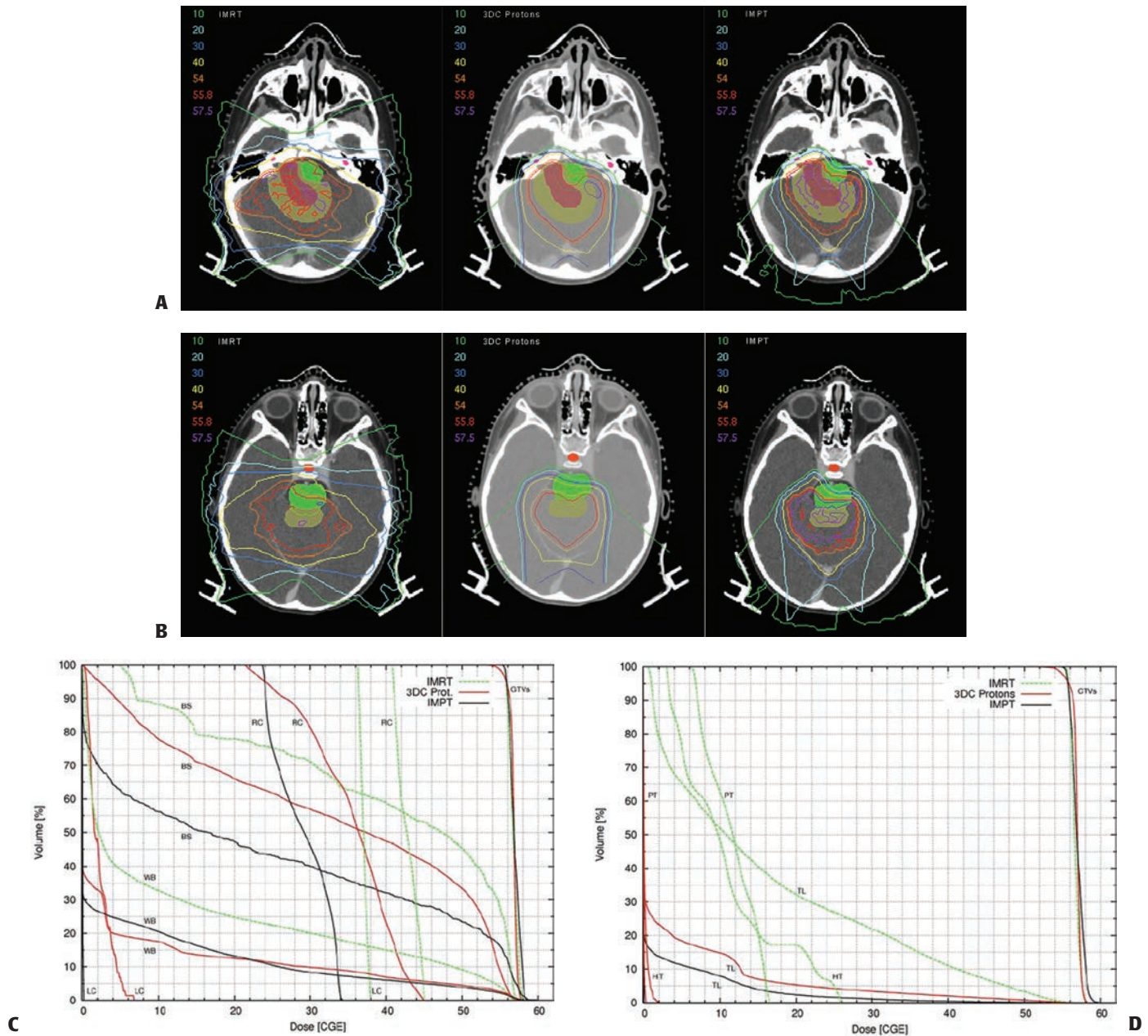


Figure 4.9 Ependymoma, fourth ventricle, following near total resection: (A,B) RT planning for 6-MeV photons using IMRT (L) compared to scatter-beam protons (*center*) and intensity-modulated proton beam therapy (IMPT, R). Axial imaging through level of cochlea (A) and pituitary (B). GTV (red) and 1-cm anatomic expansion to CTV (yellow); brainstem (green), cochlea (red), and pituitary (red) shown. C: Comparative DVH for three modalities showing coverage of GTV, cochlea (RC, LC), brainstem (BS), whole brain (WB). D: DVH showing coverage of GTV, pituitary (PT) and hypothalamus (HT) and temporal lobes (TL).

facilities in the United States and abroad. Immobilization in the prone position is most effective for fourth ventricular tumors; most often, supratentorial tumors are treated in the supine position.

Significant acute treatment-related toxicities are largely limited to cutaneous reactions. For most children treated after complete or near total resection, it is unnecessary to use corticosteroids during irradiation.

Results

Several series reflecting the MRI era document 5-year EFS at 40% to 60%, declining between 5 and 10 years to 35% to 46%

(162,192,193,199,208). Corresponding rates of 5- and 10-year OS have varied between 50% to 70% and 45% to 55%, respectively. The St. Jude experience, including a higher percentage of GTR and high-dose, focal irradiation, documents EFS of 74% and 69% at 5 and 10 years, respectively, and OS at 85% and 75%, respectively (175). Survival and patterns of failure relate to both histology (with less favorable outcome and apparently higher rate of neuraxis dissemination in anaplastic tumors) and degree of resection. Patients with metastatic disease at presentation showed 29% EFS at 5 years with OS at 43% in a multi-institutional review (187).

For infants, 5-year EFS and OS following aggressive surgery and irradiation (with preirradiation chemotherapy of varying intervals in <40% of cases) has been reported at 69% and 80%, respectively, in the Merchant's study, not different from children ≥ 3 -years-old (175). Grundy's report on the UKCCSG/SIOP trial is the most positive experience with "primary chemotherapy without irradiation," showing 5-year EFS and OS for the localized cohort at 42% and 63%; the 42% represents the most successful surgery–chemotherapy experience in this age cohort (177).

Success in retreating recurrent malignant brain tumors in children has been most apparent in ependymomas. Retrieval following surgery alone or prior surgery and irradiation has been documented with fractionated reirradiation even in children with disease progression involving the neuraxis (191,197) and with stereotactic radiosurgery (198,216).

BRAINSTEM GLIOMA

The brainstem is the connecting structure that joins the long tracts from the cerebral hemispheres and midline diencephalic nuclei with the cerebellar tracks; the white matter tracts course in all directions within aspects of the brainstem while converging caudally to form the spinal cord as the tracts exit through foramen magnum. Within the brainstem are the nuclei of the cranial nerves; coursing dorsally along the length of the brainstem is the reticular activating system, controlling vital functions (respiration, blood pressure), and general consciousness. The brainstem includes three anatomic segments: the midbrain rostrally, the pons, and the medulla caudally. The midbrain includes the cerebral peduncles (long tracts) and the reticular formation in the anterior tegmentum, as well as the nuclei of the third and fourth nerves; posterior to the cerebral aqueduct is the tectal plate, centers of coordination of ocular movements and both visual and auditory processing. Nuclei within the pons include cranial nerves V, VI, VII, and VIII; long tracts are organized longitudinally with broad connections laterally (cerebellopontine peduncles). Tracts are largely longitudinal

through the medulla, which includes nuclei for cranial nerves IX, X, XI, XII, and centers controlling the vital functions (respiration, blood pressure) (Fig. 4.10).

Brainstem tumors are a heterogeneous group of tumors that share common astrocytic histologies but evidence divergent neoplastic behavior (growth and invasiveness) and degrees of differentiation related to the anatomic region of involvement. Brainstem tumors are classified by the anatomic area(s) involved and the macroscopic appearance or pattern of growth: focal lesions are tumors that are discrete or distinctly margined on imaging (without apparent infiltration beyond the primary lesion), relatively limited in volume, and histology which is low grade, usually juvenile pilocytic astrocytoma (JPA, grade 1), less often fibrillary astrocytoma (grade 2) (Fig. 4.11) (217,218). Focal tumors occur most often in the tectal plate and adjacent to pontine nuclei, sharing low-grade histology with the largely exophytic tumors arising dorsally exophytic at the pontomedullary junction or in other "peripheral" locations of the brainstem (219–222). The more common diffusely infiltrating brainstem gliomas (DIBSG) arise in the pons, diffusely expanding the pons and extending rostrally to the cerebral peduncles of the midbrain and sometimes through the internal capsule of the thalamic region, or growing caudally to the medulla or upper spinal cord, less often through the peduncles into the cerebellum (Fig. 4.12). DIBSG account for 75% to 85% of brainstem neoplasms in children and adolescents; focal and "exophytic" tumors in sum represent 15% to 25% of cases (217,218,223,224).

The duration of symptoms correlates with the type of brainstem glioma. Children with DIBSG report a consistently brief history of neurologic symptoms, typically measured in weeks and certainly less than 6 months. Neurologic signs associated with the pontine DIBSGs include cranial nerve deficits, long tract signs, and ataxia; dyspraxia and dysphagia are also rather common (223,224). Elevated intracranial pressure secondary to obstructive hydrocephalus is often present in midbrain tumors or the expansile dorsally exophytic tumors that fill the fourth ventricle, but noted in fewer than 15% of children with pontine DIBSGs (Fig. 4.13). The focal brainstem tumors are often associated with prolonged, more limited symptoms, findings confined to deficits in one or two cranial nerves alone, ataxia, or dyspraxia, typically with minor long tract signs and a history measured in months or years (217,218,220–222,224–226).

MRI is the definitive test for diagnosis and delineation of tumor extent and type (Figs. 4.11–4.13). The typical diffusely infiltrating pontine glioma is homogeneous and hypointense on T1 imaging but readily appreciated on T2 sequence. DIBSGs expand the pons, often showing exophytic growth in the ventral, dorsal, and/or lateral directions as infiltrating lesions with indistinct margins; gadolinium enhancement is usually absent or minimal, occasionally noted in a ring-enhancing manner. Diffusion tensor imaging (DTI) and tractography often show sparing of the dorsal columns of the pons with infiltration splaying the longitudinal tracts. Focal brainstem tumors by definition show distinct margins, typically enhancing briskly. ^{18}F FDG PET is hypermetabolic in DIBSG; imaging–histologic correlations show hyperactivity only among grade 4 or glioblastoma cases; anaplastic astrocytomas were isometabolic with normal brain or hypometabolic, while low-grade fibrillary gliomas (grade 2) were isometabolic (227–229).

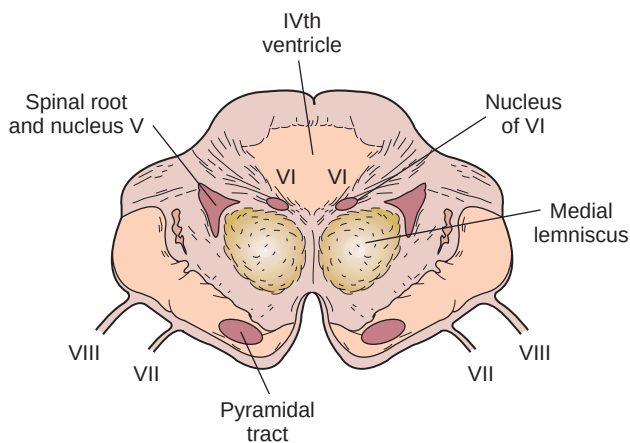


Figure 4.10 A lower pontine glioma interferes with motor function on one side of the body and with contralateral function of the sixth and seventh cranial nerves. These two cranial nerves are most commonly affected by brainstem tumors. Ataxia can result from involvement of the fibers of the middle cerebellar peduncle.

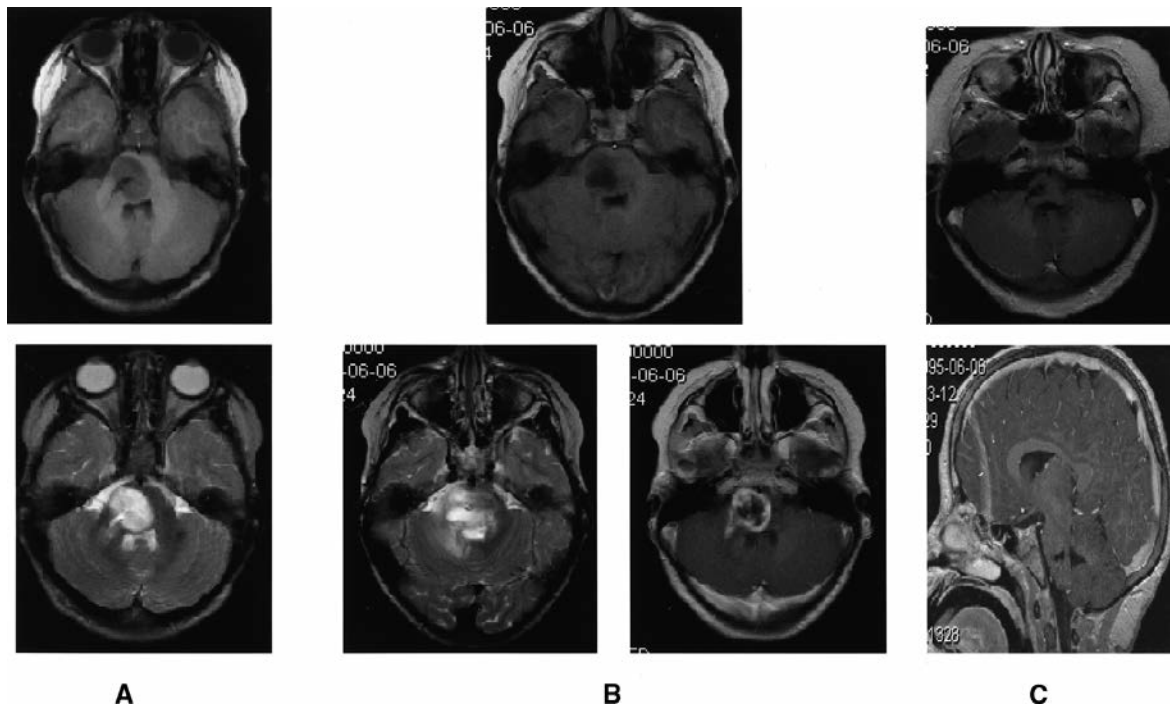


Figure 4.11 Focal, intrinsic pontomedullary juvenile pilocytic astrocytoma, after biopsy (3/12/99). Appearance 6 weeks after radiation therapy (54 Gy in 30 fractions): symptoms progressed from isolated right sixth nerve palsy with subtle left hyperreflexia to complete right seventh nerve palsy and dense left hemiparesis, associated with intralesional necrosis and expansion of the lesion (6/24/99). Patient treated supportively, with gradual improvement of left hemiparesis but persistent right seventh and sixth nerve palsies, associated with virtual resolution of lesion showing residual area of focal encephalomalacia on late imaging follow-up (3/12/03).

As a group, brainstem tumors constitute approximately 10% of intracranial tumors in children. The peak incidence occurs between the ages of 5 and 9 years; boys are affected more commonly than girls. The most common presenting symptoms for DIBSGs include diplopia, lateralizing motor weakness, and difficulty with speech, swallowing, and walking. Neurologic

signs include ataxia, cranial nerve palsies (most common are the pontine nerves, VI and VII, followed by the medullary nerves, IX, X, XI, and XII, and, less often, the midbrain nerves, III, IV, and V), and long tract signs (motor weakness, most often hemiparesis) (218,223). A review of the anatomy of the brainstem readily demonstrates why this constellation of signs occurs (Fig. 4.10).

Tumors of the midbrain and medulla may be diffuse or focal; even diffuse tumors typically show much less infiltration and expansion of the brainstem than seen with the pontine gliomas. Focal intrinsic tumors do occur in the pons, often as localized tumors of a cranial nerve nucleus or along the cerebellopontine peduncle.

Biopsy of the classic, diffusely infiltrating pontine glioma is generally unnecessary (218,223–230). Following trials in the 1980s of systematic open biopsy that yielded some of the basic knowledge correlating imaging and histopathology, biopsy-related neurologic compromise has led most US and European centers to biopsy only the 15% to 20% of “atypical” brainstem tumors, often demonstrating JPA or fibrillary grade 2 astrocytoma (227). Stereotactic guidance has resulted in a rather safe approach to the brainstem tumors, with series from Paris, Germany, and Brussels showing current histopathology and clinic-imaging correlations while reporting only minor, typically transient new neurologic deficits in approximately 10% of instances (227,231,232). The more recent biopsy series shows rather divergent histopathology, clearly dependent on selection criteria for biopsy: 22 of 24 children showed anaplastic astrocytoma or glioblastoma, with 1 PNET and 1 JPA reported from Hospital Necker-Enfants, compared to 10 of 20 in a more selected series from Brussels,



Figure 4.12 Brainstem gliomas: classic and most common diffusely infiltrating pontine glioma.

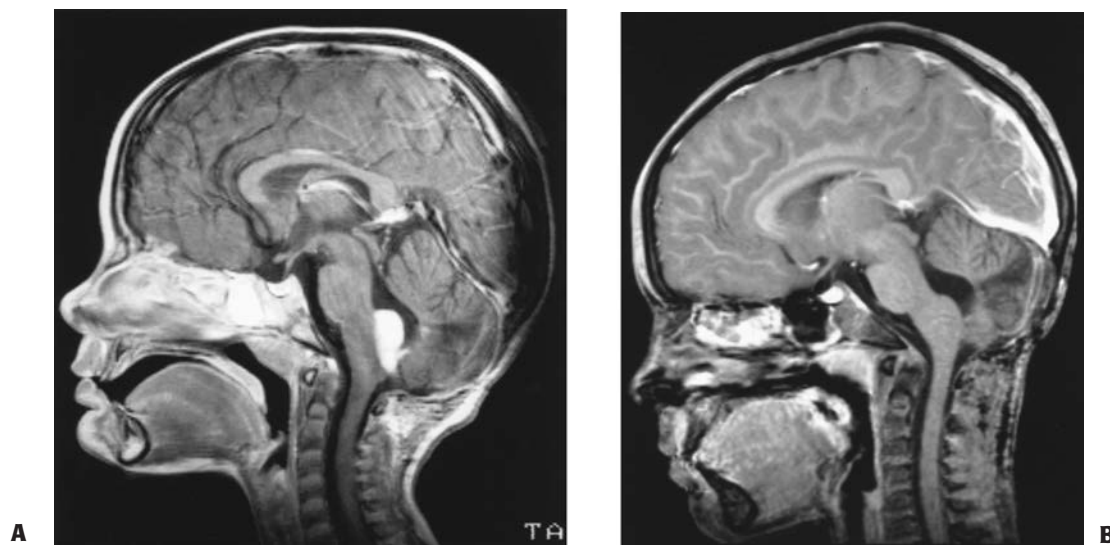


Figure 4.13 Brainstem astrocytomas. **A:** Dorsally exophytic brainstem juvenile pilocytic astrocytoma presents as a sizable lesion filling the fourth ventricle but is attached only along the floor at the level of the pontomedullary junction (**B**, postoperative); appearance 4 years after irradiation for documented postsurgical progression shows decreased mass effect and lack of enhancement.

the remainder showing grade 2 low-grade fibrillary astrocytoma, JPA, PNET, or germ cell tumor (231,232). There is no consistent correlation between histology and outcome; all diffusely infiltrating pontine tumors show extremely poor duration of response to irradiation and median survival of less than 1 year (223,226,233,234). Brainstem tumors have recently been shown to express *ERBB1*, with the degree of overexpression or less common amplification proportional to increasing histologic grade (235). The finding suggests that ErbB or EGFR inhibitors may be worth studying in these tumors, allowing “selected” therapeutic interventions. A protocol considered by the PBTC would select patients for temozolomide based on MGMT expression and erlotinib if EGFR positive.

A small subset of DIBSG may show CNS dissemination. Gururangan et al. described neuraxis metastasis in 17% of 96 patients at a median of 15 months after diagnosis, presenting as parenchymal dissemination (e.g., apparently noncontiguous disease extending from the pontine primary site to the internal capsule), leptomeningeal metastasis, or subependymal spread (236).

Hoffman et al. (221) identified a highly specific brainstem tumor: the dorsally exophytic “benign” brainstem tumor. The lesion characteristically fills the fourth ventricle, presenting with symptoms and signs of elevated intracranial pressure. In most cases, the tumor enhances briskly with gadolinium (Fig. 4.13). The origin from the floor of the fourth ventricle (the dorsal surface of the pons or medulla, with the tumor often arising at the pontomedullary junction) may be suggested by MRI but is usually apparent only at the time of surgery. These tumors are almost always JPA histologically; the prognosis has been quite favorable (230,237,238).

Focal tumors of the pons are uncommon. One specific presentation includes isolated facial nerve palsy or similar, limited neurologic dysfunction associated with a small, enhancing intrapontine lesion (220). Such tumors are JPAs and enjoy a favorable prognosis (Fig. 4.11) (223,239).

Tumors of the midbrain may involve the tegmentum or the tectal plate. Tegmental tumors usually are fibrillary astrocytomas (WHO, grade 2). The tumors may involve the

tegmentum focally or may infiltrate through much of the midbrain. Lesions may show uniform enhancement or little contrast enhancement. Presenting signs include extraocular muscle palsy or long tract involvement. Biopsy is preferred, especially for lesions contiguous with the pineal region.

Tectal plate tumors usually are quite small and well demarcated, confined to the tectal plate (Fig. 4.14). MRI shows the focal nature of tectal lesions, most often signified by brisk enhancement; biopsy generally confirms juvenile pilocytic histology (WHO, grade 1). These tumors typically are indolent; observation alone usually is the treatment of choice (222,223, 229,240). If the tumor is anatomically confined to the tectum and stable over an initial 3- to 6-month period of observation, biopsy may be deferred unless there is evidence of tumor progression necessitating therapy (223,239). When lesions are atypical (e.g., cystic), larger than 10 cc in volume, or when there is some question whether the lesion originated in the adjacent pineal region, biopsy may be needed at diagnosis. If it is confirmed as a low-grade astrocytoma, observation is appropriate.

Therapy Surgery

The role of surgery in classic pontine gliomas is limited. Interest in biopsy in the current era is largely to define the biology of the more common DIBSG and to document diagnosis for the atypical brainstem tumors, both intrinsic and exophytic (230,241,242).

For dorsally exophytic tumors, judicious incomplete resection will establish the diagnosis (by surgical observation of the origin from the brainstem and histology) and reduce the obstructing mass in the fourth ventricular region. Although there is no documented advantage to aggressive surgery, it may be advantageous to remove the bulk of the lesion posteriorly, establishing CSF flow and reducing the bulk of tumor when it can be reasonably separated from the underlying margin of normal, functioning brainstem. Aggressive resection as a primary intervention is often associated with unnecessary morbidity (237,238). Partial resection alone is associated with 50% to 70% freedom from progression at 5 to 10 years (221,225,237,238).

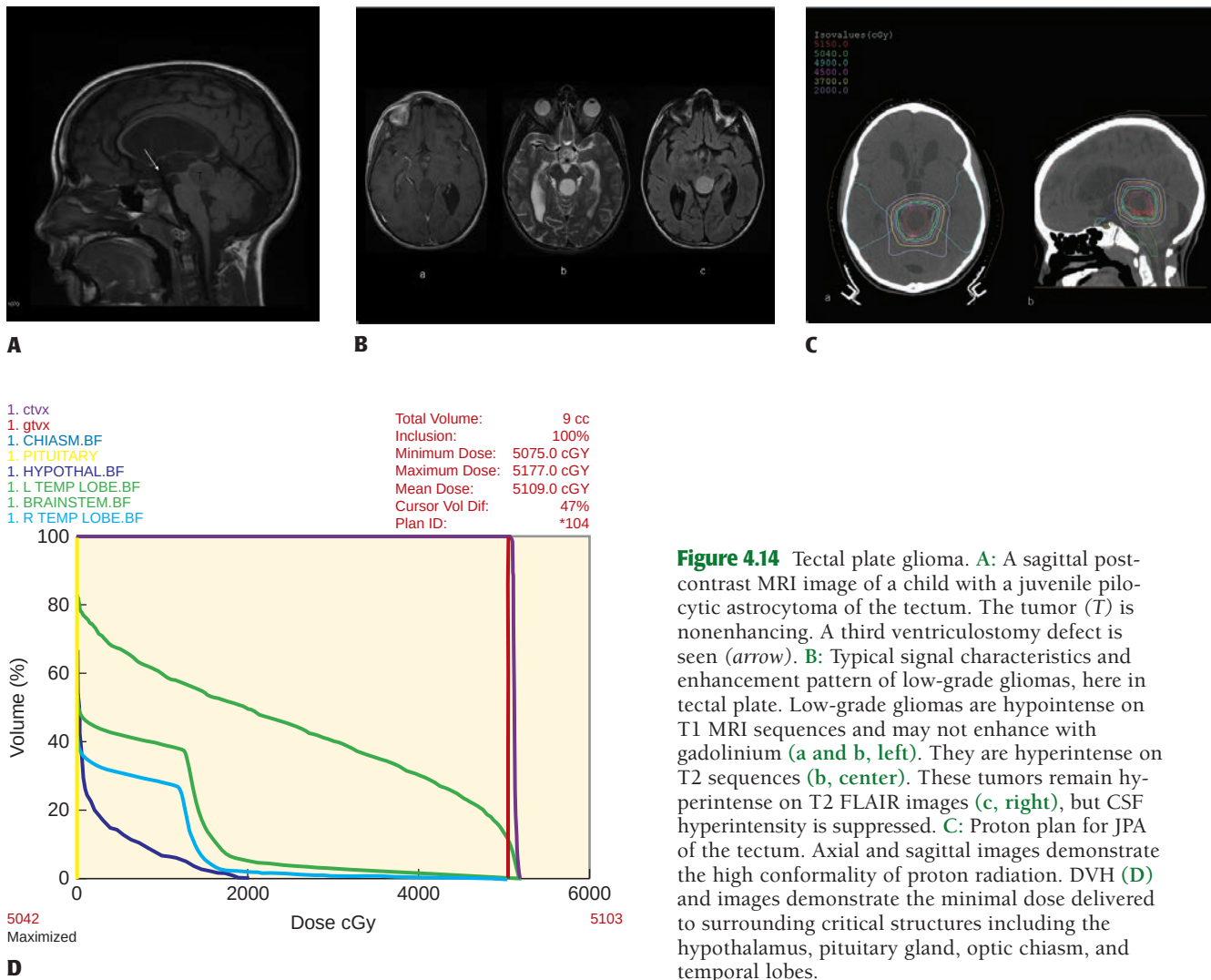


Figure 4.14 Tectal plate glioma. **A:** A sagittal post-contrast MRI image of a child with a juvenile pilocytic astrocytoma of the tectum. The tumor (T) is nonenhancing. A third ventriculostomy defect is seen (arrow). **B:** Typical signal characteristics and enhancement pattern of low-grade gliomas, here in tectal plate. Low-grade gliomas are hypointense on T1 MRI sequences and may not enhance with gadolinium (**a and b, left**). They are hyperintense on T2 sequences (**b, center**). These tumors remain hyperintense on T2 FLAIR images (**c, right**), but CSF hyperintensity is suppressed. **C:** Proton plan for JPA of the tectum. Axial and sagittal images demonstrate the high conformality of proton radiation. DVH (**D**) and images demonstrate the minimal dose delivered to surrounding critical structures including the hypothalamus, pituitary gland, optic chiasm, and temporal lobes.

Small focal lesions intrinsic to the pons may be biopsied if safely approachable; one cannot insist on biopsy if the differential diagnosis is limited and the biopsy-associated morbidity is high (220,223).

Lesions in the tegmentum should be biopsied, although the potential morbidity of stereotactic biopsy is recognized because of the proximity of the central veins. Occasional resection has been reported for midbrain tumors (219,242). Tumors of the lower medulla or cervicomedullary region are similar to low-grade astrocytomas of the spinal cord. Biopsy and attempted gross total resection have been reported; results after surgery alone have been impressive but limited to a small number of neurosurgical centers (219,241,243). Histology usually is low-grade astrocytoma (WHO, grade 2). Malignant gliomas have been reported (241).

Radiation Therapy

Children with diffusely infiltrating pontine gliomas often respond impressively to irradiation. Up to 70% show improvement in neurologic symptoms and signs over the course of irradiation; objective reduction in tumor on MRI is apparent within 8 to 12 weeks of initiating irradiation. Unfortunately,

signs of progressive disease are apparent systematically within 6 to 12 months (223,244).

Clinical response has also been noted in tegmental mid-brain lesions and tumors of the medulla, where radiation therapy is more likely to achieve long-term disease control (223,245). For tectal plate or dorsally exophytic pontomedullary astrocytomas, irradiation is typically deferred until signs of disease progression are apparent on imaging (222,225,229,237,238). Once progression has been documented on serial imaging (noted in 25% to 40% of dorsally exophytic tumors), there has been almost uniform disease control measured out to more than 5 years after local irradiation (225,237,238). Intrinsic focal pontine lesions often require irradiation at diagnosis to control attendant neurologic signs (220). With the availability of precision volume techniques (i.e., 3D CRT or fractionated radiosurgery), the risk:benefit ratio may favor earlier radiation intervention in localized, low-grade brainstem lesions (246,247).

Chemotherapy

Despite documented transient response, there is little evidence of efficacy for chemotherapy in brainstem tumors. An earlier

prospective, randomized trial of CCNU, vincristine, and prednisone showed no benefit in these tumors despite purported efficacy in supratentorial high-grade gliomas (248). Adjuvant studies with concurrent or sequential chemotherapy or, more recently, trials incorporating molecular targeting agents (inhibitors of EGFR, PDGFR; HDAC (histone deacetylase inhibitors) and VEGF inhibitors) have failed to alter the PFS or OS data in this disease (249–253). Despite efficacy in adults with hemispheric malignant gliomas, temozolomide has shown no advantage in DIBSG in children (254). Preirradiation chemotherapy regimens have shown some responsiveness, but early disease progression during chemotherapy and a lack of objective benefit in postirradiation intervals to progression have largely dampened enthusiasm for this approach, if a limited recent French trial testing preirradiation BCNU, cisplatin, and high-dose methotrexate continues to generate interest (255–258). Cross-study analyses of serial POG brainstem glioma trials actually suggested a detrimental effect when *cis*-platinum was added to high-dose hyperfractionated irradiation (70.2 Gy in 60 fractions) (259). Trials of noncytotoxic radiosensitizers have also been conducted in phases I and II settings for DIBSG; more recent experience with motexafin gadolinium has revealed little benefit (260).

Demonstration that large molecules can be perfused directly through the brainstem using via intra-axial catheter placement for convection-enhanced delivery (CED) raises the possibility of direct infusion of biologic agents for brainstem gliomas, a concept now being addressed in a phase I trial at the U.S. National Institutes of Health (261–263).

For focal, low-grade gliomas, the use of chemotherapy before irradiation is an extrapolation from diencephalic low-grade tumors, which may be rational in selected settings (264). For the majority of children, even those younger than 4-years-old, symptomatic or progressive dorsally exophytic or focal pontine lesions can be treated effectively with focal radiation techniques. It is difficult to anticipate any significant advantage in delaying definitive therapy with intervening chemotherapy.

Radiotherapeutic Management

Volume

MRI and autopsy studies document contiguous extension of pontine gliomas linearly through the adjacent medulla or midbrain and axially into the brachium pontis, the CPA, and adjacent portions of the cerebellar hemispheres (217,224,265). Neuraxis metastasis has been noted in up to 15% of children with DIBSG, involving the subarachnoid space (primarily about the brainstem, the basal cistern, or the upper cervical cord, but also into the spinal canal), direct or noncontiguous appearance cephalad into thalamic white matter, or subependymally within the ventricular system (223,236, 266,267). A small proportion of focal, low-grade brainstem lesions (often JPAs) are associated with neuraxis dissemination, most often noted at diagnosis (220,268). In almost all instances, the pattern of failure for DIBSG includes the primary pontine tumor alone or in conjunction with other sites as above (265,269). Local irradiation is indicated, with target volumes subtending both the pons and the contiguous regions both linearly (adjacent midbrain and medulla) and axially (adjacent peduncles and, where indicated, contiguous anterior cerebellum). The best estimate of tumor extent is typically on

T2 or T2 flair sequences to define the GTV (224,246). Microscopic margins along the white matter tracts provide a 1- to 2-cm anatomic expansion to identify the CTV. It is important to note that tumors extending rostrally into the midbrain or higher will show larger axial CTVs at the upper midbrain and contiguous internal capsules than at the primary pontine level, simply a matter of anatomically covering sites of direct extension. For infiltrating tumors of the midbrain and medulla, margins of 1 to 1.5 cm along white matter tracts beyond the T2 or flair extent are appropriate.

Focal lesions of the tectum can be treated with limited target volumes; treatment of discrete lesions generally entails treating only the identifiable tumor with a 1 cm or less CTV for 3D conformal or IMRT (223,246). Fractionated stereotactic radiosurgery (also called stereotactic radiotherapy) and radiosurgery have been used for the latter tumor types (173,246,247).

For dorsally exophytic tumors, the volume can conform to the disease process based on MRI; the anterior margin at the brainstem should encompass at least 5 mm of apparently normal brainstem ventral to the tumor as documented on MRI. A 3D CRT or IMRT approach can spare radiation dosage to the temporal lobes, especially important in this young age group.

Dosage

A decade-long series of trials in the 1980s and 1990s explored the impact of high-dose, hyperfractionated irradiation for brainstem gliomas. Despite dosage escalations from 66 Gy to 70 to 72 Gy and ultimately to 75.6 to 78 Gy (with twice-daily fractions of 100 to 126 cGy), no durable improvement was documented in disease control or survival. The outcome after conventionally fractionated irradiation to 54 to 55.8 Gy (180 cGy once daily) or hyperfractionated irradiation to between 70 and 78 Gy has been consistently documented at median times to progression of only 6 to 8 months, median survival approaching 1-year, and 2-year survival rates of only 10% (223,226, 244,245,259). A randomized trial ultimately documented the equivalence of conventional and hyperfractionated schedules (270). A trial of accelerated fractionation in Europe, using 180 cGy twice daily with interfraction intervals of 8 hours to 48.6 and 50.4 Gy, showed similar results, with 32% survival at 1 year and 11% at 2 years (271). It is unclear whether paucifractionated approaches with fraction sizes of 3 Gy (to 39 Gy/13 fractions) or 5.5 Gy (to 33 Gy/6 fractions) achieve equivalent or inferior results compared to conventionally fractionated regimens (272).

Technique

Diffusely infiltrating pontine gliomas classically were irradiated with parallel-opposed lateral fields intended to encompass the tumor volume with a margin of 2 to 3 cm (223,244). Current approaches more often include 3D CRT or, less often, IMRT approaches that enable one to spare the temporal lobes and aspects of the cochlea; the lack of a significant surviving cohort limit enthusiasm to pursue IMRT in most centers. The lower border of the radiation volume typically extends to C1 or C2 to allow a 1- to 2-cm linear margin beyond the GTV in defining the CTV; similar margins are utilized rostrally to the midbrain or following the cerebral peduncles into the internal capsular regions when

necessary. Axially, one typically requires a 5 to 10 mm expansion in defining the CTV, extended to 1 cm when there is imaging evidence of disease into and beyond the peduncles. With usual immobilization and repositioning, one typically identifies an additional 5-mm geometric expansion to define the PTV.

For focal brainstem gliomas (including tectal plate lesions, dorsally exophytic pontomedullary tumors, and focal intrinsic lesions of the midbrain, pons, or medulla), tumor size, margination, and location demand 3D CRT or, commonly, IMRT or stereotactic radiosurgery approaches to minimize dosage beyond the primary target volume while maintaining intralesional homogeneity in the CTV within 5% (246) (Fig. 4.14).

Children with DIBSGs usually need corticosteroids at diagnosis to control neurologic symptoms. For those not receiving corticosteroids at the initiation of radiation therapy, one should consider initiating a low-dose regimen (e.g., dexamethasone at 2 to 4 mg twice daily) only for children with large intrinsic tumors or early development of additional or progressive neurologic signs. Irradiation generally is well tolerated, and one can commonly taper dexamethasone during the course of irradiation, often discontinuing steroid support by the fifth or sixth week of therapy. Reducing the dexamethasone dose is important both for secondary drug effects and to control cushingoid features that can make repositioning in immobilizing masks problematic as the face expands secondary to steroids. The newer biologic agents often show cutaneous reactions that require management within and well beyond the radiation volumes (273,274).

A significant proportion of patients with brainstem tumors demonstrate clinical and imaging evidence of apparent progressive tumor within 1 to 4 months of completing radiation therapy (243,275). MR spectroscopy and PET studies may be of help in differentiating early tumor progression from the “pseudoprogression” often comparable to that seen in adults with hemispheric glioblastoma (224,276). Imaging changes during this interval include focal enhancement (often in a previously nonenhancing lesion), cyst formation (or cystic degeneration), or intralesional hemorrhage and necrosis (224,271,275). The problem is recognized in cooperative group trials, where patients may be coded formally as “disease progression,” but maintained on study without interruption of postirradiation therapy until resolution or progression is ultimately clear. Similar changes, with apparent tumor progression and worsening of neurologic signs, can occur 1 to 4 months after irradiation for focal intrinsic JPAs (Fig. 4.11). Medical support, including corticosteroids, may be necessary until the lesion regresses over several months.

Results

Approximately 60% to 70% of patients with classic pontine gliomas show improvement in functional status after irradiation. Time to progression may be difficult to document in this tumor system; cooperative group studies report median time to progression of 6 to 8 months. Overall survival is the primary endpoint for comparing therapies, providing an objective parameter reflecting primary management and recognizing that little prolonged secondary benefit has been documented from secondary therapies. Median survival is 8 to 12 months in patients selected for high-risk DIBSG studies, and the proportion surviving at 2 years is less than 10% to 20%

(223,224,226,244,245,253,259,269). There is some suggestion that younger children (<3-years-old) may show superior outcome, perhaps related to the biology of such uncommon presentations (277).

Children with focal, intrinsic tumors of the midbrain or medulla show long-term survival after irradiation of 50% to 70% (217,222,223,245). Survival at 10 years after surgery with or without necessary irradiation for dorsally exophytic brainstem gliomas approaches 75% (221,223,237,238). Similar rates are quoted for the focal pontine lesions of limited size after localized irradiation (220).

CEREBELLAR ASTROCYTOMAS

Cerebellar astrocytomas make up 10% to 15% of childhood brain tumors and 25% of posterior fossa neoplasms. These tumors are typically low grade, well circumscribed, and slowly growing with prominent cyst formation (278,279). The classic cystic cerebellar astrocytoma presents as a unilocular cyst with a single prominent mural nodule. Cushing (168) was the first to describe the entity in 1931, commenting on the “benign” nature of cerebellar astrocytomas, associated with low morbidity and mortality.

The cerebellum is one of the most common sites of origin for low-grade gliomas in children. The vast majority of cerebellar astrocytomas are low grade: JPAs (WHO, grade 1) comprise 80% to 95% of cases, and diffuse fibrillary astrocytomas (WHO, grade 2) account for 5% to 15% (280–283). Biphasic architecture is characteristic of JPAs, with more cellular areas that tend to have Rosenthal fibers (degenerating astrocytic processes and loose areas with microcysts). Cells are elongated, bipolar, and have thin “hair-like” processes (hence, piloid) (280). Diffuse fibrillary astrocytomas tend to be less circumscribed, more infiltrative and expansile, with a less favorable prognosis relative to JPA; the diffuse tumors arise specified, or as oligoastrocytomas (280,281,284,285). Malignant gliomas are quite uncommon in the childhood cerebellum.

The median age at diagnosis is 5 to 6 years, with 20% of cases younger than 3-years-old; astrocytomas of this location are rarely found in infants (278,282,286). Presenting symptoms often are confined to those associated with elevated intracranial pressure (headaches, vomiting, etc.), with less frequent altered cerebellar function (primarily ataxia, poor coordination, or dyspraxic speech); cranial nerve deficits are uncommon.

The majority of tumors arise in the cerebellar hemispheres; approximately one third are primary vermis lesions. Most tumors are confined to the cerebellum; a minority extend to the cerebellopontine peduncle or the posterior aspect of the brainstem (278,279,282,286,287). The most characteristic appearance on CT or MRI is a large, well-circumscribed tumor with prominent cysts (unilocular or multilocular). The nodular or solid portion of the tumor characteristically enhances briskly. The cyst wall may or may not demonstrate contrast enhancement. The nodular and cystic components are considered part of the tumor; both components should be addressed at the time of surgery (282,286,288). Cerebellar JPAs have uncommonly been associated with multifocal CNS involvement, representing either neuraxis dissemination or concurrent multifocal presentation (289,290).

Therapy

Surgery

Surgical resection is the treatment of choice for cerebellar astrocytomas. The amount or degree of resection has been found to be the most important prognostic factor for outcome in patients with low-grade gliomas (129). For classic cystic cerebellar astrocytomas, gross total resection has been reported in 70% to 90% of cases (281,282,284,291). PFS for these children is in excess of 90%. Even in the setting of documented residual, many tumors remain indolent. After surgery- and imaging-confirmed gross total resection, recurrence is uncommon, noted at 5% to 10% in major series (282,284–287,291,292). After incomplete resection, disease progression has been reported in 30% to 60% of cases at 5 years or more. Importantly, long-term survival remains above 65% (279,282,284,291). Infiltrative tumors and diffuse fibrillary astrocytomas are less likely to be amenable to gross total resection and are associated with a higher rate of disease progression or recurrence (282,293). Despite the indolent nature of these tumors, the median time to recurrence is about 2 years (279,282,284,287). Children who experience tumor recurrence amenable to surgery may benefit from a second surgery. This is generally recommended if the tumor can be totally resected or substantially debulked without great risk of neurologic compromise.

Radiation Therapy

There is no established role for radiation therapy in the primary management of cerebellar astrocytomas that are amenable to gross total resection. Prognostic factors that may predict relapse after initial surgery alone should be considered. Most series indicate greater risk of later disease progression in recurrent tumors, infiltrative tumors, astrocytomas that cannot be completely resected, and tumors with diffuse fibrillary histology or more aggressive histologic subtypes (278,279,281,282,286,291).

Indications for radiation therapy include progression of incompletely resected tumors that are not amenable to second surgery and incomplete surgical resection following recurrence. This is an uncommon situation for JPA, but is seen more frequently in tumors with diffuse fibrillary histology (282,285). Given recent data showing the efficacy of chemotherapy in delaying disease progression, chemotherapy may be the preferred initial adjuvant treatment for these more aggressive presentations in very young children (294). There are no data substantiating improvement in disease control with postoperative irradiation following a complete resection (286,291,295). Infrequent malignant gliomas seem to benefit from immediate postoperative irradiation, but overall prognosis in these cases is poor (293).

Chemotherapy

Because most low-grade gliomas located in the cerebellum are amenable to surgical resection and do not require adjuvant therapy, it is relatively rare to use chemotherapy for this specific tumor site. Multiple chemotherapeutic agents have been shown to delay progression (294,296,297). The most commonly administered regimen is the combination of carboplatin and vincristine. A more extensive review of the use of chemotherapy for low-grade gliomas is included in the “Low-Grade Supratentorial Astrocytomas” section in Chapter 3.

Radiotherapeutic Management

Indications for radiation therapy are generally limited to documented progressive or recurrent disease that has undergone a second incomplete resection, or that is felt to be unresectable upon progression or recurrence (282,295). Some centers withhold irradiation even after multiple recurrences, when further surgery may seem to be an option (287). Lesions with an infiltrative pattern involving the peduncle or brainstem may require early radiation therapy when symptomatic or progressive. Such lesions are targeted with limited anatomic expansion of 0.5 to 1 cm around the GTV as defined on MRI with image registration to include immediate preoperative disease and residual at the tumor bed (298). The prescription dose is generally 50 to 54 Gy (299).

The treatment of high-grade cerebellar astrocytomas generally includes multiple modalities. Postoperative irradiation to the local tumor is recognized as the standard of care (282,295). CSF dissemination is a recognized pattern of failure; neuraxis irradiation is typically considered only when overt CNS metastasis is documented (282,289, 290,295).

Results

OS rates in childhood cerebellar astrocytomas are more than 80% at 10 to 20 years (278,279,282,286). Survival rates are highest among those with tumors confined to the cerebellar hemispheres or vermis, JPA histology, and those amenable to gross total resection. For incompletely resected diffuse astrocytomas, long-term survival rates of 50% to 80% have been reported (278,281,282,284,287). It is interesting that children with cerebellar astrocytomas demonstrate cognitive and adaptive deficits despite posterior fossa location and therapy limited to surgery alone (300). This risk does not seem to be associated with surgical or medical complications.

SPINAL CORD NEOPLASMS

Spinal cord neoplasms are uncommon in children. These tumors are divided into two main groups: intradural and extradural. Intradural lesions are further classified into those involving the spinal cord itself (intramedullary) or arising outside of the spinal cord parenchyma from the cauda equina or intradural components of the nerve roots (extramedullary). Extradural tumors are by definition neoplasms that arise outside the nervous system with extension into the spinal canal through the neural foramina. Extradural tumors that gain access to the spinal canal can then extend linearly beyond the cord segment of entry, accounting for the “dumb-bell” description; such presentations are most common in neuroblastomas, paravertebral soft tissue tumors of the Ewing type (i.e., peripheral PNET), or neurofibromas (301). Management of extradural presentations is discussed in chapters 9, 11 and 12.

Primary (intramedullary) spinal cord neoplasms account for approximately 5% of CNS neoplasms in children (302). The median age is between 8 and 9 years with a slight male predominance (303,304). The relative histologic and anatomic frequencies of spinal cord tumors in children are almost mirror image proportions of those in adults: astrocytomas account for approximately 60% of primary spinal cord tumors in children, while ependymomas account for 30% (302,305–307). Other gliomas (gangliogliomas, oligodendrogliomas)

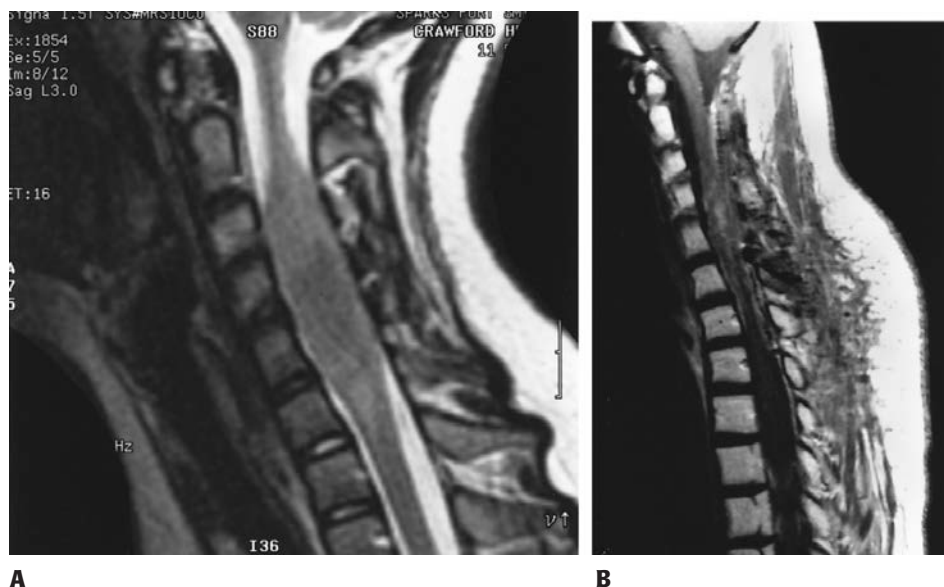


Figure 4.15 Intramedullary spinal cord astrocytoma. **A:** Lesion involving the cervicothoracic cord. **B:** The child is free of disease after subtotal resection and irradiation.

and neurilemmomas (neurofibromas usually associated with neurofibromatosis type I) comprise the remaining 10% (302,305,308–310).

More than 80% of pediatric spinal cord astrocytomas are low-grade neoplasms, most often fibrillary and less commonly juvenile pilocytic in type. Astrocytomas occur primarily in the cervical and thoracic regions of the cord, presenting as circumscribed or more infiltrating lesions (Fig. 4.15). The tumors diffusely widen the involved cord; tumor length averages six spinal cord segments (302). More than 30% are associated with sizable intraspinal cysts (305,308,310). The cysts typically extend in cephalad and caudal directions from the solid tumor, representing fluid-filled components that may be more than double the overall length of the lesion. Differentiating true tumor-derived cysts from common syrinx formation related to obstruction of the central canal is often difficult. Malignant gliomas (high-grade astrocytomas: anaplastic astrocytoma and glioblastoma multiforme) account for fewer than 20% of astrocytic lesions. Spinal malignant gliomas are clinically aggressive lesions and carry a poor prognosis. The literature suggests that such tumors may be more common in infants (305,307,308,310). Holocord astrocytomas extend over much of the length of the cervicothoracic cord. The majority of these tumors are infiltrating (fibrillary) astrocytomas and often represent lengthy cystic extensions of relatively more localized neoplasms, recognizing the solid tumor components may yet involve a significant length of the spinal cord (306,311,312). Less common glial tumors include oligodendrogliomas and gangliogliomas. These tumors usually are discrete and well-circumscribed intraspinal lesions that occur in the cervical, thoracic, or cervicomedullary junction regions. Presenting characteristics are similar to those of the astrocytomas (306,313,314).

Spinal cord tumors represent 5% or less of all ependymomas in children (305,315). The majority arise in the low thoraco-lumbar region, involving the conus medullaris or the cauda equina. Most such ependymal lesions are histologically differentiated ependymomas, most often grade 1 myxopapillary ependymoma (306,315). These tumors are low-grade, indolent lesions signified histologically by papillary growth and mucin formation (316). Two thirds occur in the cauda equina,

presumably arising from the filum; 30% present as tumors of the conus medullaris and 5% as atypical myxopapillary tumors of the cervical or thoracic cord (316) (Fig. 4.16). Despite their benign histology and tendency for slow growth, local recurrence is not uncommon, particularly after incomplete resection. As compared to adults, children have been shown to have a more aggressive disease course with a greater risk of recurrence and dissemination to other regions of the spine (317). In contrast, ependymomas of the cervical or thoracic cord tend to be discrete, focal intramedullary lesions (309,318).

Spinal cord tumors usually present with slowly progressive symptoms. The average duration of symptoms in most studies is 2 to 9 months, but some children report symptoms for years prior to diagnosis (301,319,320). The most common symptoms include pain and weakness corresponding to the level of the lesion. Pain is classically greater at night, when the child is recumbent (312,313). Younger children may present with torticollis or hypotonia and/or variability of reflexes on examination (320). It is not rare to see lower thoracic cord pain evaluated as an intra-abdominal process, including by laparotomy for suspected appendicitis. Numbness or sphincter dysfunction occurs in 10% of cases (305,306,311). Symptoms and signs of elevated intracranial pressure may be noted at diagnosis of a primary, localized spinal cord tumor (321).

MRI is the standard imaging mode for assessment of spinal cord neoplasms. One can usually distinguish intramedullary from extramedullary lesions; tumor extent is generally well appreciated. It is sometimes difficult to discern subtle cystic changes from solid tumor extension; intraoperative ultrasound can be a more sensitive tool in this regard. Fibrillary astrocytomas and gangliogliomas usually are nonenhancing tumors, best delineated on T2 sequences. JPAs enhance uniformly. Ependymomas typically are enhancing lesions. In evaluating spinal cord tumors, it is important to image the entire length of the spinal canal; one can see “skip” intramedullary involvement uncommonly in astrocytomas. In ependymomas, it is standard to image the entire neuraxis; rarely, intracranial ependymomas can present symptomatically as a “primary” intraspinal or cauda equina tumor with an occult intracranial primary. Subarachnoid dissemination



Figure 4.16 Myxopapillary ependymoma of the cauda equina, documenting extensive disease that involves the cauda and nerve roots (A); postoperative imaging shows residual and subarachnoid deposits (B) and (C). Disease controlled at 5 years following surgery and CSI.

can occur in malignant gliomas and ependymomas (308,318).

Therapy Surgery

The primary management for most intradural spinal tumors is surgery. Current technology and experience with intramedullary lesions have greatly facilitated gross total resection for a large percentage of pediatric intraspinal neoplasms. The use of midline myelotomy and ultrasonic dissection has allowed discrete dissection of intraspinal gliomas. Pediatric neurosurgeons report low rates of long-term morbidity after judicious complete resection, often technically approached from just outside the tumor margin, rather than after biopsy with attendant intraslesional swelling or potential hemorrhage (306,307,309,311, 314,315,322). Spinal evoked potentials guide the surgical procedure, allowing intraoperative monitoring to confirm preservation of long tract function (311,314). Postoperative increased neurologic deficit is reported to be limited and often transient for tumors above

the T9 level; intraspinal astrocytomas at the T9–T12 level may be associated with greater postoperative morbidity, in part due to complexities of the vascular supply in this region (306,307,309,311).

The goal of surgery for spinal cord tumors is to establish a pathologic diagnosis and perform a complete excision without major compromise of neurologic function; when complete excision is not possible, maximal safe removal will often relieve symptoms with less compromise postoperatively than biopsy alone. Summary data from 10 earlier studies combining pediatric and adult experience indicated total excision in 16% of low-grade spinal gliomas (primarily astrocytoma) (308,311, 312,322). For low-grade histologies, Epstein's New York experience indicates PFS after surgery alone exceeding 90% at more than 5 years in spinal cord and cervicomedullary junction tumors, data that have been confirmed in smaller studies (223,305,310,311,315). The high rates of disease control after surgery, with acceptable morbidity, confirm the role for primary surgical management for low-grade astrocytomas in experienced neurosurgical centers, most data suggesting a correlation between degree of resection and outcome (319,323). For

incompletely resected tumors, second surgery may be considered immediately (when anatomically approachable, before postoperative gliosis sets in) or at relapse when added risks may seem more justified. For high-grade gliomas outcome is poor regardless of degree of resection, with only anecdotal survival beyond 3 years for anaplastic astrocytomas or glioblastomas (305,308–310).

For spinal ependymomas, gross total resection has been documented in 25% to 100% of cases in series often combining pediatric and adult experience (306,309,316–318,324). Myxopapillary ependymomas in children are often amenable to gross total resection. Although detailed dissection often is necessary for lesions that adhere to numerous nerve roots comprising the cauda, earlier data from the Royal Marsden Hospital indicate total resection in 42% of 24 cases of cauda equina tumors, with 92% PFS at 5 years (318). For lesions of the conus medullaris, the earlier studies indicated resection in only 2 of 14 cases (318). By contrast, McCormick et al. (324) indicated resection in all 23 children and adults with intramedullary tumors, only 1 of whom experienced recurrence. A recent study indicates a higher rate of recurrence in children (64% vs. 32% in adults at a median follow-up of 6.1 years) (317). Surgery alone has been associated with survival rates at 5 years of 86% to 100% (243,306,314,315,318).

Chemotherapy

Experience using chemotherapy is limited, but small series do report apparent efficacy for carboplatin and vincristine in low-grade spinal astrocytomas (325). The combination of irinotecan and cisplatin was also found to be safe and effective in a small cohort of children under the age of 3 years with progressive disease after administration of carboplatin and vincristine (326). Currently, there is no clear role for chemotherapy for the treatment of spinal cord ependymomas. For high-grade tumors of the spinal cord multimodality therapy including chemotherapy is generally used, but despite aggressive treatment, prognosis is poor (327).

Radiation Therapy

The use of postoperative irradiation for spinal cord tumors has been controversial and largely inconsistent. With improved neurosurgical methods, there appears to be no clear benefit from systematic postoperative radiation therapy for low-grade spinal gliomas or ependymomas in children (306–308,315).

The literature documents 50% to 60% survival rates at 5 years after surgery and irradiation for largely incompletely resected spinal astrocytomas (305,308,315,328,329). Lacking comparative data, a rational approach includes maximal surgical resection. For incompletely resected tumors, one can support observation for low-grade gliomas (especially pilocytic histologies, but also other low-grade gliomas in prepubertal children where the risk:benefit ratio may favor delaying radiation intervention). Although long-term freedom from progression has been documented after incomplete surgery alone, postoperative radiation therapy is generally indicated for sizable residual tumors that are unlikely to be amenable to later, more complete resection (305,307,315,328,330). If one elects to follow a child with suspected or definite residual disease, it is important to commit to later second surgery (when feasible) and irradiation (unless the second surgery results in imaging-confirmed total

resection) with evidence of progressive disease (based on imaging or on changes in symptoms or neurologic signs).

For spinal cord ependymomas, there is evidence supporting surgery alone for intramedullary tumors and for initial management of cauda equina tumors (306,309,314,324,329). The indolent nature of myxopapillary tumors favors observation in the setting of total resection or minimal residual disease (308,315,318,330). Recurrence rates after complete resection are relatively low, but disease progression after incomplete resection for children may be high (308,309,318). In the setting of recurrence or tumor progression, treatment generally consists of second surgery followed by irradiation. Although the impact of histologic grade in ependymomas is apparent in adult studies, anaplastic ependymomas of the spine are uncommon in children; extrapolation from the adult data suggests a role for postoperative irradiation for such lesions (309,318,328).

Radiotherapeutic Management Volume

Neuraxis staging is an important component of preirradiation assessment for intramedullary tumors of all types. When radiation is indicated, local irradiation is used for most spinal cord tumors. Localized intramedullary astrocytomas and ependymomas are generally treated to the tumor bed, based on preoperative and postoperative MRI; a margin of 1 to 2 cm longitudinally is indicated for low-grade, focal lesions. For astrocytomas, one typically sees decompression or obliteration of the rostral and caudal cystic components after resection of the solid tumor. In such instances, it appears that radiation therapy can be limited to the solid tumor bed (308,310,311,315,318,322). For spinal ependymomas, local volumes are also indicated (308,315,318). For cauda equina tumors, there is some debate regarding the use of local or craniospinal volumes. Recent studies suggest regional irradiation that includes a 2- to 3-cm margin above the initial tumor volume (typically into the conus), and caudal coverage to include the proximal sacral nerve roots axially and the bottom of the thecal sac longitudinally (315,316,318). For patients with disseminated low-grade astrocytomas, the radiation volume is controversial with some advocating the use of local irradiation and others recommending inclusion of the entire craniospinal axis (331,332). Age-dependent consideration of full neuraxis irradiation is indicated when the pattern of involvement is truly leptomeningeal. Careful consideration of tumor and patient characteristics in these cases is paramount.

Dosage

The local radiation dose for spinal cord astrocytomas and other glial histotypes has typically been reported as 50 Gy using daily fractions of 180 cGy. This is based at least as much on estimated cord tolerance as it is on documentation of dose to achieve local control. Single-institution and collected studies indicate no apparent dose–response relationship beyond 50 Gy; it is difficult to find data differentiating outcome at 50 versus 54 Gy for astrocytomas (308,329). For ependymomas, similar analyses indicate a response at the 45- to 50-Gy level, although recent studies have favored a dose of 50 Gy (308,329,330). With current localization techniques, the use of 50 to 54 Gy at 180 cGy per fraction is considered acceptable

to target volumes discussed above (315). In cases of disseminated disease, 36 to 39.6 Gy is common for areas that are not involved with imaging evident disease.

Technique

Current techniques for spinal cord tumors use image-guided definition of the target volume, with 3D CRT or IMRT approaches to avoid excessive irradiation of the underlying viscera, especially the kidneys, lung, or heart. Electrons have also been used. Protons provide excellent sparing of tissues anterior to the spinal canal or vertebral body and should decrease rates of acute and long-term toxicities to these anterior organs (Fig. 4.6B). Among the planning parameters should be reasonably homogeneous irradiation of the vertebral bodies for children who have not reached full height.

Results

OS in spinal cord astrocytomas is estimated as 80% at 5 years and 55% at 10 years (305–310,314). Prognosis is affected by histologic grade and the extent of surgical resection. For ependymomas, OS is comparable, with recent figures indicating 90% 5-year survival. Outcome depends on the site of origin (with long-term survival rates greater than 90% for cauda equina tumors and 60% for intramedullary tumors or those arising in the conus medullaris) (306,307,309,318,330). Patients with complete resection appear to enjoy a favorable outcome in some studies (307–309,318).

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Retinoblastoma

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HISTOLOGY AND PATTERNS OF GROWTH

Retinoblastoma (RB) is the most common malignant intraocular tumor of childhood. The tumor is of neuroepithelial origin and arises from the nucleated layers of one or both eyes (1). RB consists of undifferentiated small anaplastic cells, which may be round or polygonal. Scant cytoplasm surrounds the large nuclei, which characteristically stain deeply with hematoxylin. Calcification commonly occurs in necrotic areas (2). Both Flexner and Wintersteiner described the arrangement of the more differentiated malignant cells of RB in neuroepithelial rosettes. These Flexner–Wintersteiner rosettes appear to represent an attempt to differentiate into photoreceptor cells (Fig. 5.1) (3).

As RB grows, it may cause a retinal detachment secondary to a solid or multifocal mass (endophytic type of growth). Endophytic tumors may break through the inner layers of the retina to the vitreous. The tumor may also form a pedunculated mass (exophytic type of growth). Both patterns of growth may occur in the same eye, and neither one is of prognostic significance (4). It is not unusual for RB to seed the

vitreous. These vitreous seeds may grow even though they lack a blood supply (2).

INCIDENCE

The reported incidence of RB ranges from 1 in 14,000 live births to 1 in 34,000 (3,5). There are approximately 200–350 new cases per year in the United States and 50 in the United Kingdom (2,3–7). The tumor may be more common in Latin America (8).

RB shows no predilection for sex, race, or the right or left eye. Between 65% and 80% of cases are unilateral (2,3,9–12). The frequency of bilateral tumors is higher at institutions serving as referral centers for more complicated cases. Bilaterality may be ascertained concurrently or sequentially.

The diagnosis may be made from shortly after birth until 7 years of age. The mean age of detection is 2–4 months, and most cases are discovered before 3 years of age (2,3,13,14). In general, unilateral RB is diagnosed at a later age than is bilateral disease. In the Mayo Clinic series the median ages at diagnosis were 4.5 months for bilateral disease and 22 months for unilateral disease, an observation supported by others (4,7,15).

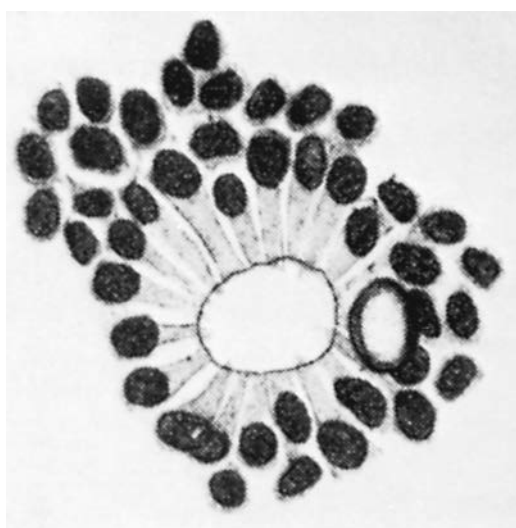


Figure 5.1 A rosette characteristic of differentiated retinoblastoma, after a drawing by Wintersteiner. Note the cylindrical nuclei and fine protoplasm extensions toward the lumen. (From Dudgeon J. Retinoblastoma: trends in conservative management. *Br J Ophthalmol*. 1995;79:104, with permission.)

THE GENETICS AND MOLECULAR BIOLOGY OF RETINOBLASTOMA

The infectious nature of some cancers was demonstrated by Francis Peyton Rous (1879–1970). In a 1910 experiment he showed that submicroscopic, filterable agents (viruses) isolated from a chicken sarcoma could induce new sarcomas in healthy chickens. Rous's work languished in obscurity before it was rediscovered and recognized with the Nobel Prize in Physiology or Medicine in 1966. In his Nobel lecture, "The Challenge to Man of the Neoplastic Cell," Rous (16) considered the possible existence of growth-promoting genes. He called them *oncogenes*; today they are called *oncogenes*.

Rous was wrong about oncogenes. Theodor Boveri (17), on the other hand, was right. In 1914, he used studies of normal mitosis in sea urchins and worms as a platform for suggesting that cancer might be caused by the abnormal gain or loss of chromosomes and their function.

Boveri predicted that the genetic abnormalities leading to the development of cancer are of two sorts: growth-promoting

genes and growth-suppressing genes. If the growth-promoting genes are excessive in number or activity, they lead to cell proliferation. If the growth-suppressing genes are defective in amount or activity, they fail to halt cell proliferation and lead to unbridled cell replication. These growth-promoting genes are called *oncogenes*. The growth-suppressing genes are called *tumor suppressor genes*.

We may think of oncogenes and tumor suppressor genes as analogous to the accelerator and brake pedals of an automobile. When it is idling with the transmission in drive, one can move the car forward by pushing on the accelerator pedal, by taking pressure off the brake pedal, or by doing both simultaneously. Similarly, cell growth and proliferation, leading to cancer, can occur by the activity of the *oncogenes* or the inactivity of the suppressor genes (17–20). Uncontrolled cell growth, or cancer, may be thought of as a set of physiologic controls of cell growth gone awry.

In 1972, Alfred G. Knudson Jr proposed a simple genetic model to explain the origins of RB. Almost 30 years after the original article was published, Knudson described the origins of his discovery.

I was interested in the fact that the germ-line mutation, which is a *de novo* mutation in 80% of the germ-line mutants, is not a sufficient condition for tumorigenesis—some children with an affected parent do not develop a tumor, but later produce an affected child, indicating that they carried the germ-line mutation. Most affected children with an affected parent develop tumors bilaterally but some do so unilaterally. Approximately 60% of all cases are unilateral in the United States and do not carry a predisposing germ-line mutation. I calculated that the numbers of tumors per heritable case fall in a Poisson distribution with a mean of 3. From this, it can be inferred that 5% ($e^3 = 0.05$) of carriers of the germ-line mutation developed no tumor, which fits approximately with observation. The distribution of bilateral cases that have not yet been diagnosed (S) at different ages showed a linear decline on a semi-log plot. That is, $\ln S = kt$ (where k is a constant that incorporates the mutation rate and t is time), as expected for a one-hit phenomenon. From this, I predicted that hereditary retinoblastoma involves two mutations and, knowing that one of these had to be a germ-line mutation, I hypothesized that the other one would be somatic. The unilateral cases with no positive family history, only a minority of whom carries a germ-line mutation, showed a distribution consistent with two mutations, so both of these ought to be somatic. The hereditary and nonhereditary forms of the tumor seem to entail the same number of events—a hypothesis that became known as the “two-hit hypothesis” (21).

Knudson (18,19) sought to understand how the disease might have a familial (i.e., hereditary) form and a sporadic (i.e., nonhereditary) form. In a retrospective statistical analysis, he plotted the logarithm of the proportion of cases not yet diagnosed against the age for bilateral (i.e., hereditary) and unilateral (largely nonhereditary) forms of RB. The graph for the bilateral type generated a straight line, whereas the unilateral type created a curved line with second-order kinetics. Knudson inferred that the bilateral type was explicable by a single random somatic event acting in the presence of an existing germ-line mutation, whereas the unilateral form resulted from two somatic events. He also analyzed the number of tumors in patients with bilateral RB. He found that the

mean number was 3 and that the distribution of the number of tumors followed the Poisson equation. He concluded that the tumor events were random and independent (18,19).

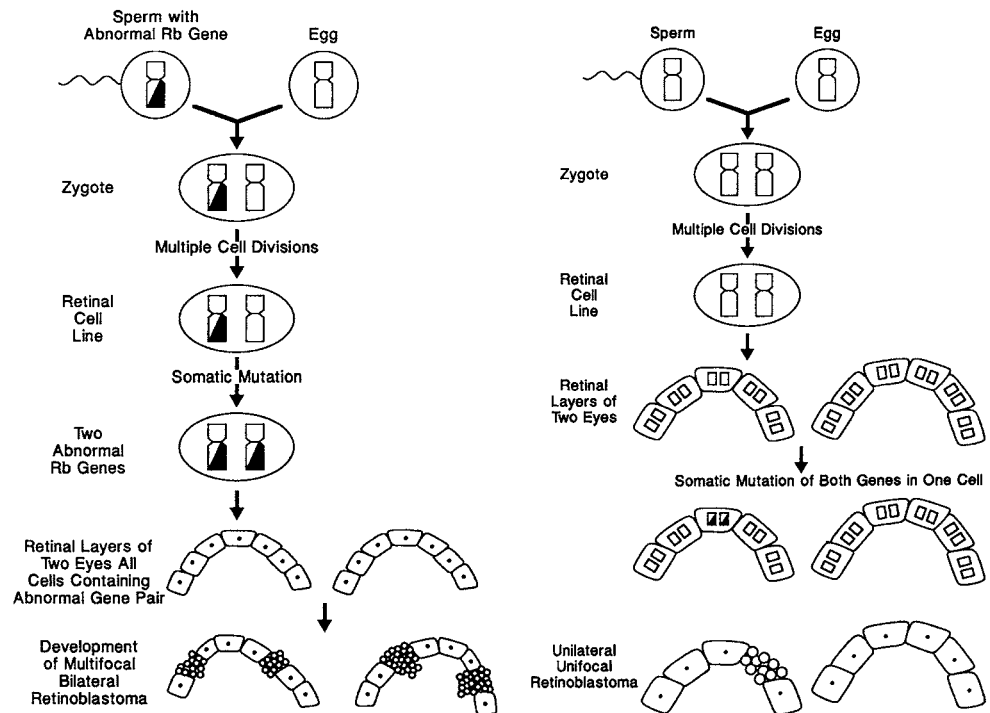
In its simplest statement, Knudson’s model suggests that children with sporadic RB are genetically normal at conception. During embryonic development, two somatic mutations (also called two genetic “hits”) occur in the cell line leading to the retinal photoreceptors. The resulting doubly mutated primordial retinal cell proliferates into RB tumors. In familial RB, the fertilized egg already carries one copy of the mutant gene (one hit). All descendants of this cell carry the mutation. If any cell sustains a somatic mutation (a second hit) to reach the doubly mutated state needed for tumor induction, RB develops. The two-hit hypothesis had the potential to explain both forms of RB (Fig. 5.2) (18,19,22,23).

Knudson’s hypothesis explained neither the precise gene affected nor the nature of the mutation or gene product that caused the malignancy. Evidence concerning the gene product came from the work of Cavenee and colleagues. They used DNA restriction fragment length polymorphisms (RFLPs) in the study of cancer. The cytogenic analysis was vital in uncovering the mechanism behind the two hits of RB. Investigators found that a few cases were associated with deletion of chromosomal band 13q14. Heterozygosities for linked but external markers of chromosome 13 were lost with the deletion but not with intragenic mutations. RFLPs supported the conclusion that either of these mechanisms can occur as a second event in RB. This work provided direct evidence for the identification of RB1 as a tumor suppressor gene (22,24,25,26).

What protein does the deleted 13q14 RB gene normally produce? How does it regulate cell growth? Why does its absence lead to malignancy? The search for the answers to these questions is at the heart of molecular cancer biology. In general, we may think of tumor formation as the possible result of mutations in two classes of genes: proto-oncogenes and tumor suppressor genes. When mutations occur in proto-oncogenes, which result in a gain of function and unbridled cell growth, they are called oncogenes. Proto-oncogenes participate in cell growth and proliferation via several mechanisms: the elaboration of cellular growth factors; the production and deployment of membrane growth factor receptors; intracellular signal transducers, which conduct growth-promoting signals from the membrane deep into the interior of the cell; and transcription factors that promote the ultimate production of proteins, which lead to cell proliferation. It is clear that proto-oncogenes have desirable physiologic functions in fetal development, normal childhood growth, wound healing, and desirable cell proliferation, as occurs in the aerodigestive tract, gut, and bone marrow. However, when proto-oncogenes go awry and become oncogenes, the persistent cell growth that results, without appropriate restraints of time and space, leads to cancer.

In contrast, tumor suppressor genes provide signals that constrain cell proliferation. Mutations in the tumor suppressor genes behave in a recessive manner at the molecular level. Consistent with Knudson’s hypothesis, when mutations occur in both alleles (two hits), the suppressive behavior of the gene is fully lost (i.e., only when both copies of the gene are inactivated by mutations does an abnormal phenotype, a malignant transformation, occur in a cell). A child born with one defective copy of a tumor suppressor gene has a predisposition to cancer. If the second copy of the gene is rendered

Figure 5.2 **A:** In heritable bilateral retinoblastoma, a gamete carrying a defective RB gene (the first hit) forms a zygote heterozygous at the RB locus. A later somatic mutation inactivates the other RB gene (the second hit), allowing bilateral multifocal tumors. **B:** In nonheritable retinoblastoma, inactivation of both genes in a retinal cell (two hits) by somatic mutations leads to the development of unilateral unifocal disease. (Modified from Toma NMG, Hungerford JL, Plowman PN, et al. External beam radiotherapy for retinoblastoma: II: lens sparing technique. *Br J Ophthalmol.* 1995;79: 112–117, with permission.)



inactive by a mutation, then the carcinogenic potential is realized. However, a child with two defective tumor suppressor genes has fully lost a constraint on cell growth, and cancer will ensue.

The RB protein (pRB) is intimately involved in control of the cell cycle. A transcription factor called E2F (the name comes from its initial identification as being involved in the adenovirus E2 promoter) helps drive the cell through the cell cycle to mitosis. When pRB binds E2F, E2F is not free to activate promoters of DNA synthesis. In addition, the pRB–E2F complex downregulates the expression of many G₁ exit-promoting genes such as *c-myc* and *c-myb*. In this way, pRB inhibits the cell from duplicating itself. If pRB is phosphorylated, the phosphorus groups displace the E2F from its binding site. Then the E2F launches into action and promotes cell division. If the pRB is absent or defective, then the factors leading to cell proliferation have no countervailing force.

The growth repressive action of RB occurs, in part, via the recruitment of chromatin-remodeling complexes to promote a region. These complexes mediate chromatin condensation and the subsequent inhibition of transcription. In addition to its role in self-cycle control, RB has been implicated in regulating a wide variety of cellular processes. These include DNA replication, differentiation, and apoptosis. RB potentially interacts with more than 100 different cellular proteins. The functional relevance of most of these interactions has not been elucidated.

A generation of pediatric radiation oncologists was taught that RB has an autosomal dominant inheritance pattern with an 80–90% penetrance (1,7). This is now known to be incorrect. RB is the result of an autosomal recessive pattern; only in the presence of damage to two alleles (two hits) will cancer develop. It must be the case that, in the presence of an inherited single defective allele, the occurrence of a

mutation in the second allele is common; this gives the impression of dominant inheritance.

RB may be inherited from an affected parent or may be the result of sporadic mutations (26). Although most cases of RB are sporadic, 25–40% are familial (inherited from an affected parent who survived RB, a nonaffected gene carrier parent who has no clinical signs of RB, or a parent with a new germ-line mutation). Hereditary cases usually are bilateral and multifocal; they occur at a younger age than sporadic cases, which are, in comparison, more often unifocal and unilateral. Of all patients with newly diagnosed RB, about 10% have a positive family history, and most of these have bilateral disease. Of the 90% with no family history, 20–30% have hereditary, bilateral disease. The remaining 65–80% are unilateral; of these unilateral cases about 10% is hereditary and 90% nonhereditary (Fig. 5.3) (5).

There is also new information in which the effect of the human papilloma virus (HPV) has been questioned as a possible inducement agent for development of RB in both the sporadic and familial cases (27–29). These reviews have shown various HPV subtypes identified in RB tumor samples. The question remains as to whether they are part of the natural environment of these cases or, in fact, are agents for viral intervention for the development of RB.

WORKUP

RB commonly presents with a white pupillary light reflex (called *leukocoria*) (4,10,11). The parents may notice this abnormal appearance in a flash photograph (Fig. 5.4) because a photographic flash bounces light through the pupil and conjunctiva to produce a red appearance in a color snapshot. However, large RB, or an RB-producing retinal detachment, produces the white reflex when the flash bounces off it. This

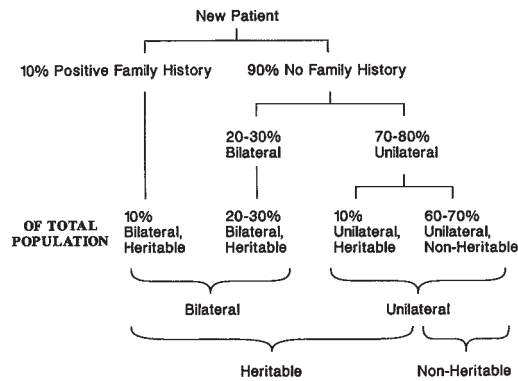


Figure 5.3 The distribution of unilateral, bilateral, heritable, and nonheritable cases of retinoblastoma.

effect can also be seen with a handheld ophthalmoscope. A pediatrician or ophthalmologist doing a surveillance examination of a child with a positive family history or during the course of a routine examination may also discover RB.

On physical examination one notes a raised white, white-yellow, or white-pink mass (2). Tortuous vessels may be seen feeding the tumor. Cells may break off from the main tumor mass and grow as small vitreous seeds (4). Because RB may be multifocal, it is necessary to examine the entire retinal surface, generally with the patient under anesthesia.

When RB presents as a mass, the differential diagnosis includes astrocytic hamartoma, *Toxocara canis* granuloma, the infected emboli of subacute bacterial endocarditis or toxoplasmosis, and other types of severe uveitis. When RB causes retinal detachment, the differential diagnosis includes Coats disease, retrolental fibroplasia, and persistent hyperplastic vitreous (2,3–5,7). Biopsy of a suspected RB or vitreous aspiration for enzyme studies is generally felt to be contraindicated because of the risk of choroidal seeding (4). The

consequences of intraocular procedures in patients with RB are discussed later in this chapter.

Retinal drawings and photographs, along with a written description, are used to record whether single or multifocal tumors are present (Fig. 5.5). Ultrasound is also useful for documenting tumor location and size. The distance from the cornea to the back of the lens can also be measured with ultrasound to aid in lateral field radiotherapy planning. Computed tomography (CT) scan is effective in demonstrating tumor calcification. A cranial CT scan may accompany the orbital study to assess the presence of intracranial extension of the primary tumor and the possibility of a synchronous pineal tumor.

Among the tests used to detect metastatic disease are a lumbar puncture with cerebrospinal fluid (CSF) cytology and a bone marrow biopsy and aspirate. Pratt et al. (30) reported no positive CSF cytologies or bone marrow aspirates in 109 children with RB confined to the globe. The only positive studies were in patients with extraocular tumor extension (i.e., through the sclera or beyond the cut end of the optic nerve) or with bone, distant soft tissue, or brain metastases. These data are supported by other reports (31,32). In modern practice, routine lumbar puncture and bone marrow aspiration are not justified for RB confined to the retina without optic nerve involvement or other suggestion of extraocular extension. In the presence of symptoms suggestive of metastatic disease, a bone scan and plain bone films are indicated.

PROGNOSTIC FACTORS AND STAGING

The staging system for RB must fulfill at least two requirements. First, it must predict the likelihood of cure, a requirement of all malignancy staging systems. However, an important goal of RB treatment is preservation of sight in the affected eye. To this end, some eyes are treated with chemotherapy,

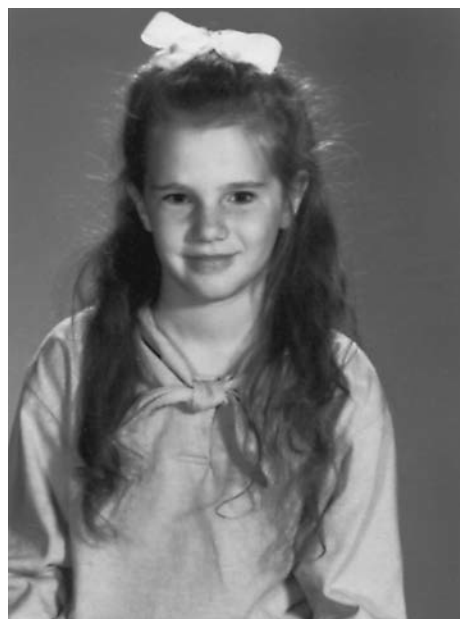


Figure 5.4 Leukocoria in a flash photograph of a 6-month-old girl with retinoblastoma. Over time, the eye improved, and irradiated with 43.6 Gy, she retained excellent vision at 20-year follow-up. (Reproduced with permission of the patient's parents.)

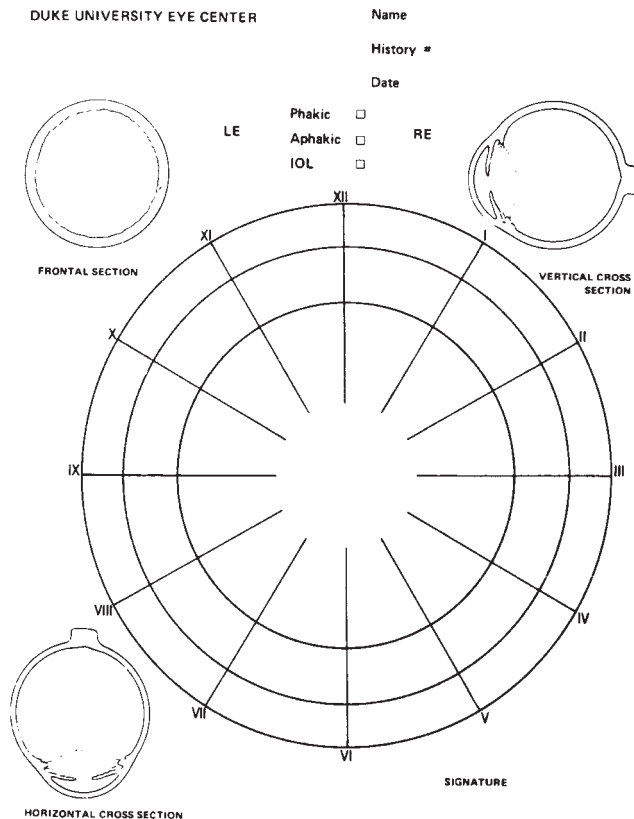


Figure 5.5 A standard retinal drawing used to localize intraocular tumors. The drawing represents the inner curved surface of the eye. The space between the outermost circle and the middle circle represents the pars plana. The middle circle is the ora serrata, the anterior termination of the retina. The most inner circle is the geometric equator of the globe. The central area of the drawing indicates the macula, the yellow spot in the center of the retina. The macula contains a pit, the fovea centralis, where closely packed cones function as the area of most acute vision. The optic nerve's exit (the optic nerve head or disc) is 2 mm medial to the macula. The disc is approximately 1.5 mm in diameter and is often used as a measure of tumor dimensions.

cryotherapy, laser photocoagulation, hyperthermia, radioactive plaque, and external beam radiotherapy as an alternative to enucleation. Therefore, the second requirement for staging is to predict the likelihood of visual preservation.

The most widely used grouping system for RB was proposed by Algernon Reese (5) and Robert Ellsworth (Table 5.1) (33). This system does not predict survival probability well. However, it does predict the chance of visual preservation with conservative therapy. At least two staging systems have attempted to predict prognosis for survival and include information on disease extension beyond the globe (8,30). Of these systems, the St. Jude Children's Research Hospital (SJCRH) system has been used somewhat more frequently. The most recent clinical protocols for combined-modality RB therapy use a new system based on the work of the Children's Oncology Group (COG) and Murphee et al. of Children's Hospital of Los Angeles. This staging system is gaining increasing popularity (Table 5.2). It attempts to assess viability and outcomes related to chemotherapy administration.

Table 5.1

The Reese–Ellsworth System of Classifying retinoblastoma

Group I: Very Favorable

- A. Solitary tumor, less than 4 DD^a in diameter, at or behind the equator
- B. Multiple tumors, none larger than 4 DD in diameter, all at or behind the equator

Group II: Favorable

- A. Solitary tumor, 4–10 DD in diameter, at or behind the equator
- B. Multiple tumors, 4–10 DD in diameter, all at or behind the equator

Group III: Doubtful

- A. Any lesion anterior to the equator
- B. Solitary tumors, larger than 10 DD in diameter, behind the equator

Group IV: Unfavorable

- A. Multiple tumors, some larger than 10 DD
- B. Any lesion extending anterior to the ora serrata

Group V: Very Unfavorable

- A. Massive tumors involving more than half of the retina
- B. Vitreous seeding

^aThe optic nerve's exit (the optic nerve head or disc) is approximately 1.5 mm in diameter. The disc diameter (DD) often is used as a measure of tumor dimensions.

Based on Refs. 2, 6, 15, and 34.

There is also a system that addresses intraocular and extraocular RB described by Grabowski and Abramson.

HISTOLOGIC EVALUATION OF RETINOBLASTOMA

RB is a poorly differentiated malignant neuroectodermal tumor. There are often significant necrotic and apoptotic changes. Although the cytologic details of the tumor may vary from case to case, the cell type, the degree of differentiation, and necrosis have not been defined in themselves as risk factors for local recurrence or metastasis (35). Some have asserted that poorly differentiated tumors are more likely to respond to radiation, but this information is not available at the time of radiation treatment. Some investigators believe that there is an association between vascular density and prognosis in RB. This may merit further investigation.

Classically, four growth patterns are recognized in RB:

- Endophytic RB, which grows from the retina toward the vitreous, appears to be a mass protruding into the vitreous chamber. These often friable and necrotic tumors may produce small clusters of tumor cells that are detached from the main mass and form satellite tumor nodules. These can range from localized tumor nodules within the vitreous, known as vitreous seeding, up to diffuse involvement, which some call the *snowstorm effect*.
- Exophytic RB typically grows from the outer retinal layers and extends beneath the detached retina toward the choroid. Dislodged masses may implant on the retinal

Table 5.2
ABC Classification for Intraocular Retinoblastoma

Group A
• Small tumor confined to the retina • No tumor greater than 3 mm in diameter • No tumor less than 2 DD (3 mm) from fovea or 1 DD (1.5 mm) from optic nerve • No vitreous seeding • No RD
Group B
• Tumors confined to the retina, any location • No vitreous seeding • No retinal detachment more than 5 mm from tumor base
Group C
• Fine diffuse or localized vitreous or subretinal seeding • No tumor masses, clumps, or snowballs in the vitreous or subretinal space • More than 5 mm RD to total RD
Group D
• Massive vitreous or subretinal seeding • Snowballs or tumor masses in the vitreous or subretinal space • More than 5 mm RD to total RD
Group E
• No visual potential or presence of one or more of the following • Tumor in the anterior segment • Tumor in or on the ciliary body • Neovascular glaucoma • Vitreous hemorrhage obscuring the tumor or significant hyphema • Phthisical or prephthisical eye • Orbital cellulitis-like presentation

DD, disc diameter; RD, retinal detachment.

- pigment epithelium and erode through the Bruch membrane into the choroid.
- Diffuse plaque-like RB defies common morphologic patterns. It grows diffusely and insidiously in the retina without forming a detectable mass. Such a growth pattern can present a confusing clinical picture.
 - A mixed endophytic and exophytic pattern may also occur (36).

RISK FACTORS FOR METASTASES IN RETINOBLASTOMA THAT CAN BE IDENTIFIED AT THE TIME OF ENUCLEATION

The ocular pathologist plays a crucial role in determining whether RB has a risk of dissemination because it has broken out of its ocular confines. Reported risk factors include the following:

- Optic nerve invasion: The presence of tumor beyond the lamina cribrosa is a risk factor for metastatic disease

because access to the subarachnoid space allows RB cells to spread to the spinal fluid and central nervous system. Optic nerve invasion is present in approximately one third of nucleated globes and often correlates the presence of choroidal or scleral extension. Optic nerve invasion is categorized as preliminary, laminar, postlaminar, and up to the line of transection. The latter occurrence is quite rare. In a study of 261 cases, the multivariate risk of metastasis was 9 when the optic nerve was involved up to the resection line, compared with 4 when the RB extended retrolaminar but not up to the resection line. A study of 172 patients found that the disease-free survival rate was 97% when the optic nerve was not involved and 55% when it was involved up to the line of resection. The prognosis was intermediate with retrolaminar involvement. When patients with extrascleral extension and optic nerve involvement up to the resection line were excluded, retrolaminar involvement still was a significant prognostic factor for metastasis (37).

- Uveal invasion: Choroidal invasion has long been considered an important risk factor for metastatic disease because it allows the tumor access the scleral and emissary veins. However, choroidal invasion is difficult to quantify. In a study from Wills Eye Hospital, it appeared that patients with choroidal invasion were more likely to develop distant metastasis than those without. However, when patients with optic nerve invasion were excluded, there was no longer a significant risk, although there was still a trend toward the metastasis with choroidal invasion ($p = 0.1$) (36).
- Orbital invasion: When tumor extends to the sclera, it gains access to the vascular and lymphatic channels outside the eye. This creates a significant risk for metastatic disease and is generally considered an indication for more aggressive local and systemic treatment. Microscopic orbital extension often is impossible to diagnose by clinical examination. Preoperatively, larger extensions may be imaged by ultrasound, CT, or magnetic resonance imaging (MRI).
- Choroidal involvement: Invasion of the choroid usually is considered a poor prognostic sign. It is almost certainly true that hematogenous spread of RB occurs via choroidal vessels. However, choroidal invasion is not rare; it occurs in up to 62% of cases. Distant metastases are rare. It seems that the prognostic correlation is less with choroidal invasion alone than with the *volume* of choroidal invasion and its correlation with other risk factors.

Involvement of the optic nerve beyond the lamina cribrosa is a risk factor for orbital recurrence and central nervous system (CNS) dissemination. Even worse is the involvement of the distal cut end of the optic nerve with tumor (35). Tumor involvement of the scleral and emissary veins and episcleral tissues also forebodes a poor prognosis. Multivariate analysis of data from 330 children at St. Bartholomew's Hospital and Moorfield's Eye Hospital showed that the deleterious effect of extensive choroidal invasion as a prognostic factor was lost in the absence of retrolaminar invasion or invasion of the cut end of the optic nerve. Two patient groups had a particularly poor prognosis: retrolaminar extension and extensive choroidal invasion (5-year survival, 31%); and extensive choroidal invasion and invasion of the cut end of the optic nerve (5-year survival, 25%) (4). In 62 children only 1 death was attributable to metastatic disease from choroidal invasion alone (38,39).

SELECTION OF THERAPY

The primary goal of RB therapy is cure. Because RB infrequently metastasizes, the chance of cure is excellent. However, this must be viewed with the knowledge of potential deleterious effects of the local therapy, which in its worst scenario includes development of second malignant tumors.

The actuarial overall 5-year survival rate for 731 children with RB seen at St. Bartholomew's Hospital and Moorfield's Eye Hospital from 1960 to 1988 was 87% (4). The 50-month actuarial overall survival of 52 SJCRH patients with initial intraocular disease was 97% (8).

Therefore, it is appropriate that a secondary goal of treatment is preservation of vision in the affected eye. Enucleation is recommended only in a blind eye or an eye for which there is no reasonable expectation of sight after cryotherapy, phototherapy, or radiotherapy. Every effort should be made to preserve vision in a sighted eye. This rule pertains to both bilateral and unilateral diseases. Often, however, children with unilateral disease have locally advanced tumors with little hope of vision, so many of these patients undergo enucleation. In bilateral disease, enucleation of the more severely affected eye is indicated only if the eye is blind. If both eyes are sighted, then an effort should be made to preserve both eyes.

Enucleation

In an enucleation for RB, anterior traction is placed on the globe after the rectus muscles are severed. The optic nerve is then cut near its exit from the socket. Obtaining a long segment of nerve is important if the tumor is within the nerve. In young children, orbital growth slows after enucleation. As the child grows, the orbit appears small. This may be ameliorated by a properly fitting orbital prosthesis.

As we have gained knowledge in the treatment of RB, there has been a noted reduction in the use of enucleation for both unilateral and bilateral cases. (36–38).

Enucleation is indicated in unilateral RB, where the eye is blind. In bilateral RB when both eyes are blind, a bilateral enucleation is done. If one eye is blind, a unilateral enucleation is done. It is also recommended when local recurrence of tumor can no longer be controlled with more conservative measures (13,40) (Fig. 5.6).

Exenteration

An exenteration is the removal of the globe, extraocular muscles, lids, nerves, and orbital fat. Blood loss may be significant. In the opinion of some ophthalmologists, the indications for exenteration in RB include extensive local tumor breaching the globe (exenteration in this situation generally is followed by postoperative radiotherapy and chemotherapy) and recurrence of tumor in the socket after enucleation. However, some cases of local recurrence may be locally managed with external beam radiotherapy, a radioactive implant or a radioactive mold, and chemotherapy.

Local Therapy

The four local therapies for RB are cryotherapy, photocoagulation, laser hyperthermia, and radioactive plaque applications.

Until the early 1990s, in children at high risk for multicentric disease, local therapy was thought to be appropri-



Figure 5.6 Bilateral retinoblastoma treated with enucleation on one side with a prosthesis in place. A calcified macular lesion is seen in the remaining eye.

ate only when there could be serial follow-up with repeated local therapy or with external beam radiotherapy when necessary. In children with bilateral disease, an average of five tumor foci are randomly distributed (2,41). These foci may not appear simultaneously but may occur months after successful local treatment of the sentinel lesion, sometimes as long as 60 months after the initial index lesion. In children with multifocal disease or in those at high risk of developing multifocal disease, as well as in children with large tumors, it was believed that local therapy generally should not be used.

More recently, thinking concerning local therapy is very different. With the increase in use of systemic chemotherapy, local therapy is now used in multifocal disease. Local therapy may be interspersed with chemotherapy or may follow it. Programs using focal therapy in this way are reviewed later in this chapter.

Photocoagulation

The technique of photocoagulation is based on obliteration of the retinal vessels. With the child under anesthesia, a white retinal burn, surrounding the tumor by 1 mm, is painted with the laser beam. Special attention is directed to closing feeding vessels (42). The tumor is encircled by the burn and regression depends on interruption of blood supply. Direct photocoagulation of RB should be avoided because small explosions can release viable tumor cells into the vitreous and lead to tumor recurrence (4). In primary therapy, photocoagulation may be used for tumors up to 4.5 mm at the base and up to 2.5 mm thick if they were not close to the macula or disc, where retinal damage would generate a large scotoma. Vitreous seeding is a contraindication (11,43). Photocoagulation may be used for small tumor recurrences after irradiation to avoid the risks of reirradiation. With proper case

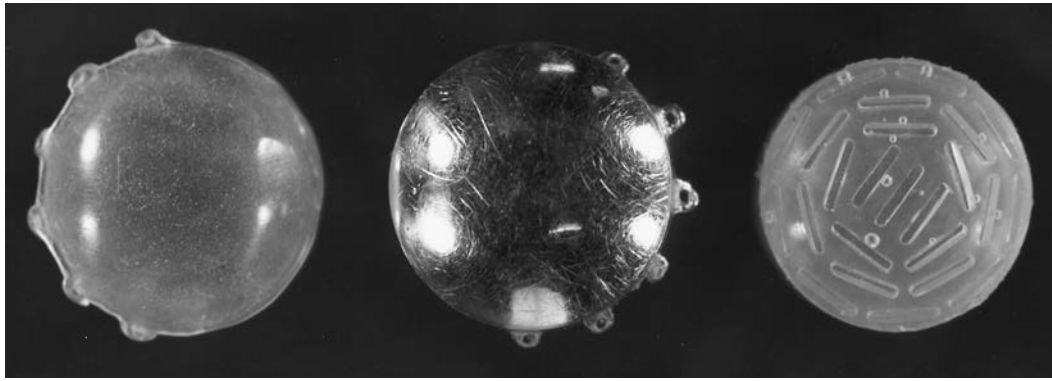


Figure 5.7 Equipment for ^{125}I ocular plaque construction and placement includes a dummy plaque to aid in the placement of the necessary retention sutures (left), a gold backing with lug holes for sutures (center), and a plastic insert to hold the radioactive ^{125}I seeds (right).

selection, photocoagulation has a local tumor control probability of about 70% (42).

Laser Hyperthermia

Laser hyperthermia is generated by a diode laser (810 nm) on continuous mode. A single spot, 0.8–2.0 mm in diameter, is placed on the center of the tumor using the aiming beam. An output of 300–700 mW is selected based on the tumor size. Tumors are heated for 10–30 minutes per session. It is estimated that a central tumor temperature of about 46°C is reached. As the heat disperses through the tumor, the temperature decreases about 2°C for each millimeter beyond the treatment spot. In this technique the heat is used principally to enhance the binding and cytotoxicity of platinum drugs, a method supported by experiments using rabbit ocular melanoma (42,44,45). Whole eye hyperthermia in combination with external beam irradiation has been shown to be effective in controlling murine transgenic RB but to our knowledge has not been used in humans (46).

Cryotherapy

With cryotherapy a tumor is localized and indented, transsclerally, with a nitrous oxide cryoprobe. The freeze (80°C) is then applied until the tumor is completely covered with a frozen vitreous. The freeze–thaw cycle is repeated at least three times (41). Cryotherapy is indicated for the primary therapy of RB in small tumors anterior to the equator, without vitreous seeding, which can be reached with the cryoprobe (posterior tumors are difficult to reach, and the risks of freezing the macula or nerve increase); in local recurrence or tumor persistence after irradiation; and in conjunction with chemotherapy (44).

Cryotherapy can induce acute retinal edema and accumulation of subretinal fluid. To avoid retinal detachment, some ophthalmologists use the laser to create a retinal barrier to fluid leakage. Disruption of the retina by cryotherapy may increase intravitreal penetration of systemic carboplatin.

Radioactive Plaque Application

Plaques are used for solitary 2- to 16-mm basal diameter unilateral lesions located more than 3 mm from the optic disc or fovea, generally less than 10 mm thick, for two lesions that

are small enough or close enough to be covered by one plaque, and for local failure after other therapies (Fig. 5.7). Plaques can be used if there is a small amount of vitreous seeding over the tumor apex (10,47–50).

Before the operative procedure, the tumor's maximum basal diameter and maximum height are ascertained by physical examination and ultrasonography. In treatment planning, it is customary to allow 1 mm for scleral thickness, although there is some normal variation in this measurement (51). The operative procedure begins with a careful eye examination using magnifying lenses. After confirming the tumor anatomy, the surgeon opens the conjunctiva around the periphery of the limbus (a peritomy). Muscle hooks are used to snare rectus muscles and rotate the eye. Traction sutures sometimes are used. It may be necessary to disinsert a muscle in order to visualize the tumor. With the room darkened, a transilluminator is placed over the pupil. The shadow cast by the tumor is marked on the sclera with a marking pen or with electrocautery. Tumors that cannot be transilluminated are located by ultrasound. A clear dummy plaque is then brought into the operative field. Allowance for a 2 mm of margin on either side of the basal diameter is standard. A dummy plaque, which is an exact copy of the to-be-used radioactive plaque, is used to assure correct coverage; it is also used to assist in the initial retention suture placement, thus reducing exposure to the surgical team. The “live” plaque is substituted and the retention sutures are tightened down, and the eye is rotated back into place. The conjunctiva is then closed. The patient generally remains hospitalized for the duration of the application. The plaque is then removed after the appropriate dose is delivered (52).

Several plaque types are available. The ^{60}Co plaque (1.17 and 1.33 MeV, half-life 5.2 years) may be purchased in a circular or crescentic configuration to fit around the optic nerve. The ^{125}I plaque (27–35 keV, half-life 60 days) with lip consists of ^{125}I seeds glued in a carrier within a gold shield. These plaques are available in a circular or notched configuration. ^{192}Ir (295–612 keV, half-life 74.5 days) and ^{109}Ru (beta emitter) plaques are also available (53).

Each of the four available plaques (^{60}Co , ^{125}I , ^{192}Ir , and ^{109}Ru) has advantages and disadvantages. ^{60}Co plaques may be purchased and assembled in standard sizes. The long half-life means that the plaque may be used for several years before

the treatment times become unacceptably long. The high-energy ^{60}Co and the breadth of the high-dose isodose curves mean that thick and infiltrative tumors can be treated. However, shielding of periocular normal tissues behind the plaque is impossible. Effective shielding on the back of the plaque is achievable with ^{125}I and ^{109}Ru . Shielding from the gold lip on the ^{125}I plaque necessitates expert placement lest tumor be missed. ^{125}I plaques must be assembled for each case; although this involves extra work, it allows individualization of the plaque. Hospital personnel exposure is minimal with ^{125}I or ^{109}Ru . A shielded ^{125}I plaque with a lead eye patch allows the nursing staff and the child's parents to provide care while observing appropriate radiation safety precautions.

Using ^{60}Co plaques, Stallard administered 40 Gy to the tumor apex in 1 week. Of 69 children with tumor involving one fourth of the retinal area or less, 63 were successfully treated with a plaque. When the tumor involved one fourth to one half of the retinal area, success was achieved in 8 of 10 cases (54).

Among the best-characterized clinical series of plaque, brachytherapy for RB is that of the Wills Eye Hospital of Philadelphia (49,50,53). This series describes the outcomes for more than 140 children with RB treated between 1976 and 1999. In these children, 148 tumors were treated with radioactive plaques for recurrent or residual RB after other therapies failed, and 60 tumors were treated primarily. The median tumor dosage at the tumor apex was 40 Gy, with ^{125}I used in about 90% of all plaques. With a median follow-up of 34 months, recurrences developed in 17% and 20% of cases at 1 and 4 years, respectively. In tumors treated with a radioactive plaque as primary therapy, recurrences were observed in 12% and 20%. Metastases developed in only four patients, all with Reese–Ellsworth group Vb tumors. On multivariate analysis, the risk of recurrence was increased significantly by the presence of vitreous or retinal seeds and by increasing age at diagnosis. In earlier studies, visual acuity of 20/400 or better was obtained in 62%. A series on a subject of patients treated with chemoreduction (CRD) and who subsequently failed and were treated with ^{125}I plaque reported a 95% 5 year local control rate in 59 eyes treated initially with CRD and 100% 5 year local control in 25 initially receiving CRD and external beam irradiation.

In another recent series, ^{106}Ru was utilized in 41 eyes. It was used as first- and second-line therapy in 16 and as salvage in the remaining. Of 41 patients, 31 have eye retention. Complications included cataract (9.7%), retinopathy (2.4%), and retinal detachment (17%), again showing effectiveness in controlling relapsed RB (55).

In the past, it was reported that for large tumors with vitreous seeds, multiple sequential plaques (rotating plaques) could be used. In this technique, two plaques are applied in one operation to opposite quadrants of the eye. In a second operation, these two plaques are rotated to the remaining quadrants. In a third operation, the plaques are removed. This technique delivers about 40 Gy to the midvitreous and 160 Gy to the sclera. Initial reports indicated that useful vision was retained in 14 of 16 patients treated with plaques

as the single irradiation modality. Useful vision was retained in 22 of 36 patients plagued after failure of some other treatment (10,49,52). Later reports showed a significant incidence of radiation retinopathy with this technique, and it has been largely abandoned (52).

In carefully selected patients with small primary RB or for recurrent tumors after other treatment, a radioactive single-plaque application of 30–40 Gy to the tumor apex is reasonable therapy. With growth in the use of chemotherapy as primary treatment for RB, plaque therapy has joined photocoagulation, laser treatment, and cryotherapy as an adjuvant focal treatment after or interspersed with chemotherapy. When a plaque is used in a child who has also received chemotherapy, many believe that 40 Gy as an apical dosage is too high. The occurrence of postbrachytherapy retinitis has led to a dosage reduction to 25–30 Gy to the tumor apex. Plaques have little chance of producing orbital bone hypoplasia and should not contribute to the risk of orbital bone sarcoma. Long-term complications of plaque radiotherapy include retinopathy, cataracts, maculopathy, papillopathy, and glaucoma (49,54). In the Wills Eye Hospital series of more than 140 children treated with plaque radiotherapy, only one second cancer was observed in the field of plaque irradiation over a mean follow-up of 49 months.

External Beam Radiotherapy

When RB is multifocal or close to the macula or optic nerve with preservation of vision, it has been found that cryotherapy, photocoagulation, or plaque therapy is not adequate and that enucleation is too drastic. In such situations, which are quite common, external beam irradiation or chemotherapy with focal therapy is used. These types of therapy are also indicated for large tumors and vitreous seeding. Hilgartner (56) reported treatment of a case of bilateral RB with x-rays in 1910. Verhoeff cured a case of RB with x-ray treatment in 1918. The patient died in 1972 with tumor controlled (57). Historically, the Reese–Ellsworth grouping system has been used to predict the probability of success for external beam irradiation (Table 5.1). Large lesions tend to fail after teletherapy. Some say that anterior lesions are also more likely to fail after teletherapy, but the risk of failure of anterior lesions probably was related to the practice, by some radiotherapists, of treating with a lateral beam with the anterior field edge at the rim of the bony orbit. This technique underdoses the anterior globe (8,58–61). Technical factors play a large role in the probability of success of external beam therapy and the frequency of complications.

Technique

The goals of conventional external beam radiotherapy are to provide a homogeneous and tumoricidal dose to the retinal anlage and vitreous and to respect tolerance of normal tissue structures. At least five arguments have been put forward in support of this expansive view of treatment volume. First, in many cases RB represents a field change in which all retinal cells have a genetic neoplastic potential; therefore, the entire retina must be treated. Second, vitreous seeding can occur. Third, multiple tumors may arise from a primary RB. Fourth, the tumor may spread via the subretinal space. Finally, retinal differentiation progresses from posterior to anterior and from superior to inferior. Subclinical disease may exist in the

immature retina and must be included in the treatment (15). The argument in favor of a more restrictive tumor volume is that selected cases will be unilateral and unifocal and therefore amenable to more focal irradiation, as might be delivered to a fixed target with protons.

The dimensions of the eye of young children have been well characterized. The outer sagittal diameter of the eye varies from 16 to 17 mm at birth and increases rapidly to an average of 22.5–23 mm at 3 years of age (51). In any individual patient the axial intraocular dimensions may be measured by ultrasonic biometry and ocular CT.

Reese developed one of the earliest techniques for the external beam irradiation of RB in the 1930s. Using an orthovoltage unit, treatment was delivered through temporal and nasal portals. The technique attempted to avoid the lens by having the nasal portal angled 24–30 degrees (Fig. 5.15). A high bone dosage was given by the orthovoltage apparatus. A “saddle nose” deformity developed in long-term survivors along with depression of the temporal bone (6).

In modern pediatric radiation oncology, patient immobilization is recognized as crucial to delivering the designated treatment volume precisely while minimizing radiation to normal tissue. In RB treatment, anesthesia is generally needed.

Immobilization and anesthesia for pediatric radiotherapy are fully discussed in Chapters 21 and 22. Two special points are warranted in this discussion. When a plaster or thermoplastic head holder is prepared for treatment and the anesthesia gas mask is placed, care must be taken to allow an unobstructed view of the eye so that the fields may be correctly set. Second, ketamine anesthesia produces lateral nystagmus. If a blocking technique is used that relies on the eye being a stable target, then ketamine generally is unacceptable as the anesthetic agent.

The contemporary radiotherapist may consider a large number of techniques. However, several have passed from favor as conformal radiotherapy has gained popularity.

- A lateral-beam megavoltage technique with the anterior field border set at the lateral bony orbit has been used. A direct lateral field is used after enucleation in the contralateral side. When the contralateral globe is in place, the beam is slightly angled posteriorly in an attempt to avoid exit radiation into the lens of the other eye (11). The distance from the back of the lens to the ora serrata is 1–1.5 mm, making techniques that endeavor to treat the entire retina from a lateral approach but miss the posterior part of the lens highly impractical (60). Use of only a lateral beam may result in tumor recurrence at or near the ora serrata (6,11,61). However, small anterior failures can be treated with cryotherapy, so if there is no gross disease near the ora serrata, this technique may be adequate (6). The lateral field is shaped to spare the pituitary and some of the tooth buds. This produces a D-shaped field (Fig 5.8).
- A direct anterior ^{60}Co or linear accelerator field, using either photons or electrons, treats the entire eye and spares the opposite eye. There is no sparing of the lens, cataract formation is almost certain, the lacrimal gland is fully irradiated (thereby potentially impairing tear production), and radiation exits through the brain. However, the single anterior field is easy to set up, is reproducible, and homogeneously irradiates the entire vitreous and retina (6,13,32). Because

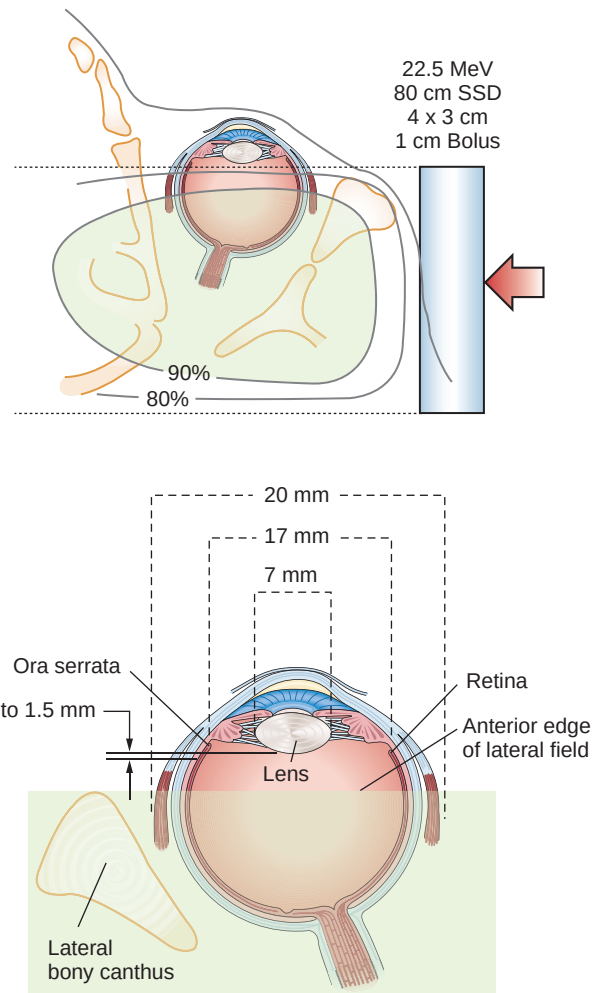


Figure 5.8 A direct lateral supravoltage field with anterior border set at the bony orbit. (From Cassidy JR, Sagerman RH, Treter P, et al. Radiation therapy in retinoblastoma. *Radiology*. 1969;93:405–409, with permission.)

the cataract takes time to develop, mitigating the problem of disuse amblyopia, and may be treated surgically, advocates of the anterior field are comforted in its use (62–64).

- A half-beam blocked lateral field has been used to sharpen the beam edge. Field sizes ranging from 3×6 cm to 5×10 cm typically are used for a 3×3 cm to 5×5 cm treatment area. The field edge may be set at the bony orbit or between the bone and the limbus. A field anterior edge about halfway between the limbus and the edge of the bony orbit will cover the ora serrata. Treatment may be given with a lateral beam with photons alone or with mixed photon and electron straight lateral and lateral oblique beams (6,54,58,60,65). For children with unilateral disease, many clinicians replace straight lateral fields with oblique fields. Superior and inferior oblique fields miss the uninvolved eye. The price of an inferior oblique field is exit radiation into the frontal lobe of the brain. A superior oblique field exits into the maxillary sinus and mouth.
- A two-field technique using a lateral field and an anterior field with a hanging lens block is an attempt to achieve a homogeneous retinal dosage yet spare the lens (Fig. 5.9) (65–68). The fields are weighted 75–80% from the lateral

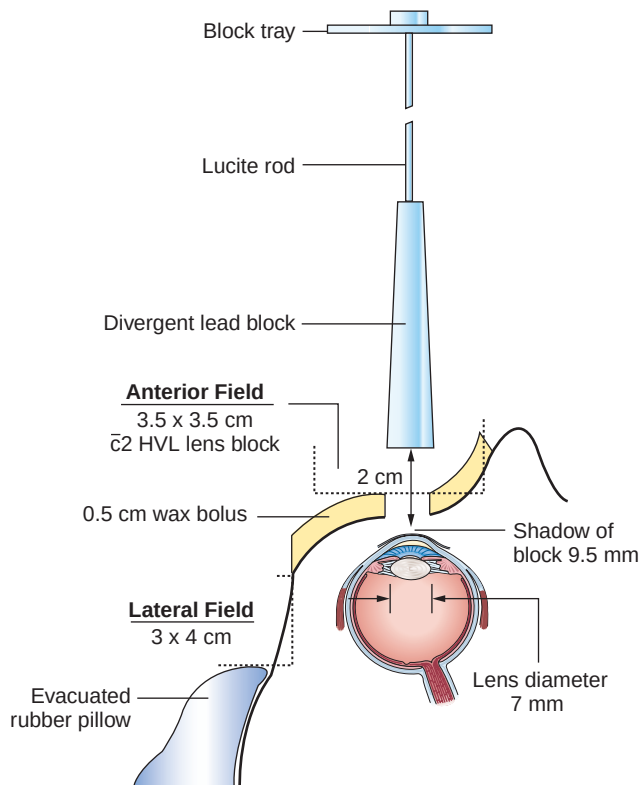


Figure 5.9 A two-field technique using a lateral field with an anterior field and a hanging eye block. If the contralateral eye is in place, the lateral field is angled posteriorly. (From Weiss DR, Cassady JR, Peterson R. Retinoblastoma: a modification in radiation therapy technique. *Radiology*. 1975;114:705–708, with permission.)

and 20–25% from the anterior. There are two alternative techniques. One continues to use the lateral field but uses an anterior electron field with a contact lens-mounted lead block for the lens. Small displacements of the contact lens will significantly affect the dosage from the anterior field (33,58,69). A second modification uses anterior photons without the hanging eye block when it is feared that the hanging block will shield a posterior pole tumor.

- Schipper (66,67) has described a precision lateral technique that calls for a specially devised machine-mounted device that, by way of a scale, sets the anterior field edge just behind the lens (Fig. 5.10). Measurement of the lens depth in each patient is necessary for proper beam alignment. This elegant technique is particularly appropriate for posterior pole lesions (4). Schipper's technique uses a linear accelerator, modified with a beam splitter and extended collimation system, to produce a nondivergent and almost penumbra-free anterior beam edge. The depth of the posterior margin of the lens is measured by ultrasound. A contact lens or plumb bob with an attached rod and scale measuring system allows placement of the beam behind the lens. A straight or angled lateral beam is used, depending on whether the clinician wants to avoid exit radiation to the other eye (68).
- A superior dosage distribution for RB treatment might be achieved with a proton beam. With a lateral approach, the patient with unilateral RB would benefit from sparing of the other eye because of the stopping characteristics of the protons related to deposition of energy via the Bragg peak. Even in bilateral cases the possibility of sparing some normal tissue is held out as a benefit to reduce the risks of radiation-induced malignancy. Several institutions worldwide are treating RB with proton therapy. The conformal

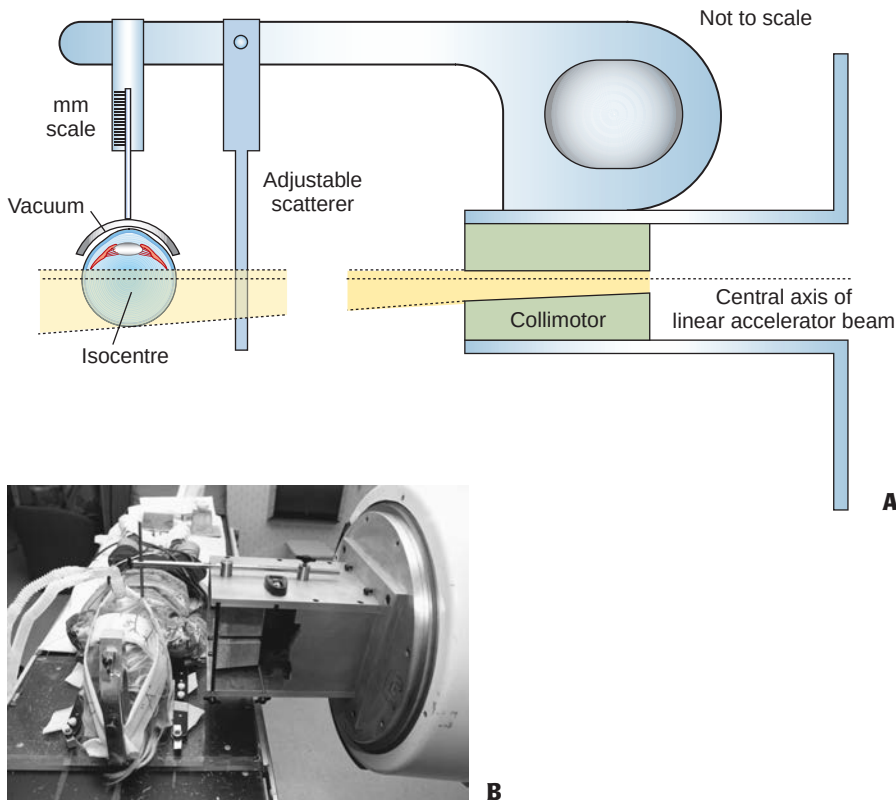


Figure 5.10 A: A special retinoblastoma treatment applicator designed to set the treatment beam just at the posterior pole of the lens. The position is adjusted with the scale and contact lens assembly. (From Harnett AN, Hungerford J, Lambert G, et al. Modern lateral external beam [lens sparing] radiotherapy for retinoblastoma. *Ophthalmic Paediatr Genet*. 1987;8:53–61, with permission.) **B:** A modification of such a device in operation. Such devices have been replaced by intensity-modulated radiation therapy techniques.

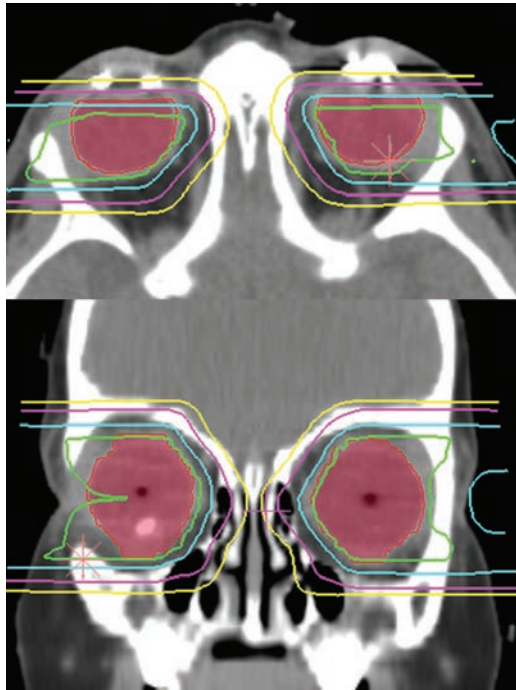


Figure 5.11 Proton beam dose profile for RB treatment. (Courtesy of Judith Adams; Massachusetts General Hospital, Boston, Massachusetts.)

dosage distribution related to the spread-out Bragg peak of proton beams makes it attractive in the external beam treatment of RB. One would hope to reduce late effects by using protons insofar as one can minimize the dosage to surrounding bone and soft tissue and to possibly reduce the risk of treatment-related second malignant neoplasms. Proton irradiation conformal techniques in a fractionated schema are also available (70,71) (Fig. 5.11).

- Intensity-modulated radiation therapy (IMRT) is used to externally irradiate RB at many centers. It can be used to treat the entire globe or to spare the lens while irradiating all or part of the retina. IMRT may deliver substantially less radiation to surrounding periocular bone or soft tissues than conventional photon or electron beams do (68). Six to eight lateral or oblique fields may be used (Fig. 5.12) (72).

Which is the best technique for external beam treatment of RB? In a retrospective review from Riyadh, Saudi Arabia, Pradhan et al. (31) compared eye survival in 26 children treated with external beam radiotherapy with lateral fields to 38 children in whom anterior fields were used for part or all of the treatment. Of the total population of 64 children, 44 (84%) had group IV or V disease. No difference in eye survival was found between the two groups. However, Foote et al. (15) at the Mayo Clinic reported a benefit to whole eye irradiation using anterior fields rather than a lateral lens-sparing technique. The tumor control rate with the former (7 of 11, 64%) was stated to be superior to the latter (29%), but the overall ocular survival was comparable between the two techniques (whole eye 82%, lens sparing 79%). An excellent retrospective comparison of lens-sparing and whole eye irradiation for disease groups I–III from St. Bartholomew's Hospital, London, included 201 children. The eye preservation rate

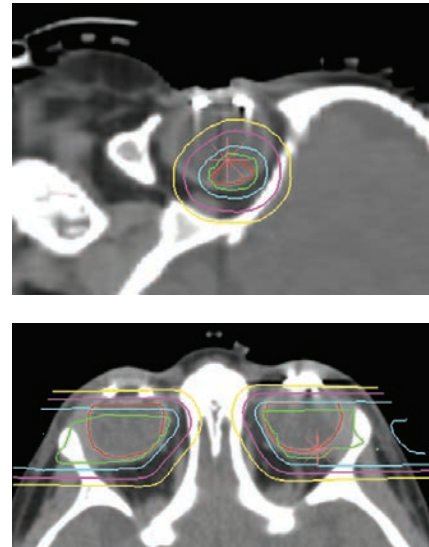


Figure 5.12 The 9-field IMRT plan with 6 MeV transverse coronal and sagittal views with and without lens sparing. Note dose reduction to surrounding bony structures. (Courtesy of Vicki Williams, Botsford Cancer Center, Farmington Hills, Michigan.)

was 85% after whole eye radiotherapy and 92% after lens-sparing radiotherapy ($p = 0.55$) (61,70).

Blach et al. (58) updated a series by McCormick et al. (60) that indicated, in a retrospective review, that a lateral beam technique with the beam edge set 2–3 mm behind the limbus is preferred to a technique using a more posteriorly set lateral beam and an anterior electron field with lens-sparing block. The more posterior field arrangement was associated with anterior failures. Many other series confirm anterior failures when anterior segment-sparing techniques are used. At Duke, 20 patients with large macular RB were treated with a lateral 4-MV photon half-blocked beam set halfway between the limbus and bony orbit and an anterior field (sometimes using a hanging eye block, weighted lateral to anterior 4:1 or 5:1). With 1–8 year follow-up, there have been no local failures and four clinically significant cataracts (73).

Scott et al. (74) reviewed children irradiated at the University of Miami and the University of California at San Francisco and retrospectively compared a lateral beam technique (the anterior field border is 2–3 mm behind the limbus) with a relative lens-sparing technique that treats the entire globe and the optic nerve to the conus. A total of 42 patients were described. Eye conservation rates were equivalent, but local control with radiotherapy was superior with the lateral beam technique. Cataract rates were similar.

Inspection of Table 5.3 shows that, in general, control of disease groups I–III with lens-sparing external beam irradiation alone is fairly good in contemporary series (i.e., 40–80%). The addition of photocoagulation, cryotherapy, and plaque therapy results in an ultimate eye preservation rate of 67–100% for disease groups I–III. When new tumors develop in patients treated with lens-sparing external beam techniques, the majority of the recurrences are located anterior in the eye (68). Clearly, failure to irradiate the anterior retina in a tumor in which the entire retinal surface is at risk for tumor will lead to recurrence. Even when careful placement of the anterior beam edge is done with a half-beam blocked lateral field or a

Table 5.3
Visual Preservation Following External Beam Irradiation: Selected Series Reese–Ellsworth Group

Reese–Ellsworth Group						
Author (Reference)	Year	I	II	III	IV	IV
Cassady (11)	1969	84%	67%	69%	30%	66%
Egbert (12)	1978	88%	60%	67%	0%	33%
Schipper (67)	1985	100%	100%	83%	79%	0%
Foote (15)	1989	100%	100%	85%	50%	53%
Amendola (10)	1990	100%	83%	100%	67%	50%
Buckley (75)	1992	—	—	100%	100%	100%
Fontanesi (63)	1995	100%	67%	67%	100%	57%
Fontanesi (76)	1996	75%	100%	50%	100%	43%
Toma (68)	1995	78%	67%	64%	100%	—
Blach (58)	1996	67%	67%	67%	44%	44%
Pradhan (31)	1997	86%	100%	50%	50%	54%
Scott (74)	1999	—	—	—	—	54%
Merchant (77)	2002	—	95%	—	66%	—

Schipper device, it is almost impossible to perfectly irradiate the most anterior retina and reproducibly miss the lens. It is for this reason that many radiation oncologists supplement a lateral beam with some radiation from an anterior field (with an 80:20 lateral-to-anterior weighting) or use three-dimensional (3D) conformal therapy or IMRT to raise the dosage anteriorly. The overall eye preservation rate in patients with anterior failures after lateral beam-alone treatment remains quite good. This is because of the frequent success of focal salvage therapies such as cryotherapy, laser therapy, or plaque therapy.

Perhaps the most provocative recent report is that from Reissner et al. It used a single patient and compared various external beam techniques to IMRT. After obtaining a CT an ophthalmologist outlined the orbital and adjacent structures. The 13 described treatment techniques were then applied to the case. Doses to the ora serrata retinae, lens, orbit, vitreous optic nerve, lacrimal gland, and cornea were recorded. The four-field IMRT technique used provided the superior treatment plan with the greatest reduction in doses to the orbit and lacrimal gland while maintaining sufficient doses to the ora serrata and vitreous (78).

There will undoubtedly be a move toward IMRT techniques for RB. Such techniques allow highly conformal fields around the globe with lower dosages to the surrounding tissue. IMRT may prolong treatment and pose some problems for the anesthesiologist. There is also the theoretical risk that a higher integral dosage may increase the risk of second malignant neoplasms. Several recent reports have had differing conclusions as to this risk. Mansur reported on 3D conformal therapy and IMRT in five pediatric CNS/base of skull cases. A phantom was used to evaluate dose to thyroid, breast, ovary, and testes. What was discovered was that at close points (thyroid) IMRT delivered lowered peripheral doses, presumed due to less internal scattering; however, the more distant points had higher doses presumed due to higher MU use and increased head leakage (79). Another report evaluating IMRT, 3D conformal therapy, and protons did not distinguish between near and distant site dose evaluation but had similar conclusions regarding im-

proved target dose coverage and reduced surrounding dose at the expense of more tissue receiving “some” dose (80).

Any external beam RB technique should encompass the entire retinal anlage, avoid the other eye if uninvolved, and limit the dosage to normal tissue. Radiotherapists must adopt a technique that fulfills the aforementioned criteria within the context of their own equipment and expertise and the patient’s needs.

DOSAGE

Two recent studies have evaluated the radiosensitivity for RB grown in culture. Zhang et al. (81) found that the clonogenic survival rates after 2 Gy of two RB cell lines were 14% and 6%—highly radiosensitive (Fig. 5.13). Hayden et al. (82) found that murine transgenic RB was locally controlled at a significantly lower dose by 1.2 Gy twice daily than 2 Gy once daily.

Is there a clinical radiation dose–response relationship for external beam therapy for RB? Stallard performed serial sections of RB treated with brachytherapy and concluded that 35 Gy was the appropriate dosage delivered in 7 days (54). A large number of dosage and fraction schemes have been proposed for external beam treatment, ranging from 2 to 3.8 Gy per fraction to a total dosage of 30–60 Gy. Objective data that speak to the establishment of an optimum tumor dosage include a 1969 report by Cassady et al. (11) that 32–35 Gy was no less effective than 40–45 Gy and the observation that late ill effects of irradiation on the retina (i.e., chorioretinitis) are uncommon at dosages of 50 Gy or less (61). In 1972, Thompson et al. published an analysis of treatment time and total dosage suggesting improved local control at higher dosages (83). These authors recommend 2.5 Gy per fraction, four fractions per week, to 50 Gy per fraction.

In 1985, Abramson et al. (6), reviewing the Cornell and Columbia experience, reported no influence of tumor size on the control rate with radiotherapy. Tumors less than 3 disc diameters (DD) were cured as often as those 3 DD or larger.

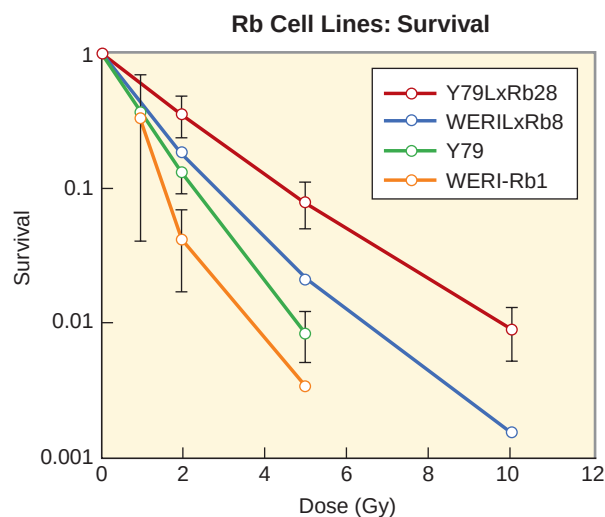


Figure 5.13 Clonogenic survival curves were obtained using a linear quadratic model for human RB cells grown in culture. All cell lines are extremely sensitive, with a small B component and no shoulder region. (From Zhang M, Stevens G, Madigan MC. In vitro effects of radiation on human retinoblastoma cells. *Int J Cancer*. 2001;96(suppl):7–14, with permission.)

However, Abramson did observe a dose–response relationship as a result of dosage inhomogeneities from lateral beam treatment. This is shown in Figure 5.14. A review of the Mayo Clinic experience by Foote et al. (15) in 1989 found no dose–response relationship over the 45- to 50-Gy dose range in 4–5.5 weeks for tumors less than 4 DD in diameter, tumors 4–10 DD in diameter, or Reese–Ellsworth group III disease. Based on a small number of patients, local control was thought to be associated with higher dosages in group V cases and in tumors more than 10 DD in diameter. However, in 1996 a group from Wills Eye Hospital in Philadelphia found an inverse relationship between tumor control and tumor size after external beam irradiation. Tumor control with radiation alone as a function of maximum basal tumor diameter was 88% (less than 5 mm), 93% (5.1–10 mm), 72% (10.2–15 mm), and 50% (more than 15 mm) (84).

Messmer et al. (85) from Germany reported a higher tumor recurrence rate with a mean dosage of 40 Gy versus 50 Gy (49% vs. 22%). However, Fontanesi et al. (63,64) found the reverse in a small number of patients: Control with less than 36 Gy (71%) was superior to that obtained with more than 36 Gy (50%).

What can we conclude? First, a high dosage per fraction is associated with an increasing risk of late effects. Second, with improvements in anesthesia technique, it is not plausible to argue in favor of high-dosage irradiation with three fractions per week because the anesthesia is too difficult. Patients with RB should be treated 5 days per week at 2 Gy or less per fraction. Third, in view of the somewhat contradictory data, most clinicians choose a dosage based on the tolerance of normal tissue rather than on an unfounded belief in unassailable dose–response information. Daily dosages of 1.8–2.0 Gy, 5 days per week, are used.

Finally, the most controversial aspect of external beam dosage selection is the appropriate total dosage. Let us consider this matter in some detail. As described earlier, the

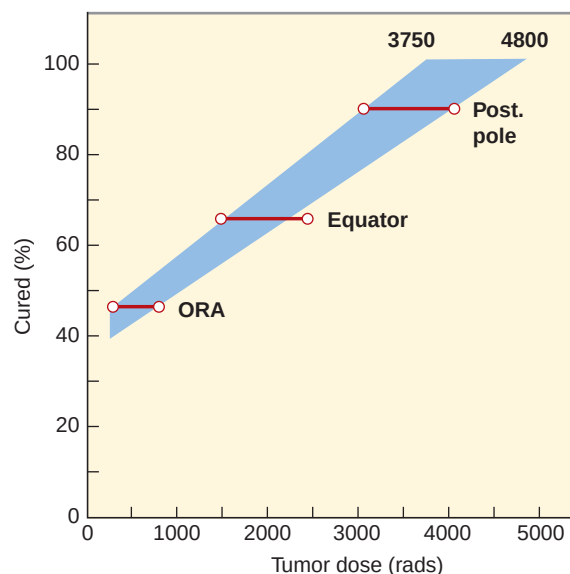


Figure 5.14 With a single lateral photon technique for the treatment of retinoblastoma, particularly if the beam is not half-beam blocked, the dosage across the retinal anlage is quite heterogeneous. Abramson has observed that if the beam's anterior edge is not set sufficiently close to the limbus, then the ora serata may receive only 10–30% of the prescribed dosage, the equator 50%, and the posterior pole 90–100%. He plotted the local control of tumors as a function of their ocular location. The more posterior the tumor, the higher the rate of local control. By relating the dosage that was probably administered to the eye at the ora, equator, and posterior pole and plotting it against the local control rate, one can generate a dose–response curve. Although the observation is interesting, it only argues in favor of a dosage of at least 37.5 Gy. This analysis does not provide guidance as to the best dosage in the 37.5- to 50-Gy range that can be administered homogeneously with a multiple-field technique. (From Abramson DH. Treatment of retinoblastoma. In: Blodi FC, ed. *Contemporary Issues in Ophthalmology*, vol. 2: *Retinoblastoma*. New York: Churchill Livingstone; 1985:63–93, with permission.)

traditional dosage for treating intraocular RB with external beam radiotherapy is 40–45 Gy. When radiation therapy is used after cytoreduction with chemotherapy and intensive focal therapy, however, one must consider modifying the dosage. The arguments in favor of reducing the dosage, in this setting, are as follows:

- In pediatric radiation oncology, there is precedent for using a reduced dosage for “consolidation” after surgery and chemotherapy. For example, in Wilms tumor, Hodgkin disease, and neuroblastoma, radiation oncologists have reduced conventional dosages of radiation for the purpose of “boosting” or “consolidating” treatment after chemotherapy.
- There may be a higher risk of toxicity with the use of 40–45 Gy of irradiation after chemotherapy. This would further argue for a dosage reduction in an attempt to minimize ill effects.
- There is some evidence that institutions using dosages on the order of 36 Gy have reasonable control of RB when radiotherapy is used alone (86).

Based on these arguments, protocols in development for treating locally advanced RB call for chemotherapy and focal

therapy (cryotherapy, laser therapy, or laser hyperthermia). Then, after completion of chemotherapy and focal therapy, 26 Gy of irradiation in 2.5 weeks is administered with conformal fields. It is hoped that protocols of this sort ultimately will maintain a high rate of local control of RB with a lower risk of second malignant neoplasms and bone growth abnormalities.

Clearly, if dosage reduction is used in external beam treatment of RB, careful attention must be paid to defining which patients are being “consolidated” and which patients have relapsed. For example, a child whose tumors regressed on chemotherapy and focal therapy and who is promptly referred for radiotherapy, to begin within 4 weeks after the chemotherapy, would be considered “consolidated.” But what are we to make of a child whose tumors start to grow immediately after chemotherapy or during chemotherapy? If this latter patient is judged to have relapsed, then one cannot justify using 26 Gy of irradiation. Clearly, as the role of chemotherapy in RB management evolves, radiation oncologists will have to use careful judgment to choose the correct dosage. Careful studies of patterns of failure and late effects over the coming years may better define appropriate treatment guidelines. However, inclusion of RB patients into these developing national protocols will more quickly help to resolve these issues.

POSTENUCLEATION CHEMOTHERAPY

A multi-institutional study conducted under the auspices of the Pediatric Oncology Group (POG) and the Children's Cancer Study Group (CCSG) and reported in 1981 evaluated chemotherapy (cyclophosphamide 30 mg/kg and vincristine 0.05 mg/kg) every 3 weeks for 37 weeks in 88 children with group V disease after enucleation. No overall survival or disease-free survival advantage was shown over enucleation alone (4,6,7,87,88).

Initially, cyclophosphamide was said to be the most active agent in treating metastatic RB. However, many clinicians favor carboplatin combined with vincristine and etoposide in the setting of extraocular extension, trilateral RB, or distant metastases. In addition, adjuvant chemotherapy may be effective in reducing the frequency of postenucleation metastases in patients at high risk for metastatic disease (i.e., tumor in the cut end of the optic nerve, massive choroidal invasion, and retrolaminar optic nerve invasion) (8). In a retrospective review of patients at high risk for postenucleation RB treated at Wills Eye Hospital, Honavar et al. (89) reported metastases in 2 of 46 (4%) patients treated with adjuvant chemotherapy and 8 of 34 (24%, $p = 0.02$) patients not receiving adjuvant chemotherapy. Chemotherapy consisted of vincristine, adriamycin, and cyclophosphamide in 21 patients and vincristine, etoposide, and carboplatin in 26 patients. The addition of chemotherapy significantly reduced the incidence of metastases in patients with massive choroidal infiltration or retrolaminar optic nerve invasion.

Mustafa et al. (90) described the results of treatment with vincristine, adriamycin, and cyclophosphamide in a group of 26 patients at high risk for postenucleation RB. With a median follow-up of 5.6 years, 5 of 36 patients developed distant metastases and subsequently died. All of these patients had massive tumors. Six other patients developed recurrent disease in the intact eye. On multivariate analysis, only optic nerve in-

volvement was a significant factor in predicting poor outcome. Uusitalo et al. (91) analyzed the histopathology and outcome in 129 patients with high-risk, unilateral RB treated by enucleation with and without chemotherapy followed for a median of 54 months. Patients with prelaminar optic nerve disease or isolated choroidal involvement did not receive chemotherapy, and none of these patients developed metastatic disease. Of the 11 patients receiving adjuvant multiagent chemotherapy for positive surgical margin of the optic nerve or tumor extending more than 1 cm beyond the posterior extent of the lamina cribrosa, only 1 patient developed metastases.

A retrospective analysis of 122 patients who had enucleation after chemotherapy reduction was performed to determine if any risk factors could be identified for development of extraocular relapse. All patients received carboplatin as sole chemotherapy (20.5%) or in combination with vincristine (13.9%) or with vincristine and etoposide (65.6%). The results found that only scleral involvement and bilateral enucleation were associated with extraocular relapse (67).

CHEMOTHERAPY FOR INTRAOCULAR DISEASE

Beginning in 1996, a series of publications in refereed journals, as well as platform presentations, described attempts to treat intraocular RB primarily with chemotherapy (92). Because the control of advanced RB is poor with external beam irradiation alone and because external beam irradiation is associated with orbital and midfacial bone deformity, lacrimal gland dysfunction, and an increased risk of second malignant neoplasms, it was not unreasonable to seek alternatives. Chemotherapy is seldom used as the sole treatment modality; however, if a complete response occurs and is durable no other therapies are required. More often, however, chemotherapy typically is combined with one or more focal therapies (cryotherapy, laser photocoagulation, laser hyperthermia, transpupillary thermotherapy, or plaque radiotherapy) (93). This dependency on focal therapies has caused some to question the usefulness of the chemotherapy. If in fact we are delivering drugs that have the potential for different second malignancies than those seen after external radiation have we really gained any advantage (94).

There is also investigation as to the best route for administration (systemic vs. focal) and whether single- or multidrug utilization is best in terms of local control and response rates. Two recent animal trials, using rabbit models, looked at how best to deliver carboplatin and topotecan. Using atomic absorption spectroscopy, it was shown that use of subconjunctival or Coulomb-controlled iontophoresis administration of carboplatin led to increased dose to the retina, vitreous and optic nerve when compared with IV administration (95). With topotecan, a drug being investigated for RB use, it was found that similar level was achieved whether IV or focal application was made. However, trans-scleral entry in vivo was constrained due to rapid clearance from the administration site (96).

There have also been recent reports on use of single agent chemotherapy. Dunkel et al. reported a phase II trial on IV-administered carboplatin. Patients received a median of two cycles (range 1–5). In Reese–Ellsworth groups I–III, 5-year ocular event-free survival was 43.5%. For Reese–

Table 5.4
Chemotherapy as Primary RB Treatment: Selected Series

Author (Reference)	Year	Eyes	Primary Chemotherapy CTX Control	CTX/PLUS Local Treatment Control	FU
Murphree (44)	1996	–/73	–	34%	N/A
Chan (98)	1996	21/26	–	89%	53 mo
Pradhan (31)	1997	28/31		78% RE I–III	
				28% RE IV–V	49 mo
Beck (99)	2000	24/33	–	71% RE Groups I–III	31 mo
Friedman (100)	2000	47/75	74%	–	13 mo
Wilson (101)	2001	20/36	8% RE I–III	–	19 mo
				0% RE IV–V	
Lumbroso (102)	2002	51/63	–	92%	30 mo
Gombos (94)	2002	36/42	57%	–	33 mo
Shields (103)	2004	63	55%	–	7 years
		394	–	82%	7 years
Shields (104)	2009	–/64	53%	–	5 years
		–/12	–	91%	5 years

Ellsworth groups IV–V, the same 5-year ocular event-free survival was 8.3%. It was, however, considered inferior to other more intense regimens (97).

More than 400 patients with RB treated with primary chemotherapy have been described in detail (Table 5.4). These cases include a mix of Reese–Ellsworth groups, focal therapies, classification of responses and failures, and reporting of results by the number of patients, eyes, and, in some series, tumors. Although chemotherapy most often consists of a combination of carboplatin, etoposide, and vincristine, the number of cycles, dosage, and sequencing of these drugs and the optimum regimen have not been established (105).

The largest single institutional report reviewed 457 tumors treated with six cycles of carboplatin–vincristine–etoposide (CVE). They were managed with CVE alone or in conjunction with focal therapy. At 7 years, 45% of Group A and 18% of Group B/C/D relapsed. They identified, using multivariate analysis, macular location for all groups, female sex for Group A and increasing tumor thickness for Group B/C/D as risk factors (103).

Nevertheless, multiagent chemotherapy combined with vigorous focal therapy appears to permit some patients to avoid, or at least delay, enucleation and external beam radiotherapy or allow the dosage of radiotherapy to be reduced. This strategy appears most effective in patients with Reese–Ellsworth groups I–III disease. It appears for the data that about 25–50% of those eyes receiving “aggressive” chemotherapy may not require any further therapy. Conversely, the presence of vitreous seeding (i.e., Reese–Ellsworth group Vb disease) or subretinal seeds is associated with a worse outcome. For example, Shields et al. reported a respective study of 103 patients with RB treated primarily with carboplatin, etoposide, and vincristine plus focal therapies at the Wills Eye Hospital. At 5-year follow-up, EBRT or enucleation was needed in 10% and 15%, respectively, of Reese–Ellsworth groups I–IV patients. In contrast, EBRT or enucleation was needed in 47% and 53% of Reese–Ellsworth groups IV–V. On multivariate analysis, only the presence of subretinal seeds predicted tumor

recurrence (92,106,107). Similar observations were made in retrospective studies of multiagent chemotherapy in intraocular RB at other institutions (93,99,101). However, a recent report from the same institution evaluated Group E RB eyes treated either with chemoreduction alone ($n = 64$) or with planned consolidative external beam irradiation (26 Gy). Twelve patients received the consolidative radiation and had a 2- and 5-year globe salvage rate of 91% and 80% compared to the chemoreductive group rates of 53% and 48%, thus suggesting that in these advanced cases the use of consolidative low-dose irradiation may allow for improved globe retention and sight (104).

The use of cyclosporine A in the Toronto series is based on the notion that the activity of the multidrug resistance gene (MDR) correlates with chemotherapy resistance in RB. The MDR gene product is a transmembrane pump that promotes the efflux of many drugs from cells (98,108). Cyclosporine A blocks the MDR pump and might increase tumor cell kill by increasing the intracellular drug levels. However, the importance of MDR in human tumors and the efficacy of cyclosporine A are both matters of debate. MDR has been shown to be of questionable importance in neuroblastoma, and the clinical data for RB are conflicting.

The current clinical trials of the COG are summarized in Table 5.5.

SPECIAL SITUATIONS

Trilateral Disease

Trilateral RB is a rare but well-recognized entity consisting of bilateral RB associated with ectopic RB of the pineal or suprasellar region. A forme fruste of trilateral RB has been described in which unilateral RB is associated with intracranial tumor (109). The intracranial lesion can cause signs of raised intracranial pressure (anorexia, ataxia, lethargy, vomiting) or, when the lesion is suprasellar, diabetes insipidus (110).

Table 5.5
The Current Trials of the Children's Oncology Group Concerning the Management of Retinoblastoma

Protocol Number	Title	Summary of the Protocol
ARET0231	A Single Arm Trial of Systemic and Subtenon Chemotherapy for Groups C and D Intraocular Retinoblastoma	Children with newly diagnosed retinoblastoma with at least one remaining eye classified as Group C or D receive intravenous carboplatin, etoposide, and vincristine, local therapy such as laser, cryotherapy, or plaque, and subtenon carboplatin. Failure of protocol therapy is defined as the need for any non-protocol therapy such as non-protocol chemotherapy, external beam radiotherapy, and/or enucleation.
ARET0321	A Trial of Intensive Multi-Modality Therapy for Extra-Ocular Retinoblastoma	This single-arm trial will attempt to confirm that conventional chemotherapy, high-dose chemotherapy with stem cell rescue, and external beam radiotherapy can favorably affect survival in metastatic retinoblastoma.
ARET0331	Trial of Systemic Neoadjuvant Chemotherapy for Group B Intraocular Retinoblastoma	Patients with Group B disease will receive six cycles of vincristine and carboplatin. After the first cycle there will be an assessment of response. Additional local therapies may be employed such as cryotherapy, thermotherapy and laser photocoagulation, and plaque brachytherapy. Progressive disease is defined as the need for enucleation, non-protocol chemotherapy, or external beam radiotherapy.
ARET0332	A Study of Unilateral Retinoblastoma With and Without Histopathologic High-Risk Features and the Role of Adjuvant Chemotherapy	In unilateral disease following enucleation, there will be a histologic assessment of the enucleated eye. High-risk features are defined as posterior uveal invasion including choroidal invasion, any concomitant choroids and optic nerve involvement by tumor, tumor involving the optic nerve posterior to the lamina cribrosa as an independent finding, sclera invasion, anterior chamber seeding, ciliary body infiltration, and/or iris infiltration. High-risk patient will receive adjuvant carboplatin, etoposide, and vincristine.

Since the publication of earlier editions of this book, several estimates of the incidence of trilateral RB have appeared in the literature from the United Kingdom and the United States (Table 5.6). Most cases appear in children with bilateral RB. They normally occur earlier with suprasellar presentations (median time from RB diagnosis 6.5 months) than if they are pineal-based (median 32 months). The frequency of trilateral RB, especially in the bilateral familial patients, has led some authorities to argue in favor of screening neuroimaging. A meta-analysis from Kivela suggests that with the use of routine screening with neuroimaging, earlier and smaller presenting tumors may be identified, which may lead to improved 5-year survival rates (111). Those at prime risk are children with bilateral RB within the first 3–4 years after diagnosis (109,110); however, reports of development as late as 7 years after the diagnosis of RB have been noted.

A Wills Eye Hospital study compared the frequency of trilateral RB in patients treated with carboplatin, etoposide, and vincristine chemotherapy with those receiving no chemotherapy. During the mean follow-up of 47 months, no associated intracranial neuroblastic tumor was observed in

Table 5.6
Incidence of Midline Intracranial Tumors in RB (Trilateral Disease)

	Overall	Bilateral Familial RB	Bilateral Sporadic RB
West	3%	5%	12.5%
Midland Regional Children's			
Wills Eye	4%	8%	5%
NY	5%	10%	6%
Hospital/MSKCC St. Bartholomew's	2%	—	—

99 patients at risk for trilateral RB receiving multiagent chemotherapy. Based on the results of the meta-analysis of trilateral RB, 5–15 cases were anticipated. In contrast, 1 of 18 at-risk patients treated without chemotherapy developed an associated intracranial tumor (112). Thus, it seems reasonable to perform intracranial imaging at the diagnosis of all cases of RB (when many clinicians do CT of the orbits) and every 3–6 months thereafter for 3–4 years in bilateral RB. If a pineal or suprasellar mass is found, a decision must be made concerning biopsy.

For some clinicians the presence of a calcified, discrete midline mass of the pineal or suprasellar regions in the setting of heritable bilateral RB is sufficient to make the diagnosis of trilateral disease (4). However, other oncologists feel more comfortable with a biopsy of the intracranial lesion. The authors of this chapter recently saw a 10-month-old with heritable RB and a pineal mass who, on pineal biopsy, was shown to have a benign pineal cyst.

The treatment of trilateral disease with surgery alone or in combination with radiotherapy resulted in a few long-term survivors (109,113,114). Six cases of trilateral RB were reported in 1994 from Memorial Sloan-Kettering Cancer Center. Three were treated with craniospinal irradiation (CSI) and chemotherapy, two with chemotherapy alone, and one with no treatment. All patients died of the tumor in 2–12 months (115). Five patients with trilateral RB seen in the West Midlands Health Authority, United Kingdom, reported in 1996, died at 1–31 months after diagnosis (109). In 1986, the pediatric neuro-oncology group at Duke reported that cyclophosphamide and vincristine were active in patients with recurrent trilateral RB (113). Subsequently, the same group has described three children with newly diagnosed trilateral RB treated with systemic (cyclophosphamide, vincristine) and intrathecal (methotrexate, hydrocortisone, cytarabine) chemotherapy along with orbital irradiation and, in two cases, CSI. Two patients are alive without evidence of disease 3 and 8 years after diagnosis. One is alive with persistent disease 2 years after diagnosis (116).

Paulino performed a Medline search of all English-language articles pertaining to trilateral RB published between 1977 and 1997. Of the 94 different cases identified, the median age at the time of diagnosis of RB was 6 months. In 78 patients (83%) the intracranial tumor was in the pineal region, and in 16 patients (17%) it was in the suprasellar region. The location of the tumor had no impact on survival. For patients who received no treatment the median survival was 1 month, whereas it was 8 months for those who received treatment. Therapy in 25 of the patients was craniospinal radiotherapy with chemotherapy, 20 patients received CSI, 10 received chemotherapy alone, and a variety of other treatment combinations were used in the remainder of the patients. The median survival was 8 months. Of the six children who survived more than 2 years after diagnosis of intracranial primitive neuroectodermal tumor, all received chemotherapy and four received craniospinal radiotherapy. For the 75 children for whom patterns of failure were reported, 55% had disseminated neuraxis disease (110).

The use of radiotherapy in trilateral RB poses an interesting challenge to the radiotherapist. The orbital disease usually is irradiated first, accompanied and followed by chemotherapy, with CSI given last in the sequence. Knowing this, the radiotherapist must set up the orbital fields with the

understanding that they will be called on to partially overlap and then match the CSI fields.

Particular attention is paid to the optic chiasm dosage in this situation. Using rigid patient immobilization and 3D treatment planning, it is possible to administer CSI and a boost to the intracranial tumor with reasonable safety even apart from ocular irradiation (114).

Ocular Retreatment

Among the most difficult problems confronting the pediatric radiation oncologist is therapy selection in a child who has suffered recurrent RB in an eye previously externally irradiated to full dosage. If the recurrent lesion is small and favorably located, it may be treated with photocoagulation, cryotherapy, or a radioactive plaque, often with success. Amendola and coworkers (10,59) plaqued 29 eyes, 28 with group V disease for recurrent tumor. Tumor progression in 14 eyes ultimately necessitated enucleation. The remaining 15 eyes (52%) have preservation of vision.

In some situations, the clinician faces the choice of enucleation or reirradiation with external beam. Abramson reported retreatment of 15 eyes that, at the time of tumor recurrence, could be classified as groups I–III. Twelve (80%) of these eyes survived. Of the 89 eyes that were group IV or V at the time of tumor recurrence, only 2 (2.2%) survived. Nine of the 14 salvaged eyes had useful vision. The overwhelming cause of enucleation was progressive tumor, not radiation damage. There appears to be no increase in secondary nonocular tumors in children receiving two courses of radiotherapy (117). An interesting report from St. Jude's Children's Hospital looked at enucleated eyes after chemoreduction and eye salvage therapy to determine the histological findings. What was noted was that prolonged time to enucleation was significantly associated with the likelihood of choroidal and ciliary body invasion. Coexisting retinal detachment and vitreous hemorrhage increased the likelihood of optic nerve involvement at the time of enucleation (118).

MANAGEMENT OF EXTRAOCULAR EXTENSION, ORBITAL RECURRENCE, AND METASTATIC DISEASE

In developed countries, cases of extraocular extension or orbital recurrence after initial treatment of RB are rare. At academic centers, such cases often are referred from institutions where the initial treatment was given by physicians who thought, at first, that they were dealing with another diagnosis. By making the best possible use of the available data and by relying on sound clinical reasoning, the pediatric radiation oncologist can make the best of these vexing cases.

Earlier in this chapter, we pointed out that histologic evaluation of the enucleated eye could predict prognosis to some extent (119–121). Extensive involvement of the choroid along with retrolaminar extension of tumor or, even worse, involvement of the cut end of the optic nerve predicts a poor outcome. Patients with these problems are subject to either local recurrence of tumor in the orbit, CNS disease, or systemic tumor. It is reasonable to consider more aggressive adjuvant treatment in these cases in an attempt to improve the outcome.

Another important prognostic factor is the performance of a prior intraocular procedure in patients with RB. RB may be initially misdiagnosed. Children who have undergone an intraocular operative procedure before definitive enucleation are at risk for orbital recurrence of tumor and nodal and hematogenous dissemination.

Historically, recurrence of RB in the orbit after enucleation has carried an extremely poor prognosis for survival. Only 1 of 16 children with orbital recurrence was a long-term survivor in the St. Bartholomew and Moorefield Eye Hospital's 1987 report. Children succumbed to CNS tumor, systemic disease, and uncontrolled orbital tumor.

Fortunately, clinical results are now better. We will now consider the appropriate treatment for children found to have one or more identified risk factors.

Optic Nerve Involvement

Tumor may extend beyond the lamina cribrosa or to the end of the transected optic nerve. The mortality rate when the optic nerve is involved up to the line of transection is 40–45% (120,122). Retrolaminar involvement also markedly affects survival, although not as severely. This argues strongly for the use of adjuvant therapy, but there are no prospective, randomized data proving the value of adjuvant therapy in this situation.

Contemporary practice generally includes adjuvant chemotherapy for optic nerve involvement (carboplatin and etoposide or vincristine, carboplatin, and etoposide). Orbital external beam irradiation, using various dose schedules, is commonly used for tumor up to the line of transection. The posterior aspect of the irradiated volume should encompass the pathway of the optic nerve back to the optic chiasm. Some radiation oncologists advocate whole brain and orbital irradiation in this situation, but this approach is less popular. Retrolaminar tumor, without extension to the line of transection, is treated by adjuvant chemotherapy and orbital irradiation by some and by chemotherapy alone by others (8).

When postoperative radiotherapy is used for the orbit, external beam treatment is most commonly used. Popular field arrangements include an anterior wedge pair, a single anterior field, or a 3D planned set of fields, usually four to six. However, use of intensity-modulated radiation is gaining favor for all cases where external beam is called upon. Coralline hydroxyapatite prostheses do not significantly affect the radiation dosage distribution (123).

Some institutions prefer to treat the postenucleation socket with brachytherapy. There are at least three techniques. The Groote Schuur Hospital of Cape Town, South Africa, has described a technique using six rows of ^{125}I arrayed around the periphery of the orbit, one central row, and seeds on a metal disc sutured beneath the eyelids. The median dosage is 34–40 Gy in about 3 days. The benefits of this procedure compared with external beam treatment are felt to be a lower risk of bone growth abnormality, less failure of tooth eruption, a reduced risk of neuroendocrine injury, and a possible reduction in second malignant neoplasms. Local tumor control in the South African series has been excellent, although there have been some deaths from distant metastases (124).

Another technique for postenucleation orbital brachytherapy is the creation of a mold. This technique is similar to that used at some institutions for brachytherapy for cervical or vaginal carcinoma. At the time of the actual implant of the

mold, if skillfully prepared, it should readily go into place, the seeds are loaded, and a covering lead eye patch placed. A dosage of 35–45 Gy is given to the orbital wall in 3–4 days. The mold usually is prepared so that there is room for some petroleum jelly gauze between the mold and the orbital wall for a better depth dosage.

A third brachytherapy technique uses a spherical orbital prosthesis. The prosthesis is drilled and ^{192}Ir or ^{125}I is placed in the center of the sphere. This creates an applicator with a uniform dosage on the sphere's surface (125).

Orbital Extension and Orbital Recurrence

As previously described in this chapter, orbital extension of intraocular RB or orbital relapse after enucleation is associated with a high mortality rate. Small series have been reported showing long-term survival with postoperative chemotherapy and radiotherapy (126,127). As regards chemotherapy, there is some debate concerning whether systemic treatment is adequate or intrathecal chemotherapy should also be used. Concerning radiotherapy, there is some debate as to whether orbital or whole brain radiotherapy is appropriate (4). It would be best if we had detailed patterns of failure analyses that made it clear what predicted for orbital only, brain only, systemic only, or some combination of sites relapses. This would guide us in selecting radiotherapy treatment volumes. Because most clinical series are small and describe a mixture of patients with orbital involvement at presentation, at relapse, and of varying sizes and extent, it is impossible to make unequivocal pronouncements on this topic. For the radiation oncologist, a sound policy is to irradiate the orbit alone unless there is extension into the brain or there are brain metastases. If the orbital disease is bulky, some treat with a combination of external beam and brachytherapy (4, 14,126).

Metastases

Radiotherapy has been used in the curative and palliative treatment of metastatic RB. Whole brain irradiation or CSI is used for brain metastases or leptomeningeal dissemination. Bone or nodal metastases often respond to involved-field irradiation. When bone marrow transplantation is attempted for advanced disease, total body irradiation (TBI) has been included in the preparative program, albeit infrequently (128,129).

High-dose chemotherapy (HDC) with autologous stem cell rescue may also be an option in treating advanced disease. In a study of 25 patients with RB receiving HDC with autologous stem cell rescue for relapsed or high-risk disease, Namouni et al. (130) reported a 67% disease-free survival at 3 years. Of the eight patients who relapsed, seven of the relapses were in the CNS. Seven patients died with disease at a median of 13 months after HDC. Hertzberg et al. (131) described the use of HDC with peripheral hematopoietic stem cell transplantation in five children with RB metastatic to bone marrow and one child with extraorbital disease. One child was salvaged with surgery and conventional therapy after suffering a meningeal relapse and is alive at 105 months after treatment. The other 4 did not relapse and are in complete remission 8, 9, 57, and 107 months after HDC. Others have also reported successful salvage of metastatic cases using ABMT and focal therapy such as external beam irradiation for "bulky" sites; however, these cases are limited and there is no consensus as to the best therapy to use (132–135).

Results in the Management of Extraocular Retinoblastoma

Patients with extraocular RB limited to the orbit or preauricular nodes, treated with postoperative radiotherapy and chemotherapy, have a widely variable reported progression-free survival. With 1–5 years of follow-up, in small series, it ranges from 30% to 80% (8,126,136,137). Widespread metastatic disease outside the CNS, treated with HDC, local irradiation or TBI, and stem cell rescue, may be curable in about one fourth to one half of cases. The prognosis of CNS metastases, treated with cranial or craniospinal irradiation and systemic and intrathecal chemotherapy, is grim.

PALLIATION OF METASTASES

For bony metastases causing pain, palliative radiotherapy is appropriate. A dosage of 20–40 Gy, similar to that for neuroblastoma, is used (7) (see Chapter 6).

LATE EFFECTS

Secondary Nonocular Tumors

The evidence is persuasive that the 13q–14q deletion of heritable RB produces a malignant diathesis. The relative risk (RR) for death from a second tumor is much higher among patients with bilateral RB (RR = 60) than among those with unilateral disease (RR = 3.8). This first manifests itself in the development of the index case of RB. In long-term survivors of heritable RB, there is an extremely high incidence of secondary nonocular tumors. The most common secondary malignant neoplasms (SMNs) occurring in the radiation field in survivors of heritable RB are osteosarcoma, fibrosarcoma, and other spindle-cell sarcomas. SMNs developing out of the radiotherapy field also include osteosarcoma and the soft tissue sarcomas. However, this list must be broadened to include malignant melanoma and thyroid carcinoma. In addition, there is a long list of less common SMNs that have developed in long-term survivors of heritable RB (19,138–140).

In children treated with hereditary RB, the incidence of SMNs increases with time. The median latency period is 15 years (139,140). At 10 years, the incidence of SMNs is about 10%, at 20 years it is about 20%, at 30 years it is estimated to be about 25%, and at 50 years, 51%. Initially, Abramson et al. (6,9) described even higher risks: 20% at 10 years, 50% at 20 years, and 90% at 30 years. A comprehensive evaluation of SMNs in RB by Eng et al. (132) is based on a large number of patients with RB, including patients from New York and Boston. In a 1993 report, at 40 years of follow-up, the cumulative mortality for all second tumors was 26% for bilateral RB and 1.5% for unilateral RB. The Eng study includes those previously reported by Abramson and therefore supersedes those reports.

In a 1997 report, the cumulative incidence of second cancer at 50 years after diagnosis was 51% (140). All the major studies agree that the risk of SMN is greater in survivors of heritable RB who received radiotherapy than in those who did not. For example, Roarty et al. (138) found a 30-year SMN incidence rate of 29% in the radiation field for 137 patients who received radiotherapy (Fig. 5.15). The incidence of 8% outside the radiation field was similar to the 6% rate for the 78 patients who did not receive radiation.

Abramson et al. also found a significant reduction in the incidence of SMN outside the field of radiation or in patients never irradiated. Among patients with bilateral RB, Eng et al. found that cumulative mortality from second neoplasms at 40-year follow-up was 30% for irradiated patients and 6% for those who did not receive irradiation. Wong et al. found that, at 50 years, the cumulative incidence of second cancers was 58% in irradiated heritable RB patients and 27% in nonirradiated patients. Dosimetry data, collected for patients with secondary bone and soft tissue sarcoma, showed a stepwise increase in secondary tumor relative risk with increasing dosage. In an analysis confined to bilateral cases the incidence of second tumors at 30 years was 34% for children irradiated at less than 12 months of age, 22% for children irradiated at more than 12 months of age, and 18% for those not irradiated.

Cavenee et al. (141) have developed some evidence to implicate cyclophosphamide as a risk factor for SMN in heritable RB. In an extensive review of heritable RB, they found that the estimated incidence rate 12 years after diagnosis for tumors in the field of radiation was 4.2% for patients given chemotherapy and 2.9% for patients not given chemotherapy. The rates for tumors outside the radiation field (including patients not irradiated) was 4.6% for those receiving chemotherapy and 1% for those not receiving it.

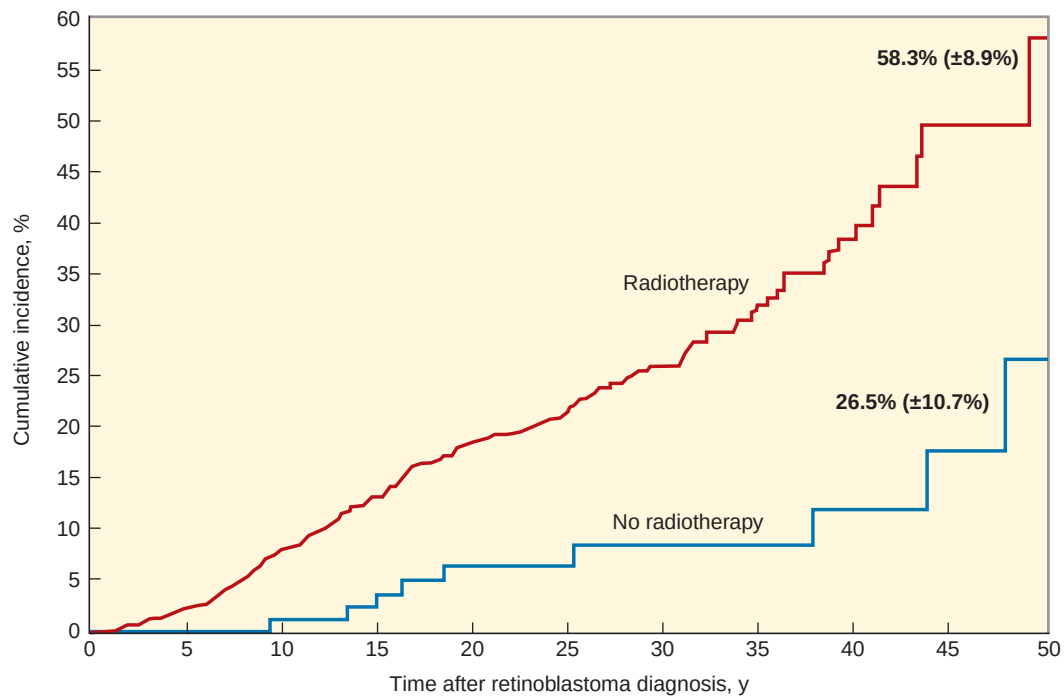
Children with heritable RB have a field change rendering them subject to malignant transformation. Radiotherapy and perhaps chemotherapy are an additional insult. Radiotherapy shortens the latent period for SMN, increases the incidence of SMN, and affects the distribution of SMN. In summary, for heritable RB radiotherapy compounds the risk of SMN on a background of high risk.

CATARACTS

Fontanesi et al. (76) noted that clinically significant posterior pole cataracts developed in 23 of 27 eyes (85%) treated with anterior fields. The Mayo Clinic reported 4 of 14 (28%) posterior cataracts using a lens-sparing technique (15). In 7 eyes followed for more than 36 months, Hernandez et al. (84), generally using lateral and anterior fields, observed lens changes in all cases, with three necessitating lens extraction. Radiation-induced cataracts after radiotherapy of RB can be removed successfully and vision can be corrected. Brooks et al. (62) removed cataracts in 38 patients with RB (42 eyes) from 1973 to 1989. Nineteen eyes (45%) had final visual acuities of 20/20 to 20/50. Twelve eyes (29%) had macular tumors with postoperative visual acuities of 20/80 to counting fingers. The risks of cataract removal after RB treatment include amblyopia, retinal detachment, and the risk of tumor dissemination if RB was not controlled by irradiation.

ORBITAL DEVELOPMENT

Children treated with radiotherapy or enucleation for RB are at significant risk for orbital and midfacial growth retardation insofar as their orbital bones are growing during treatment. In long-term survivors of RB, these orbital growth injuries may be apparent. In recent years, investigators have sought to quantify the changes in orbital development wrought by treatment.



Radiotherapy	848	619	407	165	42	5
No radiotherapy	113	96	66	40	20	6

Number of patients at risk

Figure 5.15 Cumulative incidence (plus/minus standard error) of second cancers after diagnosis of retinoblastoma in patients with hereditary disease, by presence or absence of radiation treatment. (From Wong FL, Boice JD Jr, Abramson DH, et al. Cancer incidence after retinoblastoma: radiation dose and sarcoma risk. *JAMA*. 1997;278:1262–1267, with permission.)

Imhof et al. (142) examined children treated at Utrecht University Hospital in the Netherlands and followed for a mean of approximately 8 years. Direct measurements were made of the orbital width and height and the orbital–tragus distance. In general, high-dose-per-fraction external beam irradiation had been used (3 Gy per fraction $\times$ 15 = 45 Gy, 8-MV photons). The mean orbital width, height, and distance between the tragus and the outer orbital edge were significantly shorter in irradiated orbits compared with non-irradiated orbits in patients with unilateral RB and compared with control eyes. EBRT given to children younger than 6 months old was more injurious than when it was used in older children. Enucleation with EBRT was not worse than EBRT alone.

Findings by Imhof et al. are supported by a slightly less detailed study from Essen, Germany, by Messmer et al. (143). The German researchers evaluated 99 patients, diagnosed at the median age of 10 months, and at a median age at last follow-up of 16 years. In children and adolescents with anophthalmic sockets, there was a significantly less satisfactory cosmetic and functional outcome in patients who received EBRT before or after enucleation (Fig. 5.16). Midfacial hypoplasia was also clearly related to the use of enucleation or irradiation (Fig. 5.17).

Kaste et al. (144) at SJCRH evaluated the orbital development in long-term survivors of RB using a CT scan obtained at a median age of 13 years. Because the orbital

interior is roughly conical, the orbital volume was assessed with a scan slice at the level of the optic nerve. In patients with unilateral RB, the orbit on the enucleated side was smaller in 20 of 24 cases and larger in 4 cases. The median orbital volume difference was 1.5 cm³. This small difference may be the result of the use of orbital prostheses that stimulate bony orbital growth. In 18 children with bilateral disease treated with enucleation on one side and irradiation on the other, the enucleated side had the smaller volume in 6 cases, the irradiated side was smaller in 10, and there was no difference in 2 cases.

The available literature confirms the impression of senior clinicians caring for children with RB that radiation and, to some extent, enucleation without a properly fitting prosthesis can lead to retardation of bony and soft tissue growth of the midface (orbits, ethmoid bones, nasal bridge). Hypotelorism, enophthalmos, depressed temporal bones, atrophy of the temporalis muscle, narrow and deep orbits, and a depressed nasion can be the result (141). These effects are accentuated if radiotherapy is used in the very young (younger than 6 months of age) and at dosages greater than 35 Gy (145,146).

LACRIMAL GLAND

In 1955 Cogan et al. (86), of the Massachusetts Eye and Ear Infirmary, did a series of experiments concerning the irradiation of the orbital glands of rabbits. Rabbits have two orbital

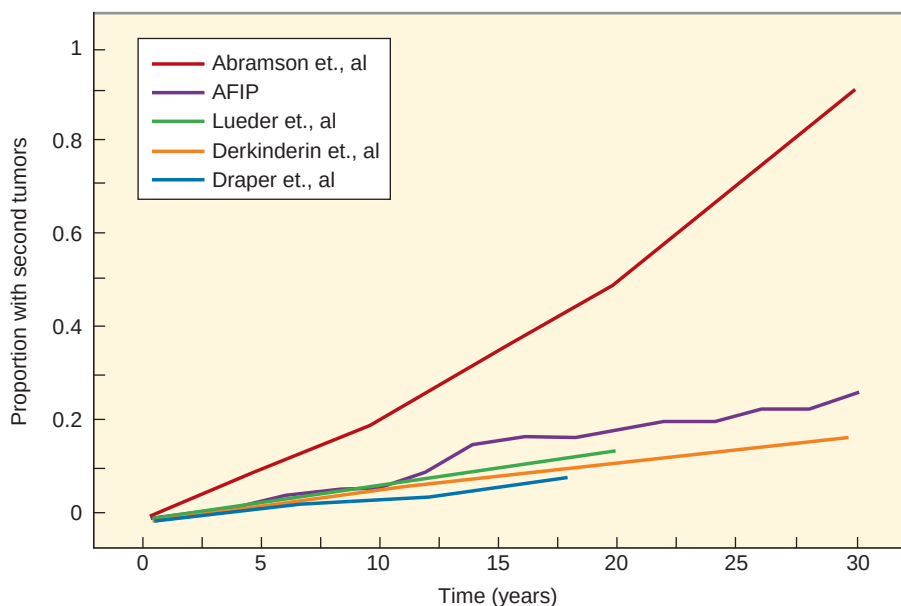


Figure 5.16 The risk of secondary nonocular tumors for children with bilateral retinoblastoma from several published studies described in the text. (From Roarty JD, McLean IW, Zimmerman LE. Incidence of second neoplasms in patients with bilateral retinoblastoma. *Ophthalmology*. 1988; 95:1583–1587, with permission.)

glands opening onto the conjunctiva; one is a sebaceous gland, called a Harderian gland, and the other is a true lacrimal gland. They irradiated rabbit orbits to varying dosages and excised and weighed the glands at 45 days or later. The results, shown in Figures 5.18 and 5.19, demonstrate a definite decrease in gland size with increasing dosage.

Imhof et al. (146) studied lacrimal function in 45 eyes of 34 irradiated patients who underwent tear function tests a mean of 86 months after irradiation. Irradiated eyes had significantly less tear production and significantly less tear protein production than a control group. Although many radiation oncologists attempt to shield the lacrimal gland, some long-term survivors of RB have diminished tears and diminished stability of the tear film. Such children may be prone to keratopathies. Keratitis as a side effect of irradiation for RB has been reported with varying frequencies: 28% by Imhof et

al., 3 of 30 patients (10%) treated at less than 1 year of age, and 2 of 15 patients (13%) treated after 1 year of age by Fontanesi et al.

Clinical Trials

Because there are so few cases of RB diagnosed in the United States per year, the best hope for improvement in local control and reducing late-term complications is through the use of clinical trials. There are some institutions that, because of reputation, see a large number of RB patients and are able to mount institutional clinical trials. However, for most pediatric centers, the numbers are too few for this activity and thus participation in group-sponsored protocols. In the United States, the COG has a designated RB committee that is responsible for development of such trials. At the present time, there are three active therapeutic trials, one therapeutic trial that is

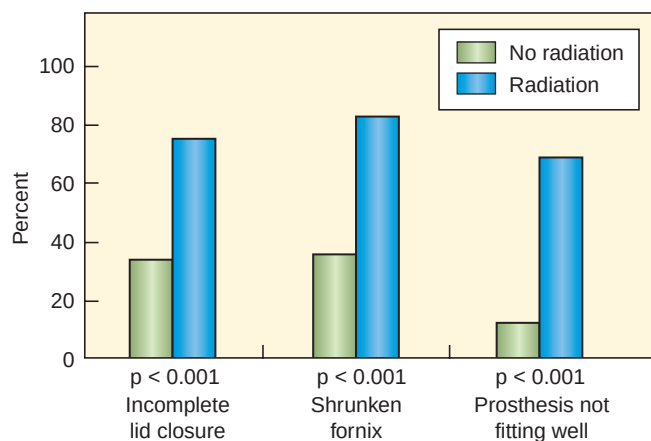


Figure 5.17 Radiation with enucleation can produce significant orbital problems. In anophthalmic children, deformities were heightened by the addition of radiation. (From Messmer EP, Frize H, Mohr C, et al. Long-term treatment effects in patients with bilateral retinoblastoma: ocular and mid-facial findings. *Graefes Arch Clin Exp Ophthalmol*. 1991;229:309–314, with permission.)

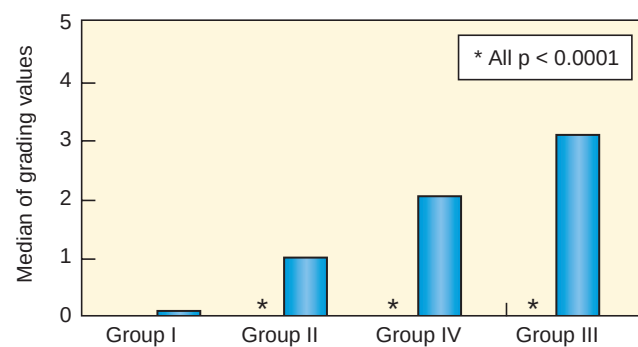


Figure 5.18 Using a clinical grading system, Messmer et al. did subjective grading of deformity of midfacial structures after treatment for retinoblastoma. Midfacial hypoplasia correlated with therapy. Group I consists of patients treated with photocoagulation or cryotherapy only, group II comprises patients treated with enucleation without irradiation, group III comprises patients treated with enucleation with radiation, and group IV includes children treated with radiation without enucleation. (From Messmer EP, Frize H, Mohr C, et al. Long-term treatment effects in patients with bilateral retinoblastoma: ocular and mid-facial findings. *Graefes Arch Clin Exp Ophthalmol*. 1991;229:309–314, with permission.)

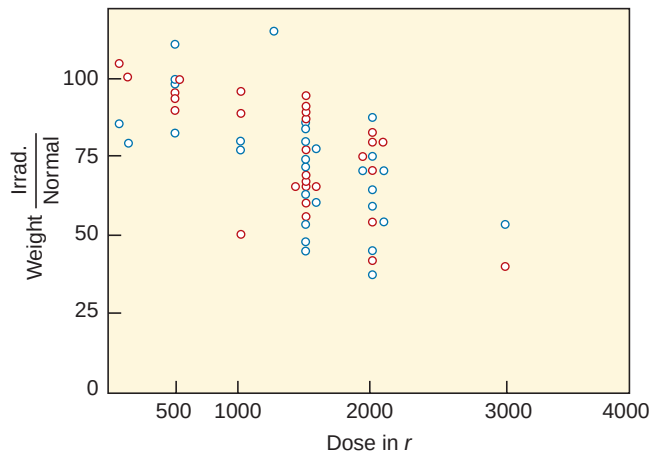


Figure 5.19 In a study by Cogan et al., the two orbital glands of the rabbit were weighed after irradiation. The Harderian gland is the sebaceous gland. Rabbits also have a true lacrimal gland. The relative weights of the irradiated and normal Harderian glands (red circles) are compared with the weights of the irradiated and normal lacrimal glands (blue circles). Although there is great individual variation, there is clearly a decrease in gland size with increasing dosages of irradiation. (From Cogan DG, Fink R, Donaldson DD. X-ray irradiation of orbital glands of the rabbit. *Radiology*. 1955;64:731–737, with permission.)

suspended and several nontherapeutic trials including a registration trial.

The active therapeutic trials are as follows:

- 1) A study of unilateral RB with and without histopathologic high-risk features and the role of chemotherapy in these cases. The high-risk features include posterior uveal and involvement (includes choroidal involvement), optic nerve involvement, scleral involvement, ciliary body/iris infiltration, and anterior chamber involvement. Patients with high-risk features receive six cycles of chemotherapy while those with non-high risk go straight to observation.
- 2) A single arm study of systemic and subtenon chemotherapy for Groups C and D RB.

This is a limited institutional trial and is investigating the use of subtenon carboplatin (course 2–4) along with systemic chemotherapy that consists of carboplatin, etoposide, and vincristine. The cycle is repeated every 28 days for 6 cycles. Local ophthalmologic treatments are allowed.

Failure is defined as the need for enucleation, external beam irradiation, or nonprotocol chemotherapy. This trial is important in that it will establish the rate of local control with chemotherapy +/- local ophthalmologic treatment, which for the first time will be standardized.

- 3) A trial of intensive multimodality therapy for extraocular RB. This trial involves the use of induction chemotherapy, and for those patients with greater than partial response there is stem cell consolidation for patients with stage IVa/IVb disease (disseminated non-CNS/disseminated with CNS involvement) and response-adapted radiotherapy. The radiotherapy is based on initial presentation. Group II/III patients will receive radiation regardless of response.

Group II/III receives 45 Gy using 180 cGy fractions. Group IVa and IVb do not receive any radiation if they have a complete response and, in IVa patients, if there is less than 5 mm of residual disease after chemotherapy. For those who do require irradiation group IVa receives 36 Gy and 4b receives 36 Gy to craniospinal fields, 45 Gy to the cranium, and 50.4 Gy to the pineal region, again using daily 180 cGy fractions.

The importance of patient recruitment to these national trials cannot be overstated; these controlled studies will help to further define and refine the role of chemotherapy, local ophthalmic therapies, surgery, and radiation therapy in the treatment of RB.

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Neuroblastoma

Katherine K. Matthay, Daphne Haas-Kogan, and Louis S. Constine

Neuroblastoma (NB) is a malignancy derived from embryonic neural crest cells of the peripheral sympathetic nervous system. It is the most common extracranial solid tumor of childhood, accounting for 15% of cancer-related deaths. The behavior of NB is marked by clinical heterogeneity, which leads to differences in behavior ranging from spontaneous maturation in some patients to inexorable rapid metastatic progression in others. It was noted as early as 1927 to be a tumor in which spontaneous maturation could occur, when Cushing and Wolbach (1) reported the case of a 2-year-old boy whose thoracic paravertebral sympathetic NB, over the course of 10 years, transformed into a completely differentiated ganglioneuroma. However, advanced NB is the most lethal of childhood solid tumors, often resistant to all attempts at disease eradication (2). The enigmatic behavior of this tumor is beginning to be elucidated by new research into the genetic and biologic diversity, but the treatment of advanced disease is a continuing challenge. This chapter discusses the biologic features of NB associated with differing behavior, the evaluation and staging, and a risk-based approach to therapy, with an emphasis on local control issues.

EPIDEMIOLOGY AND SCREENING

There are approximately 650 cases of NB annually in the United States, with an overall incidence of 10.3 per million per year from birth to the age of 15 years. NB accounts for nearly 10% of pediatric cancer in children younger than 15 years, making it the fourth most common malignancy in children after leukemias, brain tumors, and lymphomas. However, it is the most common malignancy of children younger than 18 months, with an incidence of 29.1 per million per year in children younger than 5 years (3). Ninety percent of patients with NB are diagnosed by 10 years, 79% before 4 years, and 36% are infants less than 1 year. The incidence is slightly higher in boys than in girls. The median age at diagnosis is 22 months. NB is responsible for 15% of childhood cancer mortality, with an annual mortality rate of 5 per million for all children and 9 per million for the 0- to 4-year-old subgroup (3).

NB arises from primitive (fetal) adrenergic neuroblasts of neural crest tissue, which may explain its high incidence in infancy. In the embryo, continuous columns of neural crest tissue form dorsolateral to the developing neural tissue. These columns are the precursors of the spinal ganglia, the dorsal spinal nerve roots, and the chromaffin cells, which flank the abdominal aorta (4). The largest of these masses is

the adrenal medulla (Fig. 6.1). Most cases of NB occur in an anatomic distribution consistent with the location of neural crest tissue (Fig. 6.2).

The frequency of neuroblastic nodules, resembling NB in situ, in the adrenals of autopsied infants who have died of other causes ranges from 1 in 39 to 1 in 600 autopsies, suggesting that most of these nodules regress by birth (5). This is interpreted to mean that such nodules are embryologic adrenal remnants and are the cells from which adrenal medulla NB may develop. Several studies using systematic screening of neonates for NB have confirmed the results of earlier autopsy studies by suggesting a much higher incidence of NB than is clinically evident. More than 90% of NBs secrete vanillylmandelic acid (VMA) or homovanillic acid (HVA) in the urine, for which rapid quantitative screening methods have been developed that have a high degree of sensitivity and specificity. Urinary catecholamine screening for NB was initially proposed by Woods et al. (6) because the incidence of 8.7 per 1 million children per year is comparable to or higher than that of other congenital diseases for which screening is already in place, such as hypothyroidism, galactosemia, and phenylketonuria. The poor prognosis for advanced NB in children older than 12 months at diagnosis compared with the favorable outcome for those diagnosed in infancy raised the expectation that diagnosis at an earlier

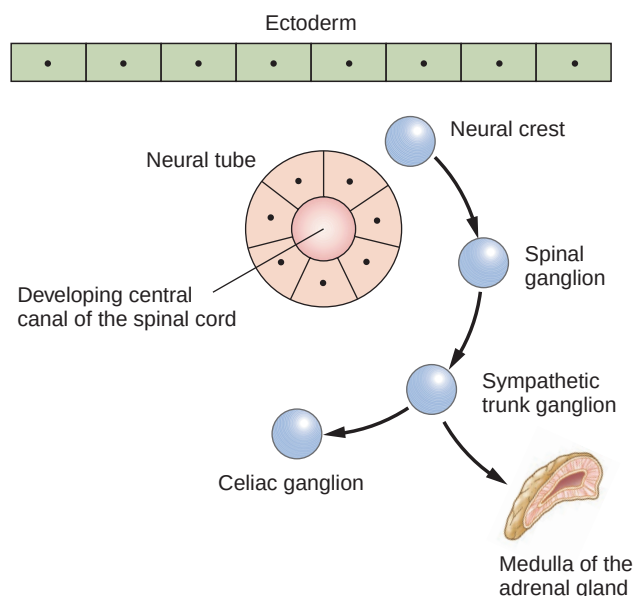


Figure 6.1 Migration of the neural crest in the human embryo.

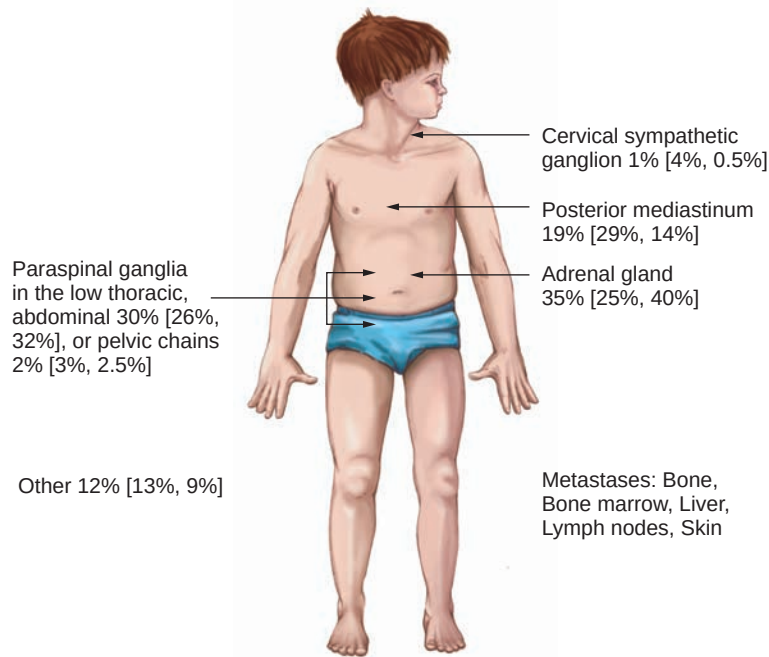


Figure 6.2 Common locations of neuroblastoma. The first percentage is the overall proportion of cases at the site. The numbers in parentheses are the percentages of cases at a given site in children 1 year of age or younger and older than 1 year of age. (Data are from Bernstein ML, Leclerc JM, Bunin G, et al. A population-based study of neuroblastoma incidence, survival, and mortality in North America. *J Clin Oncol*. 1992;10(2):323–329; and J. Shuster, PhD, Pediatric Oncology Group Statistical Office.)

age might improve overall outcome. However, the cumulative data from 30 years of screening in Japan, the Quebec Neuroblastoma Screening Project, and screening projects in Europe have shown that screening infants by 6 months of age results in a significant increase in the overall incidence of NB but fails to reduce the incidence of advanced-stage disease with poor prognosis (7–9). NBs detected by screening have almost exclusively favorable biologic features (*MYCN* nonamplified, triploid, favorable Shimada histology) (10,11). Thus, screening practices result in the overdiagnosis of tumors that would otherwise have spontaneously regressed. A recent publication from the Quebec project conclusively showed that screening at 3 weeks and 6 months in a cohort of 476,654 infants born over a 5-year period had no impact on overall mortality for the screened cohort compared with multiple control populations from Minnesota, the Delaware Valley, Florida, and the rest of Canada, verifying the results of the earlier studies (7). A second study screened 1,475,773 children at 1 year of age in German states and similarly revealed no impact on outcome (12). The screened group and children in the control area had a similar incidence of stage 4 NB (3.7 cases per 100,000 screened children and 3.8 per 100,000 controls) and a similar rate of death among children with NB (1.3 deaths per 100,000 screened children and 1.2 per 100,000 control subjects). There was a substantial rate of overdiagnosis in the screened group of children without benefit from the screening.

The environmental and inherited factors involved in the pathogenesis of NB are largely unknown, despite extensive epidemiologic and genetic studies. Given the young age at which most NBs present, it has been suggested that environmental exposures before conception or during pregnancy increase the risk of NB. Epidemiologic investigations have implicated fetal exposure to diuretics, tranquilizers, hormones, phenytoin, alcohol, and tobacco as increasing the risk of NB. However, these studies have lacked the statistical power to convincingly demonstrate that these drugs are etiologic risk factors or have

not been confirmed by subsequent studies (13). Environmental exposures are unlikely to be significant, although certain parental occupations have been associated with increased risk of NB, including those involving electrical exposures, gardening, farming, and painting (14–16). However, none of these associations has been seen consistently.

Although NB usually occurs sporadically, 1–2% of patients have a family history of the disease. This is similar to the other embryonal cancers of childhood in which a familial predisposition is observed. Familial NB is inherited in an autosomal dominant Mendelian fashion with incomplete penetrance. Affected children from these families differ from those with sporadic disease in that they are often diagnosed at an earlier age (usually infancy) or they have multiple primary tumors. These clinical characteristics are hallmarks of the two-mutation cancer predisposition model first proposed for retinoblastoma. Therefore, it seems likely that familial NB occurs as a result of a germ-line mutation in one allele of a tumor suppressor gene. Germ-line mutations have rarely been identified, with only rare case reports of familial cases with mutations in 1p36, one of the common areas of allelic loss in sporadic NB (17). Other cases may result from different hereditary-predisposition loci, now attributed to multiple different genetic aberrations. Chromosome 16p12–13 was identified as a likely predisposition locus, although no causal gene has been identified (18). NB has also been seen in several patients with constitutional chromosomal rearrangements, including deletions overlapping putative tumor suppressor loci at chromosome bands 1p36 and 11q14–23. NB has also been reported in patients with other neural crest disorders such as the Hirschsprung disease and central hypoventilation syndrome; these cases are associated with a germ-line mutation at chromosome 4p12 (*PHOX2B* gene) (19). More recently, multiple groups have identified the anaplastic lymphocyte kinase (*ALK*) gene as a predisposition gene in familial NB, and also frequently mutated in tumors from sporadic NB (20–22).

BIOLOGY

Cytogenetic and molecular studies in NB are providing new insights into its biology and prognosis. Unfavorable biologic features include amplification of *MYCN*, deletion or loss of heterozygosity of chromosome 1p or 11q, and gains at 17q, and favorable biologic features include hyperdiploidy and overexpression of Trk A (23–29). Recognizing these biologic pathways in NB has improved the ability to treat children with risk-based therapy and may lead to novel therapeutic approaches in the near future.

MYCN amplification was the first and is now the most widely accepted biologic marker of prognosis for NB (30,31). *MYCN* is in the family of *MYC* oncogenes that encode transcriptional regulatory factors involved in the control of other genes. The amplification is generally a consequence of an aberrant gain of multiple copies of the *MYCN* gene. Homogeneously staining regions (HSRs, nonbanding regions of metaphase chromosomes that stain homogeneously) and double-minute chromatin bodies (fragments of HSRs) are a manifestation of gene amplification (Fig. 6.3). They are derived from the distal short arms of chromosome 2, which contains the proto-oncogene *MYCN*. The excess number of *MYCN* genes leads to overexpression of the n-myc protein and subsequent overproduction of growth-promoting signals and stimulation of proliferation and tumorigenesis (23). Mice with aberrant overexpression of *MYCN* develop NB, providing evidence that *MYCN* plays a prominent role in NB development (32). *MYCN* amplification is most easily detected on fluorescent in situ hybridization of fresh tumor imprints, although it may also be tested by immunohistochemistry,

Southern blot, or polymerase chain reaction. Recent studies also show that circulating *MYCN* DNA can be detected in advanced-stage NB with *MYCN* amplification with a sensitivity of 75–85% (33).

Amplification of *MYCN* in primary NB has been shown to correlate with advanced stage and a poor prognosis. Such amplification occurs in 30–40% of advanced-stage NB but in only 5–10% of low-stage or 4S disease and not at all in benign ganglioneuromas (34). Children who have *MYCN* amplification in their tumor need more intensive or novel therapy to control the disease. *MYCN* usually is an independent prognostic factor such that amplification portends an unfavorable outcome, even in disease settings that would otherwise be favorable. *MYCN* amplification is seldom identified in localized stage disease (stage 1 and 2) but may predict a poor outcome in these patients when present (35). Amplification of *MYCN* is also uncommon in infants with stage 4S disease but predicts a less favorable survival (44% vs. 90%) (36). Amplified *MYCN* is more common in tumors from children older than 1 year with advanced stage and elevated ferritin, neuron-specific enolase, lactate dehydrogenase, and chromosome 1p deletion (34).

DNA ploidy is also an important discriminator of response to chemotherapy for NB. In a 1991 report, Look et al. (27) evaluated 298 children. In infants with metastatic disease, the progression-free survival (PFS) was more than 90% for those with hyperdiploid tumors and 0% in diploid cases. In children 12–24 months of age with stage D, the distinction was also striking (50–60% in hyperdiploid cases and 0% in diploid, $p < 0.001$). A subsequent Pediatric Oncology Group (POG) study of infants with unresectable or metastatic NB

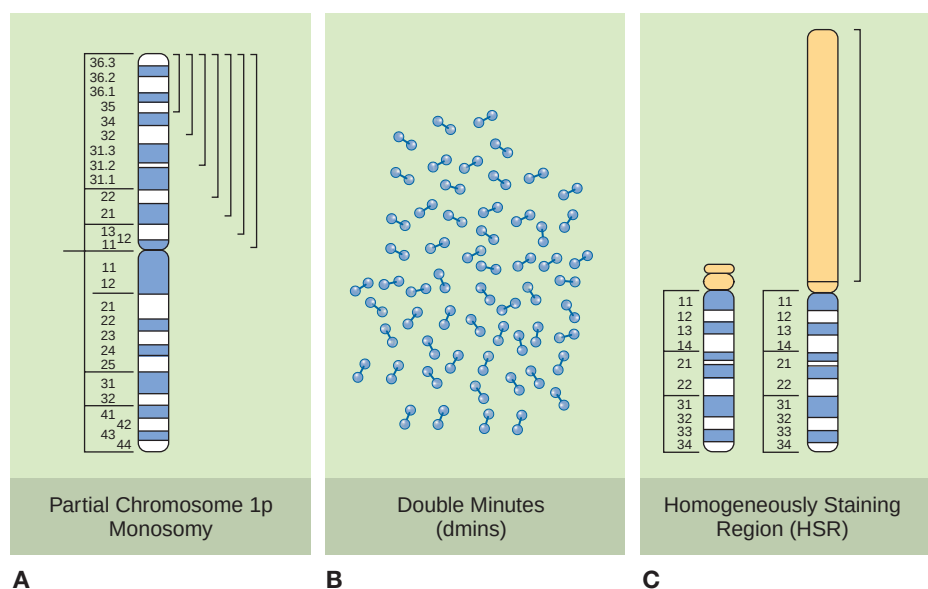


Figure 6.3 Common cytogenetic abnormalities in human neuroblastomas. Shown are diagrammatic representations of the three most common cytogenetic abnormalities seen in human neuroblastomas. **A:** Deletions of the short arm of chromosome 1. The brackets indicate that the region deleted in different tumors is variable in terms of its proximal breakpoint, but the distal short arm appears to be deleted in all cases, resulting in partial 1p monosomy. **B:** Extrachromosomal double-minute chromatin bodies (dmins). These are seen in about 30% of primary neuroblastoma and are a cytogenetic manifestation of gene amplification. **C:** Homogeneously staining region (HSR). A representative HSR on the short arm of chromosome 13 is shown in this example. HSRs are a cytogenetic manifestation of gene amplification in which the amplified sequences are chromosomally integrated. (From Bernstein ML, Leclerc JM, Bunin G, et al. A population-based study of neuroblastoma incidence, survival, and mortality in North America. *J Clin Oncol* 1992;10(2):323–329; and Powis MR, Imeson JD, Holmes SJ. The effect of complete excision on stage III neuroblastoma: a report of the European Neuroblastoma Study Group. *J Pediatr Surg* 1996;31(4):516–519, with permission.)

reported an overall 3-year survival of 94% for infants with hyperdiploid tumors and 55% for diploid (37). Hyperdiploid tumors also appear to counteract the unfavorable impact of *MYCN* amplification in low-stage tumors (28). Ploidy is probably less useful as a prognostic marker in children older than 24 months, in whom most tumors are diploid.

Specific chromosomal deletions often are present in NB. Deletion of the short arm of chromosome 1 occurs in 30–50% of primary tumors and usually lies at the distal end of chromosome 1 in the area of 1p36. Loss of chromosome 1p strongly correlates with *MYCN* amplification and is also associated with a poor prognosis. Loss of heterozygosity of 1p in tumors without *MYCN* amplification is an independent prognostic marker of outcome, although this prognostic value is lost in *MYCN*-amplified tumors (24).

Loss of heterozygosity has also been reported for chromosome 11q and is identified in nearly half of the NB samples analyzed. Unbalanced loss of chromosome 11q is associated with a worse prognosis and is inversely related to *MYCN* amplification (24). Chromosomal deletions may result in the loss of a suppressor gene. Several candidate genes for the NB suppressor gene have been mapped to 1p36 (38) and 11q; however, none have been shown to have mutations in the nondeleted allele. An alternative pathway for tumorigenesis from one of the candidate genes may relate to dosage effect, with the allelic loss causing a reduction in the level of an important protein.

Partial gains at chromosome 17q are another common genetic alteration and are associated with an adverse outcome. Gains on chromosome 17q have been linked to several prognostic factors: age greater than 1 year, advanced-stage disease, deletion of chromosome 1p, and amplification of *MYCN*. It is the most common genetic alteration found in NB, occurring in 50% of cases (39). In one study, patients with the gain of 17q had a 5-year relapse-free survival of 16%, compared with 75% in patients without this genetic alteration (25). Again, whether 17q gain is an important independent marker of prognosis must be verified in a larger prospective study.

In addition to gains and losses of genetic material, other genes that have been identified as prognostically important include nerve growth factor receptor expression, telomerase activity, and genes involved in invasion and metastasis. The neurotrophins and their receptors are important in nervous system development and hence NB tumorigenesis. Expression of Trk A and Trk C has been found to correlate with lower stage and the absence of *MYCN* amplification. Conversely, expression of Trk B correlates with amplification of *MYCN*. The balance of Trk expression may influence the spontaneous regression of NB or the differentiation into benign ganglioneuromas (40). High levels of telomerase activity may also predict an aggressive tumor phenotype. Integrins are also important in NB. The majority of NB tumors express high levels of *CD44*, except for tumors of advanced stage and *MYCN* amplification. Lack of *CD44* expression is strongly associated with *MYCN* amplification and, in multivariate analysis, is an independent predictor of overall survival (OS) (23). Another integrin, α V β 3, appears to be expressed predominantly in undifferentiated and high-risk NB (41), with an antiangiogenic integrin α V antagonist able to inhibit growth of NB in a syngeneic murine tumor model by working synergistically with an anti-GD2 antibody (42,43). The metalloproteinases *MMP2* (gelatinase A) and

MMP9 (gelatinase B) are expressed in primary NB tumors, with increased expression associated with more advanced stage and *MMP2* correlating with worse outcome (44). The angiogenic vascular endothelial growth factor has been found in both NB cell lines and primary tumors, with higher expression in high-risk disease (45).

PATHOLOGY

NB is one of the small blue round cell tumors, along with the non-Hodgkin lymphoma, the Ewing sarcoma, undifferentiated soft tissue sarcomas including rhabdomyosarcoma, and primitive neuroectodermal tumors. The classic histologic subtypes of neuroblastic tumors include NB, ganglioneuroblastoma, and ganglioneuroma, reflecting a pattern of increasing maturation and differentiation (46). The cells of NB are small and uniformly sized, with dense hyperchromatic nuclei and scant cytoplasm (Fig. 6.4). The cells may be densely packed, separated by thin fibrils or bundles, and necrosis and calcification can occur. Neuritic processes can be demonstrated in most cases, and pseudorosettes can be seen in 15–50% of cases. The other end of the spectrum, ganglioneuroma, has mature ganglion cells, neuritic processes, and Schwann cells and has more fibrillary material. Patients with ganglioneuroma or ganglioneuroblastoma generally have localized tumors with favorable biologic characteristics, explaining the excellent associated prognosis.

NB has a mixture of neuroblastic and mature ganglion cells and cells intermediate in their differentiation. Various immunohistochemical techniques and electron microscopy are used for diagnosis. Immunohistochemical stains recognize neuron-specific enolase (25), synaptophysin, chromogranin A, and neuronal filaments. Electron microscopy reveals neurofilaments, neurotubules, and neurosecretory granules that contain catecholamines.

The most widely accepted system of histologic classification is now the International Neuroblastoma Pathology Committee Classification (INPC) (47), summarized in Table 6.1. It is based on the highly prognostic system developed by Shimada et al. using patient age, the presence of stroma (“rich” or “poor”) and nodularity, the degree of differentiation, and the mitosis–karyorrhexis index (MKI) (48). Differences between the original Shimada classification (48) and the INPC are (1) to subdivide the “undifferentiated” subtype in the former classification into two subtypes of undifferentiated and poorly differentiated in the latter classification, based on the degree of cellular density and the number of tumor cells and MKI (Fig. 6.4); and (2) to change the name of “stroma-rich, well differentiated” in the former classification to “ganglioneuroma, maturing.” The INPC, based largely on the Shimada system, is now being used in protocols worldwide to facilitate comparisons of patient groups. A retrospective analysis of the Children’s Cancer Group (CCG) validated the prognostic value of this system combined with age (49). An additional modification in 2003 clarified the favorable and unfavorable subsets of ganglioneuroblastoma, nodular (50). Finally, by international consensus, it was shown that even if age were taken out of the INPC, diagnostic category, MKI, and grade of differentiation each had independent prognostic significance (29).

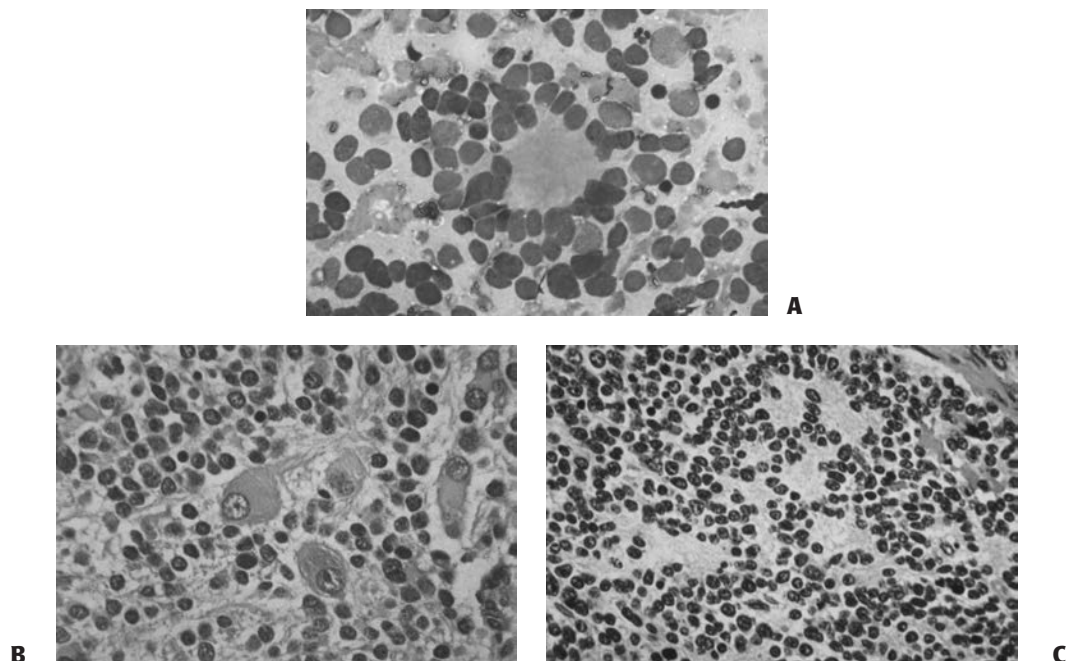


Figure 6.4 **A:** Fine-needle aspirate of neuroblastoma, showing typical Homer–Wright pseudorosettes with neurofibrillary material in the center. **B:** Differentiating neuroblastoma, Schwannian stroma-poor. **C:** Neuroblastoma (Schwannian stroma-poor), poorly differentiated subtype, composed of undifferentiated neuroblastic cells with clearly recognizable neuropil. (From Shimada H, Ambros IM, Dehner LP, et al. Terminology and morphologic criteria of neuroblastic tumors: recommendations by the International Neuroblastoma Pathology Committee. *Cancer* 1999;86(2): 349–363, with permission.) (See color plate.)

Table 6.1			
International Neuroblastoma Pathology Committee System			
Prognostic Evaluation of Neuroblastic Tumors According to the International Neuroblastoma Pathology Classification (Shimada System)			
International Neuroblastoma Pathology Classification		Original Shimada Classification	Prognostic Group
Neuroblastoma Favorable <1.5 years	(Schwannian stroma-poor) ^a Favorable Poorly differentiated or differentiating and low or intermediate MKI tumor	Stroma-poor	Favorable
1.5–5 years Unfavorable <1.5 years	Differentiating and low MKI tumor (a) Undifferentiated tumor ^b (b) High MKI tumor	Unfavorable	Unfavorable
1.5–5 years ≥5 years	(a) Undifferentiated or poorly differentiated tumor (b) Intermediate or high MKI tumor All tumors		
Ganglioneuroblastoma, intermixed	(Schwannian stroma-rich)	Stroma-rich intermixed (favorable)	Favorable ^c
Ganglioneuroma Maturing	(Schwannian stroma-dominant)	Well differentiated (favorable)	Favorable ^c
Mature Ganglioneuroblastoma, nodular	(Composite Schwannian stroma-rich/ stroma-dominant and stroma-poor)	Ganglioneuroma Stroma-rich nodular (unfavorable)	Unfavorable ^c

^aSubtypes of neuroblastoma were described in detail elsewhere.

^bRare subtype, especially diagnosed in this age group. Further investigation and analysis required.

^cPrognostic grouping for these tumor categories is not related to patient age.

MKI: mitosis-karyorrhexis index; high is >200 per 5000 cells.

From Shimada H, Ambros IM, Dehner LP, et al. The International Neuroblastoma Pathology Classification (the Shimada system). *Cancer*. 1999;86(2):364–372, with permission.

CLINICAL PRESENTATION AND EVALUATION

The clinical presentation of NB depends on the site along the sympathetic nervous system chain from which the primary tumor develops (Fig. 6.2) and on the manifestations of metastatic disease. This varies according to patient age. The abdomen is the most common primary tumor location (50–80% of cases). Intra-abdominal primary tumors arise in the adrenals or in a paraspinal location. The paraspinal tumors may have a dumbbell configuration wherein tumor extends through the neural foramina and presents with a mass lesion in the spinal canal; extradural spinal cord compression may occur (51,52). Extra-abdominal locations of the primary tumor include sympathetic ganglia in the neck (often initially thought to be lymphadenitis), posterior mediastinum, and pelvis.

The earliest symptoms or signs of NB may be a palpable abdominal mass (often large, firm, irregular, and crossing the midline), a unilateral neck mass often causing the Horner syndrome, spinal cord compression, respiratory compromise caused by thoracic disease or hepatic metastases placing upward pressure on the diaphragm, or bowel and bladder disturbances caused by compression from a pelvic mass. About 60% of children with NB have metastatic disease (either lymphatic or hematogenous) at the time of clinical presentation. The symptoms in this setting are those of systemic illness: fever, weight loss, weakness, or a general failure to thrive. In a few patients, the presenting symptoms are related to secretory products of the tumor. For example, intractable diarrhea (from vasoactive intestinal polypeptide) may rarely occur, usually in children with ganglioneuroblastoma or ganglioneuroma. In another rare paraneoplastic syndrome, seen in about 3% of patients, a child with NB presents with the opsoclonus (rapid multidirectional eye movements)–myoclonus–truncal ataxia syndrome. This paraneoplastic syndrome is associated with early-stage NB; it is probably caused by development of antineuronal antibodies, and neurologic deficits usually persist despite cure of the tumor (53,54). Bone metastases present as pain, refusal to walk, skull masses, or proptosis with orbital ecchymosis. Skin metastases are common in neonates and generally have a blue tinge (the “blueberry muffin” sign). When a skin metastasis is manually compressed, one may observe blanching of the surrounding skin secondary to liberation of vasoconstrictive catecholamine. NB may infiltrate the marrow and cause pancytopenia with resulting complications (infection, pallor, lethargy, bleeding). Intracranial metastatic disease usually is meningeal, and in infants it may cause cranial suture separation.

The standard diagnostic evaluation of NB (Table 6.2) includes imaging and laboratory testing with the goals of determining disease extent and prognosis and identifying markers of disease activity. The primary tumor typically is imaged radiographically and with computed tomography (CT) scan or magnetic resonance imaging (MRI). The classic radiographic sign of adrenal NB is calcification in a suprarenal soft tissue mass. In the thorax, a plain radiograph demonstrates a posterior mediastinal mass. In both abdomen and chest, CT scan

Table 6.2

Clinical Evaluation of Neuroblastoma (International Neuroblastoma Staging System's Minimum Recommended Studies to Determine the Extent of Disease)

Tumor Site	Tests
Primary	CT, ultrasound, or MRI with 3D measurements
Metastases	Bilateral posterior iliac bone marrow aspirates and core biopsies (four adequate specimens necessary to exclude tumor) Bone radiographs and scintigraphy by ^{99m}Tc -diphosphonate, with or without ^{131}I -MIBG or ^{123}I -MIBG Abdominal and liver imaging by CT, ultrasound, or MRI Chest radiograph (anteroposterior and lateral) and chest CT
Markers	Urinary catecholamine metabolites (vanillylmandelic acid and homovanillic acid)

CT, computed tomography; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging.

From Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol*. 1993;11(8):1466–1477; and Brodeur GM, Seeger RC, Barrett A, et al. International criteria for diagnosis, staging, and response to treatment in patients with neuroblastoma. *J Clin Oncol*. 1988;6(12):1874–1881, with permission.

and MRI are helpful in assessing possible lymph node metastases and intraspinal extension (55).

The search for distant, usually bony metastasis must include scanning with ^{123}I -metaiodobenzylguanidine (MIBG) or a technetium (Tc) radionuclide bone scan (for patients whose tumor does not take up MIBG), with conventional radiographs as indicated. Bone metastases are most often peri-orbital, metaphyseal, and axial in location (Fig. 6.5). Bone scintigraphy is more sensitive than conventional radiographs but is sometimes difficult to interpret in infants younger than 1 year. MIBG is a guanethidine derivative that is similar in structure to norepinephrine and epinephrine. The compound is taken up via the norepinephrine transporter into catecholaminergic cells and stored in the chromaffin granules. It is highly sensitive and specific for skeletal and soft tissue metastases of NB, taken up in more than 90% of primary and metastatic tumors (56). The MIBG is labeled with ^{123}I and scintigraphy is performed for imaging. Because MIBG depends on functional uptake by tumor cells, it is also useful in distinguishing residual active tumor after treatment from masses composed of scar tissue and may complement CT scans (Fig. 6.6) (56). More recently, early response by MIBG scan has been shown to be a useful prognostic marker of response and survival (57). ^{99m}Tc -diphosphonate bone scans continue to be used to detect metastatic foci in the skeleton, in patients who are negative by MIBG. Positron emission tomography scans with ^{18}F -fluorodeoxyglucose are a newer modality that may



Figure 6.5 Femoral metastases from neuroblastoma.

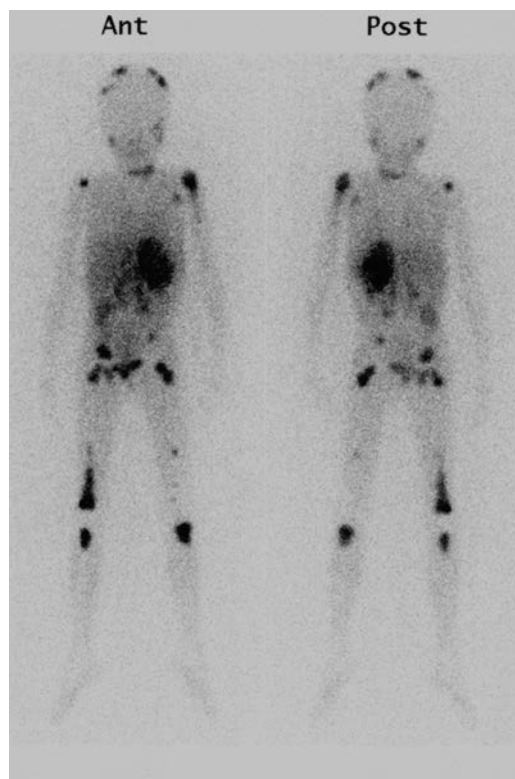
complement MIBG for determination of tumor viability. Several studies have demonstrated that positron emission tomography scanning can visualize NB, even in some cases where MIBG is negative, although in other cases the converse is true (58–60).

Liver involvement may be evaluated by CT, ultrasound, or MIBG or PET scan in older children because it is usually focal or nodular. In infants it may be diffuse and not apparent by imaging. For this reason, some authorities recommend liver biopsies for diagnostic workup of infants. Pulmonary parenchymal metastases rarely occur at diagnosis in NB, although at relapse they may be seen in 7% of cases and should be sought with CT scan (61). At diagnosis, lung metastases are associated with *MYCN* amplification and high lactic dehydrogenase (LDH), and predict a worse outcome (62).

There may be extensive involvement of the bone marrow by tumor without a change in the peripheral blood counts, with some bone marrow tumor present at diagnosis in 80–90% of children with metastatic disease (61). Therefore, bilateral bone marrow aspiration and biopsy are performed routinely, with some centers using 4–10 core biopsies to minimize sampling error. Small amounts of NB cells may be difficult to distinguish from hematopoietic elements. The diagnosis of NB in the bone marrow can be confirmed when only small amounts of tumor are present with immunohistochemical stains on the core biopsy, often using neuron-specific enolase (NSE) as a marker, or with immunostaining on a concentrated cytology specimen from the aspirate. This technology clearly is more sensitive than conventional analyses, detecting one tumor cell per 10^5 to 10^6 normal mononuclear marrow cells. The extent of tumor involvement detected by immunocytology at diagnosis in marrow or peripheral blood provides prognostic information (63,64). At present, tumor detected by immunocytology that is not extensive enough to be diagnosed by conventional bone marrow microscopy does not affect staging (55). Reverse transcriptase polymerase chain



A



B

Figure 6.6 A 4-year-old boy presented with fever, abdominal pain, and leg pain. **A:** The computed tomography scan shows a large retroperitoneal neuroblastoma that encases the abdominal aorta and displaces the inferior vena cava. The left kidney is pushed laterally, and calcifications are evident. **B:** This ^{123}I -metaiodobenzylguanidine scan shows intense localization in the primary retroperitoneal mass. Widespread bone metastases are evident, with large lesions in the distal right femur and proximal left humerus, but multiple other lesions are seen on the dome of the skull, right humerus, right rib, pelvis, and both femurs and tibias, and in a few retroperitoneal areas, probably representing nodal spread. Physiologic uptake is seen in the salivary glands, liver, and thyroid gland, which was insufficiently blocked with potassium iodide drops.

reaction (RT-PCR) is being used in a number of prospective studies to further quantify the prognostic impact of minimal residual disease (MRD) detected in blood or bone marrow (65,66). Standardized methods for both immunocytology and RT-PCR have been agreed upon by international consensus (67).

NB is associated with elevated or abnormal production, secretion, and catabolism of catecholamines (or metabolites) in 90% of cases. Catecholamines and metabolites may be

measured in the urine: norepinephrine, VMA, 3-methoxy-4-hydroxyphenylglycol, or HVA. Dopamine may be measured in urine or serum. Urinary catecholamines typically are presented as ratios to urinary creatinine. The symptoms associated with excess catecholamine production include flushing and sweating, pallor, headache, and hypertension.

STAGING AND PROGNOSTIC FACTORS

The criteria for diagnosis of NB recommended by the second International Neuroblastoma Staging System (INSS) Conference are unequivocal pathologic diagnosis from tumor tissue by light microscopy, with or without immunohistology, electron microscopy, elevated urine or serum catecholamines or metabolites (dopamine, HVA, or VMA greater than 3.0 SD above the mean per milligram creatinine for age); or bone marrow aspirate or biopsy containing unequivocal tumor cells (e.g., syncytia or immunocytoologically positive clumps of cells) and elevated urine or serum catecholamines or metabolites (55). A diagnosis of NB based only on compatible radiographic findings and elevated urinary catecholamine metabolites is insufficient because of possible confusion with ganglioneuroma or pheochromocytoma or even other solid tumors (e.g., primitive neuroectodermal tumor, rhabdomyosarcoma), which can have false positive urinary findings.

Staging

Four systems, summarized in Evans et al. (68), have been used in previous years for the staging of NB: the international tumor, node, and metastasis system (rarely used in pediatric tumors); the definition by Evans et al. adopted by the CCG; the surgical staging system of St. Jude's; and the modification adopted by the POG. Subsequent to 1993, most investigators have used the system internationally developed in 1989 and modified in 1993, the INSS (Table 6.3A), in an attempt to improve and unify the previous definitions (55). Most recently, a further modification was introduced by consensus of the International Neuroblastoma Risk Group (INRG) Task Force (69). Understanding the nuances of these systems is important for interpreting and accurately comparing data from various reports and determining therapy.

The INSS was developed in order to have a uniform staging so that studies could be compared, and tried to merge the prior systems of the CCG (Evans) and POG (Table 6.3A). In classifying tumors that cross the midline, infiltration (extending by contiguous invasion to or beyond the opposite side of the vertebral bodies) was chosen to identify tumors presumably less favorable than those that are pedunculated and simply drape over the midline (Table 6.3B). The INSS used Arabic numbers to distinguish it from the letters and Roman numerals of the prior systems. However, some inconsistencies were noted due to the fact that it was a postsurgical staging system with substantial reliance on the assessment of tumor resectability and surgical examination of lymph node involvement. In fact, many patients with stage 3 disease do not actually undergo surgical resection at diagnosis, and many stage 2 patients do not have extensive lymph node sampling, resulting in possibly inaccurate staging. Furthermore, the separation of stage 2A and 2B depending on lymph node involvement is of questionable prognostic value for OS (70). Therefore, four further international conferences were held from 2004 to 2006, and a new international staging system was proposed by the INRG task force in which anatomic staging was performed by

Table 6.3 A:
International Neuroblastoma Staging System

Stage	Definition
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically
2A	Localized tumor with incomplete gross excision; representative ipsilateral lymph nodes negative for tumor microscopically
2B	Localized tumor with or without complete gross excision, with ipsilateral lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically
3	Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or lymph node involvement
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, and other organs (except as defined for stage 4S)
4S	Localized primary tumor (as defined as stage 1, 2A, or 2B), in patient <1 year, with dissemination limited to skin, liver, or bone marrow (marrow involvement should be minimal with malignant cells <10% of total nucleated cells)

Based on Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol*. 1993;11(8):1466-1477; and Brodeur GM, Seeger RC, Barrett A, et al. International criteria for diagnosis, staging, and response to treatment in patients with neuroblastoma. *J Clin Oncol*. 1988;6(12):1874-1881.

Table 6.3 B:
International Neuroblastoma Risk Group (INRG) Staging System

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow (< 10%)

From Monclair T, Brodeur GM, Ambros PF, et al. The International Neuroblastoma Risk Group (INRG) staging system: an INRG task force report. *J Clin Oncol*. 2009;27(2):298-303, with permission.

radiologic imaging, rather than surgery. In the INRGSS (International Neuroblastoma Staging System), locoregional tumors are staged L1 or L2 based on the absence or presence of 1 or more of 20 image-defined risk factors (IDRFs) (71), respectively. Metastatic tumors are defined as stage M, except for stage MS, in which metastases are confined to the skin, liver, and/or bone marrow in children younger than 18 months of age. Within the 661-patient cohort, IDRFs were present (i.e., stage L2) in 21% of patients with INSS 1, 45% of patients with INSS 2, and 94% of patients with INSS 3 disease. Patients with INRGSS stage L2 disease had significantly lower 5-year event-free survival than those with INRGSS stage L1 disease ($78\% \pm 4\%$ vs. $90\% \pm 3\%$; $p = 0.0010$) (69).

International Neuroblastoma Response Criteria (INRC) from the first international conference are still generally used, shown in Table 6.4, which takes into account some of the unique characteristics of this tumor, such as MIBG uptake,

Table 6.4 International neuroblastoma Response Criteria		
Response	Primary Tumor	Metastatic Sites
CR	No tumor.	No tumor; catecholamines normal.
VGPR	Decreased by 90–99%.	No tumor; catecholamines normal; residual ^{99}Tc bone changes allowed.
PR	Decreased by >50%.	All measurable sites decreased by >50%. Bones and bone marrow: number of positive bone sites decreased by >50%, no more than 1 positive bone marrow site allowed.
MR	No new lesions; >50% reduction of any measurable lesion with <50% reduction in any other; <25% increase in any existing lesion.	
NR	No new lesions; <50% reduction but <25% increase in any existing lesion.	
PD	Any new lesion; increase of any measurable lesion by >25%; previous negative marrow positive for tumor.	

CR, complete remission; VGPR, very good partial response; PR, partial response; MR, mixed response; NR, no response; PD, progressive disease.

Based on Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol*. 1993;11(8):1466–1477.

catecholamine excretion, and propensity for bone and bone marrow involvement. This is currently the best accepted method for reporting response to treatment, which supplements the National Institutes of Health criteria generally used for evaluating response in phase I and II studies, the Response Evaluation Criteria in Solid Tumors Group (72). As recurrence in NB is most often in metastatic sites in bone and bone marrow, it is critical to be able to evaluate response in these sites in addition to solid masses. To improve the quantization of response in bone sites, a semi-quantitative MIBG score is now used (56).

Prognostic Factors

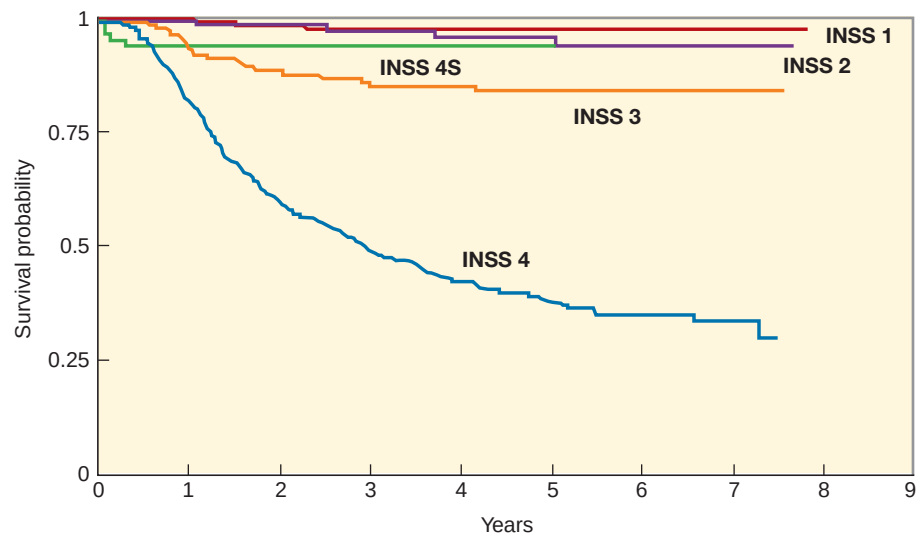
Several clinical and biologic characteristics of NB are associated with prognosis. Various cooperative groups and investigators have attempted to select certain variables and group them to identify patients with good, intermediate, or bad prognoses. The differences in various studies probably result from differences such as patient characteristics, treatment, study endpoints. As detailed genomic data are accumulated and interpreted, genetic subsets of NB that reflect clinical behavior are being identified (24,34,73,74). A study of an international database of 8800 NB patients by the INRG showed that patients could be stratified into four different risk groups for 5-year event-free survival (EFS) using age, stage, histologic category, grade of differentiation, MYCN, 11q aberration, and ploidy. The lowest group had an estimated 5-year EFS greater than 85%, while the highest risk group had an EFS below 50% (29). However, for current practical risk stratification on cooperative clinical trials, the most useful and independent variables are stage, age, histology, ploidy, MYCN copy number, and loss of heterozygosity for 1p or 11q. The prognostic values of histology, ploidy, and genetic aberrations have already been discussed above.

Clinical

Stage and age continue to be extremely important determinants of outcome, as originally reported by Breslow and McCann (75). The disease stage strongly influences prognosis (Fig. 6.7). With surgery as primary therapy, more than 90% of children with stage 1 and 2 disease survive and 85% of children with stage 4S survive, whereas with multimodality therapy, the survival is 60–90% for INSS stage 3 disease but only 40% for stage 4 disease (70,76–79). However, age at diagnosis is another strong determinant of outcome, which must be factored in with stage. Originally 12 months was recognized as the cut-off for a favorable outcome, even in advanced disease, but more recently it has been shown that this can be extended to 18 months as long as the biology of the tumor is favorable. Infants younger than 18 months of age do better than older children with the same disease stage, an effect that is dramatic for patients with advanced stage 3 and 4 disease (37,76,80–83). Infants and toddlers without MYCN gene amplification and with stage 4 disease have more than 80% long-term survival with modest chemotherapy, whereas children older than 18 months at diagnosis with stage 4 have less than 40% survival with very intensive therapy. This may be related to a higher rate of spontaneous tumor regression or tumor maturation in infants (84). On the other hand, adults and adolescents with NB have a particularly poor long-term survival, even with disease presenting without metastases, although their course may be prolonged (85,86).

Initial response to therapy is another important clinical prognostic factor for patients with advanced disease. Thus, early response by MIBG scan after two to four cycles of induc-

Figure 6.7 Overall survival according to International NB Staging System (INSS) stage of 1034 children with neuroblastoma treated on Children's Cancer Group protocols from 1991 to 1995. INSS stage 1, $n = 195$; INSS stage 2, $n = 117$; INSS stage 3, $n = 184$; INSS stage 4S, $n = 64$; INSS stage 4, $n = 474$. (Courtesy of the Children's Cancer Group Statistical Office.)



tion therapy for stage 4 disease has been shown to correlate with event-free survival (87). In addition, response at the end of induction therapy, prior to myeloablative consolidation is also prognostic of EFS (88–90).

Biologic

Several nonspecific inflammatory serum markers have prognostic value in NB, including ferritin, LDH, and neuron-specific enolase (NSE). All the three are more likely to be elevated in advanced disease and are predictive of a worse outcome in univariate analysis. Ferritin may be produced by NB cells and thus reflects tumor burden or growth, or it may be necessary for NB cell growth. An elevated serum ferritin level (more than 143 ng/mL) is found in up to half of patients with advanced-stage disease but rarely in children with localized disease. PFS is lower for children with elevated levels (91). Neuron-specific enolase is a glycolytic enzyme found in neurons; serum levels greater than 100 ng/mL are associated with lower survival (92). Neuron-specific enolase may be useful as a marker for following the response to treatment. LDH may reflect tumor cell burden or turnover, and serum elevations (750–1500 IU/mL) have been found in some studies to be independently associated with a worse prognosis (93).

Two neural markers found in the serum of NB patients may also be markers of disease activity and prognosis. Ganglioside GD2 is a sialic acid-containing glycosphingolipid found mainly in the cell surface membrane of >95% of NB tumors. Elevated circulating levels may be another marker of disease activity and response to treatment (favorable prognosis level is less than 103 pmol/mL; unfavorable prognosis level is greater than 568 pmol/mL) (94). Chromogranin A is an acidic protein co-stored and co-released with catecholamines from storage vesicles. Its serum concentration is elevated in patients with peptide-producing endocrine neoplasia. The survival rate for patients with lower serum chromogranin A levels (less than 190 ng/mL at the time of diagnosis) was 69%, whereas it was 30% for those with higher chromogranin A levels (95).

In summary, numerable clinical, biochemical, and genetic risk factors have been shown to have prognostic value

in various studies, but the recent multivariate analysis by the INRG has shown that for practical purposes patients can be effectively placed into risk groups for therapeutic assignment using the readily available clinical and genetic factors. Those that have appeared to be consistent over many years and readily available to the clinician have been combined to form a framework for risk stratification in current therapeutic studies. Age, INSS stage, histopathology, tumor cell ploidy, MYCN gene copy number, LOH 1p and 11q are the factors used in risk stratification and therapy assignment for the current COG clinical trials in North America, with very similar guidelines used internationally (Table 6.5). The survival for low-risk patients by this classification is more than 90%, that of intermediate-risk patients is more than 80%, and that of the high-risk group remains at about 30–40% (Fig. 6.8).

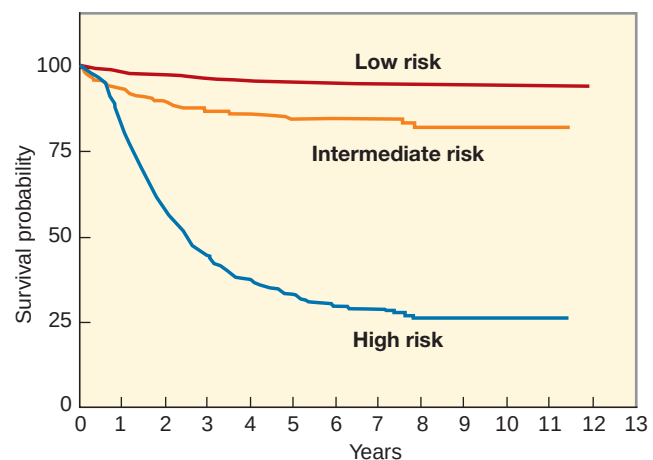


Figure 6.8 Survival in 2196 consecutive patients with neuroblastoma treated on Children's Cancer Group and Pediatric Oncology Group protocols according to clinical risk groups (Table 6.5) assigned according to International Neuroblastoma Staging System stage, age, histopathology, MYCN copy number, and DNA ploidy. Low risk, $n = 916$; intermediate risk, $n = 431$; high risk, $n = 849$. (Courtesy of the Children's Oncology Group Statistical Office.)

Table 6.5 A:**Children's Oncology Group Neuroblastoma Risk Groups for Treatment**

International neuroblastoma staging system	Age (Days)	MYCN	Histology	Ploidy	Risk
1	Any	Any	Any	Any	Low
2A/2B	Any	Nonamplified	Any	Any	Low
	Any	Amplified	Any	Any	High
3	<547	Nonamplified	Any	Any	Intermediate
	Any	Amplified	Any	Any	High
	≥547	Nonamplified	Favorable	—	Intermediate
	≥547	Nonamplified	Unfavorable	—	High
	≥365 < 547	Nonamplified	Any	Any	Intermediate
4	<547	Nonamplified	Any	Any	Intermediate
	Any	Amplified	Any	Any	High
4S	<365	Nonamplified	Favorable	DI > 1	Low
	<365	Nonamplified	Favorable	DI = 1	Intermediate
	<365	Nonamplified	Unfavorable	Any	Intermediate
	<365	Amplified	Any	Any	High

Aberrations of 1p and 11q may be additionally used to adjust therapy intensity, but do not change intermediate-risk patients to high-risk group for outcome.

DI, DNA index.

Table 6.5 B:**INRG Risk Classification**

INRG Stage	Age (Months)	Histologic Category	Grade of Tumor Differentiation	MYCN	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	<18	Any, except GN maturing or GNB		NA	No		D Low
					Yes		G Intermediate
			Differentiating	NA	No		E Low
	≥18	GNB nodular; Neuroblastoma			Yes		
			Poorly differentiated or undifferentiated	NA			H Intermediate
				Amp			N High
M	<18			NA		Hyper-diploid	F Low
	<12			NA		Diploid	I Intermediate
	12 to <18			NA		Diploid	J Intermediate
	<18			Amp			O High
	≥18						P High
MS					No		C Very low
				NA			
	<18				Yes		Q High
				Amp			R High

From Cohn SL, Pearson AD, London WB, et al. The International Neuroblastoma Risk Group (INRG) classification system; an INRG task force report. *J Clin Oncol*. 2009;27(2):289–297, with permission.

SELECTION OF THERAPY

Low-risk tumors are managed with surgery alone unless symptomatic cord compression or respiratory compromise necessitates a short course of chemotherapy. Patients in the low-risk group with stage 1 or 2 disease have an expected 4-year survival of more than 95% with surgery only (70,96), whereas infants with INSS 4S have more than 90% survival with supportive care or a short course of chemotherapy (77). The smaller intermediate-risk group consists of infants and toddlers with stage 4 disease (but no tumor *MYCN* amplification), favorable biology stage 3, or INSS 4S with unfavorable histology or DNA index. Patients in this group are expected to have an estimated survival of more than 80% with moderate dosages of chemotherapy for 4–8 months and primary tumor resection. Radiotherapy (RT) is rarely used in the low- or intermediate-risk groups because of their favorable prognosis and the fact that many of these patients are younger than 1 year. It is reserved for use in life- or function-threatening situations. It is occasionally needed for cases of unresectable primary disease remaining after chemotherapy or regional recurrences not controlled with chemotherapy.

The high-risk group in NB consists primarily of patients with stage 4 disease who are more than 1 year old at diagnosis but also includes stage 3 with either tumor *MYCN* amplification or those older than 1 year with unfavorable histopathology, stage 2 above 1 year of age with *MYCN* amplification, and stage 3, 4, and 4S infants with *MYCN* gene amplification. Despite the use of increasingly aggressive combined-modality treatments, which have higher remission rates and durations, the long-term survival for INSS stage 4 disease in children who are older than 18 months at diagnosis has remained less than 15% until the early 1990s. The most recent phase III studies indicate that the 3-year EFS of this group has increased in the past decade to 30–40% with the use of myeloablative therapy and treatment for MRD but is still far below the desired outcome (79,90,97). Therapy for high-risk NB is divided into three phases: intensive induction treatment, marrow ablative therapy, and management of MRD. The goal of induction therapy is to achieve maximum reduction of tumor burden, including reduction of bone marrow tumor (in vivo purging), within a timeframe that will minimize the risk of resistant tumor clones and clinical progression. During or at the end of this phase, local control of bulky disease is accomplished with delayed surgery and local RT, which may be given either before or after myeloablative therapy. Subsequently, very high-dose marrow ablative therapy may be used to try to overcome residual and potentially resistant tumor, followed by hematopoietic cell transplant (HCT). The relapse rate of more than 40% even after such treatment (98) has led to the approach of using tumor-targeted therapies after myeloablative treatment to try to eliminate microscopic resistant clones (minimal residual disease).

Chemotherapy

As indicated earlier, chemotherapy is used in low-risk disease only for recurrence or for symptomatic patients with compromised organ function. Intermediate-risk patients can achieve long-term survival with moderate combination chemotherapy for 4–8 months (76,82). The most effective induction regimens for obtaining complete or partial response are combination of platinum-based regimens including other active

drugs such as cyclophosphamide, doxorubicin, etoposide, vincristine, and ifosfamide. Induction regimens used in recent large cooperative studies are shown in Table 6.6, with overall response rates generally ranging from about 60% to 80% at the end of 5–6 months of treatment. Most recently, the COG has incorporated two cycles of topotecan with cyclophosphamide into the N7 type induction, with similar response rates and successful peripheral blood stem cell harvests. The European group has tested a dose-intensive schedule in a randomized trial of 262 patients that randomly assigned 132 patients to standard and 130 patients to rapid treatment. The relative dose intensity of the rapid regimen was 1.94 compared with the standard regimen. Myeloablation was given a median of 55 days earlier in patients assigned to the rapid regimen. Although OS did not differ, the 5-year EFS was 18.2% in the standard group and 30.2% in the rapid group, representing a difference of 12.0% (1.8–22.3), $p = 0.022$ (104). However, the EFS in this study is apparently not different from other recent protocols using less dose intensive regimens. Most of these regimens also include surgery for residual disease, although the overall impact of complete resection on survival in stage 4 disease is still contradictory. Some newer single agents have also been effective in newly diagnosed NB, using the “upfront phase II window” approach. After two courses of single-agent therapy before induction treatment, response rates for effective agents (more than 30% response) were easily detectable, including ifosfamide, carboplatin, iproplatin (99), and topotecan (105). Two agents that were less effective in this setting were epirubicin and paclitaxel. There was no evidence that such a design adversely affected the subsequent outcome of patients when compared with the outcome of patients treated with similar induction without the phase II window.

Myeloablative Therapy with Hematopoietic Stem Cell Support

Myeloablative high-dose chemotherapy with or without total body irradiation (TBI) has been incorporated as consolidation treatment for high-risk NB for the past two decades, beginning with early studies using melphalan ablation. Numerous single-arm studies using varying myeloablative regimens from 1985 to about 1995 showed an apparent improvement in EFS, usually reported from the time of transplantation. The 3-year EFS ranged from 26% to 62%, with an average of about 40% for the large studies (more than 20 patients) shown in Table 6.7 (89,98,106–109, 111,113,114). This approach introduced some bias into the interpretation of results because only patients who survived for 5–6 months and responded to induction chemotherapy were able to receive the high-dose myeloablative treatment with autologous or allogeneic transplantation.

Several retrospective comparisons of concomitant and similar groups of patients treated with standard dosages of chemotherapy and those treated with high-dose therapy and autologous bone marrow transplantation (ABMT) have been performed, with conflicting assessments of the value of myeloablative therapy. The CCG-treated children with high-risk NB either with monthly cycles of four-drug chemotherapy over 1 year or, at investigator discretion, with myeloablative therapy with cisplatin, etoposide, melphalan, and TBI followed by purged ABMT. In a retrospective nonrandomized comparison of ABMT and traditional chemotherapy, EFS of patients who were progression free at 8 months from diagnosis

Table 6.6

Induction Regimens for High-Risk neuroblastoma Since 1985 (More than 50 Patients)

Group and Reference	Year	Regimen	N	CR + PR (%)
Pediatric Oncology Group 8742, regimen 1 (99)	1987–1991	Days 1–5, CDDP 40 mg/m ² /day Days 2–4, VP16 100 mg/m ² /day This alternates q21 days with Days 1–7, CPM p.o. 150 mg/m ² /day Day 8, DOX 35 mg/m ²	111	77
Pediatric Oncology Group 8742, regimen 2 (99)	1987–1991	Day 1, CDDP 90 mg/m ² Day 2, VP16 100 mg/m ² Days 3–10, CPM 150 mg/m ² /day p.o. Day 11, DOX 35 mg/m ² Repeat q21 days	115	68
SFOP CADO/PE (100)	1987–1992	Days 1–5, CPM 300 mg/m ² /day Days 1 and 5, VCR 1.5 mg/m ² /day Day 5, DOX 60 mg/m ² /day Alternates q21 days for 2 cycles each with Days 1–5, CDDP 40 mg/m ² /day Days 1–5, VP16 100 mg/m ² /day	183	64
Study Group of Japan (101)	1985–1997	Day 1, CPM 1200 mg/m ² , VCR 1.5 mg/m ² Day 3, THP-ADR 40 mg/m ² Day 5, CDDP 90 mg/m ² Repeat q28 days × 6 cycles	168	92
Children's Cancer Group 3891 (90)	1991–1996	Day 1, CDDP 60 mg/m ² Day 3, DOX 30 mg/m ² Days 3 and 6, VP16 100 mg/m ² /day Days 4 and 5, CPM 900 mg/m ² /day Repeat q28 days × 5 cycles	539	78
Memorial Sloan–Kettering Cancer Center (102)	1990–2002	<u>CYCLES 1,2,4,6</u> Days 1 and 2, CPM 70 mg/kg/day Days 1–3, VCR 0.1 mg/kg/day Days 1–3, DOX 25 mg/m ² /day	90	96
N6		<u>CYCLES 3,5,7</u> Days 1–3, CDDP 50 mg/m ² /day Days 1–3 VP16 200 mg/m ² /day		
French Society of Pediatric Oncology (SFOP)	1998–1999	<u>CYCLES 1,2,4,6</u> Days 1 and 2, CPM 70 mg/kg/day Days 1–3, VCR 0.067 mg/kg/day Days 1–3, DOX 25 mg/m ² /day	48	43
NB97 (103)		<u>CYCLES 3,5,7</u> Day 1–3, CDDP 50 mg/m ² /day Day 1–3 VP16 200 mg/m ² /day		CR/VGPR
ENSG/Children's Cancer and Leukemia Group (CCLG) (104)	1990–1999	<u>Standard timing (OPEC–OJEC);</u> <u>cycles q21 days</u> <u>OPEC CYCLES 1,3,5,7</u> Day 1, VCR 1.5 mg/m ² , CDDP 80 mg/m ² , VP16 200 mg/m ² , CPM 600 mg/m ² <u>OJEC CYLES 2,4,6</u> Day 1 VCR 1.5 mg/m ² , CaP 500 mg/m ² , VP16 200 mg/m ² , CPM 600 mg/m ² <u>Rapid timing (COJEC) cycles q10 days</u> <u>CYCLE 1, 5</u> Day 1 VCR 1.5 mg/m ² , CaP 750 mg/m ² , VP16 350 mg/m ² <u>CYCLE 2,4,6,8</u> Day 1 VCR 1.5 mg/m ² , CDDP 80 mg/m ² <u>CYCLE 3,7</u> Day 1 VCR 1.5 mg/m ² , VP16 350 mg/m ² , CPM 2100 mg/m ² Day 2 CPM 2100 mg/m ²	109	62
			82	CR/VGPR
				72 CR/VGPR

VCR, vincristine; VP16, etoposide; CDDP, cisplatin; CaP, carboplatin; DOX, doxorubicin; CPM, cyclophosphamide.

Table 6.7**EFS for High-Risk Neuroblastoma in First Remission Using Myeloablative Therapy and Hematopoietic Cell Transplant for Studies of More than 20 Patients**

Reference	Regimen	N	Toxic Death	3-Year EFS (%)
106	Melphalan, TBI	54	7	32
107	Cisplatin, VM-26, doxorubicin, melphalan, TBI	45	7	42
	Cisplatin, VP16, melphalan, TBI	54	5	50
	Carboplatin, VP16, melphalan, TBI	48	4	41
108	Vincristine, melphalan, TBI	62	13	30
109	Vincristine, melphalan, TBI	34	1	29
110	Etoposide, melphalan or cisplatin, etoposide, THP-adriamycin, melphalan, with (n = 6) or without TBI	31	3	50
111	Melphalan with or without VP16, vincristine, cisplatin, BCNU	39	7	35
89	European Bone Marrow Registry Data	439	60	24 (5-year EFS)
90	Carboplatin, VP16, melphalan, TBI	129	12	43%
112	Busulfan, melphalan	116	7	47%

Unless otherwise stated, event-free survival (87) measured from time of transplantation.

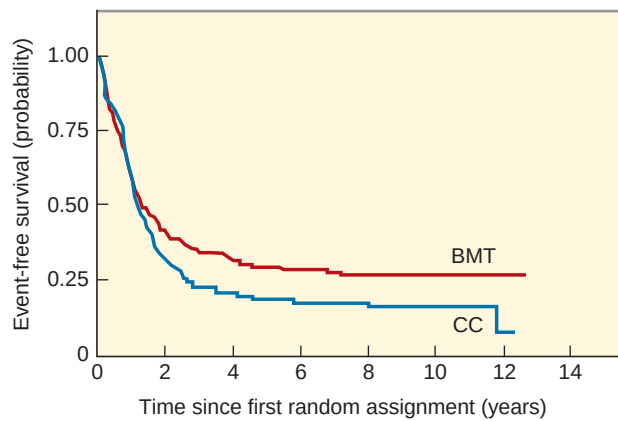
BCNU, carmustine; TBI, total body irradiation; THP, adriamycin; VM-26, teniposide; VP16, etoposide.

Modified from Matthay KK. Hematopoietic stem cell transplantation for neuroblastoma. In: Blume KG, Forman SJ, Appelbaum FR, eds. *Thomas Hematopoietic Cell Transplantation*, 3rd ed. Oxford: Blackwell, 2003.

was significantly superior for those receiving ABMT (40% vs. 19%). An even more significant advantage for ABMT was seen for patients who were only in partial, as opposed to complete, remission at the end of induction and for those with tumor MYCN amplification (107). These results were consistent with results from the Lyon group, in which Philip et al. (113) showed a difference in 2-year survival of 39% versus 12% for concomitant patients treated with myeloablative therapy and ABMT or with standard chemotherapy. In contrast, a retrospective comparison from the POG of 116 patients achieving complete or partial remission did not show any significant difference in outcome for those undergoing bone marrow transplantation before progression (113). A smaller study by the German cooperative group evaluated 39 patients undergoing megatherapy and HCT with a variety of conditioning regimens and either allogeneic or autologous bone marrow, all with a melphalan “backbone,” compared with 49 patients receiving continued chemotherapy by investigator choice. All patients achieved complete or partial remissions. EFS was significantly better in the transplanted patients than in the chemotherapy group, although the curves nearly converged by 6 years (111).

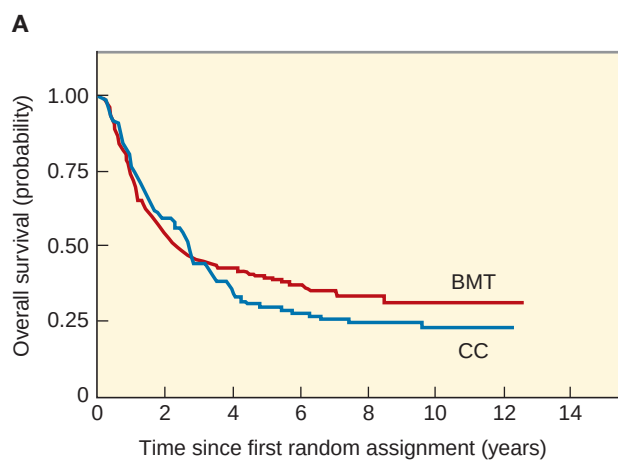
A randomized prospective trial was necessary to eliminate the bias inherent in such retrospective comparisons. The European Neuroblastoma Study Group (ENSG) reported the earliest attempt at a randomized trial of high-dose therapy with autologous bone marrow support for NB, with improvement noted for ABMT in the final report (115). However, this report included only 65 randomized patients, with widely varying times to ABMT. A randomized trial in Germany of myeloablative consolidation therapy compared to a low-dose oral maintenance therapy in 295 patients again showed an advantage for high-dose consolidation, with estimated 3-year EFS of 47% vs. 31% ($p = 0.0221$) (97). The CCG conducted the first large prospective, randomized study from 1991 to

1996, comparing a single course of myeloablative chemoradiotherapy supported by purged ABMT with three cycles of a dose-intensive, nonmyeloablative, continuous-infusion consolidation chemotherapy. Of 379 eligible patients who were randomized, 85% had INSS stage 4 tumors. Randomized patients were assigned equally to ABMT ($n = 189$) or consolidation chemotherapy ($n = 190$), and 118 were nonrandomly assigned to consolidation chemotherapy because of parental or investigator refusal. Overall toxicity and total mean hospital days were similar between the two randomized arms. The 3-year EFS was 27% for all patients, $34\% \pm 4\%$ for those assigned to ABMT, and $22\% \pm 4\%$ for the cases randomly assigned to consolidation chemotherapy ($p = 0.034$) (Fig. 6.9). The outcome advantage noted with ABMT was also significant in the subgroups of patients with MYCN-amplified tumors and in those who were more than 2 years old at diagnosis. The 3-year EFS from the time of transplantation for those 129 patients actually receiving ABMT (as-treated analysis) is shown to be $43\% \pm 6\%$, similar to that of previous single-arm studies and significantly higher than the $27\% \pm 5\%$ EFS of the 150 patients receiving the chemotherapy consolidation (90). A recent update with 8 years of follow-up confirmed that the EFS for patients randomly assigned to ABMT was significantly higher than those randomly assigned to chemotherapy; the 5-year EFS (mean $\pm$ SE) was $30\% \pm 4\%$ versus $19\% \pm 3\%$, respectively ($p = 0.04$). The 5-year EFS ($42\% \pm 5\%$ vs. $31\% \pm 5\%$) from the time of second random assignment was higher for cis-retinoic acid than for no further therapy, although it was not significant. OS was significantly higher for each random assignment with survival estimates at 5 years ($P < .01$). The 5-year OS for stage 4 with ABMT was 37%, compared to 28% OS for the group randomized to consolidation chemotherapy. The 5-year OS from the second random assignment of patients who both underwent random assignments and were assigned to ABMT/cis-retinoic acid was $59\% \pm 8\%$; for ABMT/no



Number of patients at risk

BMT	79	57	42	19
CC	63	39	28	19



Number of patients at risk

BMT	110	75	52	23
CC	101	66	44	28

Figure 6.9 Results of CCG 3891, a randomized study comparing myeloablative chemoradiotherapy and purged autologous bone marrow transplantation with intensive nonmyeloablative therapy. A second randomization was performed on all consenting patients completing the consolidation therapy without progression to test the efficacy of 13-*cis*-retinoic acid for minimal residual disease. **A:** Superior event-free survival (79) with myeloablative therapy compared with standard-dose chemotherapy. The difference in 5-year EFS for the 379 randomized patients was 30% versus 19%, respectively ($p = 0.04$). **B:** The difference in 5-year overall survival was 39% versus 30%, respectively ($p = 0.39$); however, in patients who survived more than 3 years, there appears to be a benefit of ABMT. At 5 years, the curves are significantly different ($p < 0.0001$) in a test of the log ($-\log(\cdot)$). (From Matthay KK, Reynolds CP, Seeger RC, et al. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-*cis*-retinoic acid: a Children's Oncology Group study. *J Clin Oncol*. 2009;27(7):1007–1013, with permission.)

cis-retinoic acid, it was $41\% \pm 7\%$; for continuing chemotherapy/*cis*-retinoic acid, it was $38\% \pm 7\%$; and for chemotherapy/no *cis*-retinoic acid, it was $36\% \pm 7\%$ (79).

Different myeloablative regimens have been used, although most are melphalan-based. The very first myeloablative regimen used to treat NB was high-dose melphalan alone. This progressed to various combinations of other agents, including cisplatin, etoposide, and doxorubicin, melphalan with busulfan, and melphalan with carboplatin and etoposide. Other centers used a thiotepe base coupled with cyclophosphamide, or etoposide, or busulfan combined with cyclophosphamide. More recently, attempts have been made to incorporate topotecan into the conditioning regimen in combination with thiotepe and etoposide (116,117). Few studies have tried to compare two myeloablative regimens in a randomized fashion. However, the retrospective analysis by the European Group for Blood and Marrow Transplantation failed to show any difference in EFS using different high-dose regimens (89). Only one analysis, from the Institut Gustave-Roussy, has shown that patients treated with busulfan and melphalan appeared to have better EFS than those on other conditioning regimens at a single institution (112).

These data may depend on the chronology of the protocols and the fact that the busulfan regimen was compared with a combination of a variety of other regimens. The European Cooperative Neuroblastoma Group (HR-ESIOp) is testing this hypothesis in a randomized study, comparing the COG regimen of melphalan, etoposide, and carboplatin with the busulfan and melphalan regimen. Other pilot studies have suggested that additional benefit may be obtained from double or triple tandem transplants (118,119). An ongoing COG trial (ANBL0532) is currently testing the value of tandem transplant compared to single ablative regimen in a randomized phase III study. Phase I and II studies have now shown the tolerability and possible benefit of combining the targeted radiopharmaceutical ^{131}I -MIBG with carboplatin, etoposide, and melphalan for a myeloablative regimen with responses and some long-term survivors in patients with relapsed or refractory NB (120). A pilot trial of this regimen in the COG for newly diagnosed high-risk NB will open shortly.

Bone marrow involvement is present in 70–90% of patients at diagnosis, and residual tumor cells can still be detected in bone marrow samples by sensitive immunodetection methods even after several cycles of induction therapy. For this reason, allogeneic bone marrow transplantation (BMT) has been proposed as an alternative to ABMT. It is also hoped that the allogeneic cells will provide a further “graft-versus-NB” effect, although the rationale for this concept is weak because NB cells express little human leukocyte antigen (HLA) class I. To date, lack of evidence of any immunologic benefit, coupled with the problems with frequent lack of a HLA-compatible sibling donor and the significantly higher toxic death rates, has discouraged extensive use of allogeneic BMT. Two reports directly compared allogeneic and autologous transplantation in NB. A CCG study compared 36 patients receiving an autologous purged BMT and 20 patients receiving the same induction who received allogeneic matched-sibling BMT. There was no significant difference in relapse rate and an apparently higher toxicity in the allogeneic group. Four of 20 patients died of causes other than relapse in the allogeneic group, compared with 3 of 36 in the autologous group (not significant); the estimated PFS was 25% for the

allogeneic group versus 49% for the autologous group ($p = 0.051$) (121). In a comparison from the European Bone Marrow Transplant Registry, 17 allogeneic transplant and 34 ABMT cases were matched based on a number of prognostic factors. The PFS was not significantly different: 35% for autologous and 41% for allogeneic at 2 years, respectively (122).

The other way to overcome the problem of possible tumor contamination of autologous bone marrow or stem cells is with *ex vivo* purging of the hematopoietic cells. Although bone marrow and peripheral blood often show gross disappearance of tumor cells after a few courses of chemotherapy, sensitive methods of detection with immunocytology and RT-PCR have shown persistence of low levels of tumor in 10–40% of hematopoietic cell collections (64,65,123), and the most common method for removal of NB cells currently employed is either with immunomagnetic beads or using positive CD34 selection, which has been shown to reduce tumor cell content but may rarely lead to later lymphoproliferative disorders (124,125). The most widely tested and validated method with 4–6 logs of tumor cell removal and no impairment of engraftment is immunomagnetic purging. COG studies showed that bone marrow can be successfully harvested; shipped at room temperature overnight; purged using sedimentation, filtration, and immunomagnetic bead separation; and cryopreserved without injury and with successful tumor cell removal and engraftment (90). Recently, the COG study (A3973) tested in a randomized fashion the impact of immunomagnetic purging of peripheral blood stem cells, collected after only two cycles of induction therapy, on patients subsequently receiving myeloablative therapy and treatment of MRD with *cis*-retinoic acid. The results of this study, presented at American Society of Clinical Oncology (ASCO) in 2008, showed no benefit to EFS for the group undergoing the tumor cell removal (126). Thus, due to the increased cost and apparent lack of benefit, stem cell purging is not currently considered essential.

THERAPY FOR MINIMAL RESIDUAL DISEASE

Despite improvements in EFS using myeloablative therapy, the relapse rate, even for patients transplanted in complete response, remains high (79). For this reason, it has become increasingly important to find new approaches to eliminate MRD with agents that will be tolerable after myeloablative therapy. Immediately after HCT, when disease is likely to be minimal, is the ideal window of time to eradicate resistant clones that are still present using novel therapies not dependent on standard cytotoxic mechanisms.

In vitro, both all-*trans*-retinoic acid and 13-*cis*-retinoic acid cause decreased proliferation and differentiation in NB cell lines, including some established from refractory tumors (127,128). A phase II trial in children with relapsed NB using 13-*cis*-retinoic acid on a single daily administration schedule of 100 mg/m² showed only 2 of 22 responses (129). However, based on *in vitro* experiments with higher intermittent dosing, a phase I trial in children with high-risk NB after HCT determined that a high-dose intermittent schedule of 13-*cis*-retinoic acid after BMT had minimal toxicity, achieved levels that were effective against NB cell lines *in vitro*, and resulted in complete bone marrow responses in 3 of 10 patients (130). A subsequent phase III randomized trial

by the CCG of children with high-risk NB completing consolidation chemotherapy or ABMT showed that the 3-year EFS from the time of randomization was significantly better for the patients randomized to receive 13-*cis*-retinoic acid ($46\% \pm 6\%$) than for those randomized to receive no further therapy ($29\% \pm 5\%$; $p < 0.03$) (Fig. 6.9). A European randomized trial of very low-dose continuous 13-*cis*-retinoic acid given after transplant did not show any benefit (131). Other retinoids, such as fenretinide, are under investigation for use in MRD (132).

Another approach to MRD after transplant is the use of antibody-targeted therapy. Antibody therapy in relapsed NB using murine, chimeric, and humanized antibodies against the membrane ganglioside GD₂ has provided promising response and toxicity profiles that warrant further investigation of these agents in randomized studies (133–138). With granulocyte-macrophage colony-stimulating factor (GM-CSF) or interleukin-2 (IL-2), anti-GD₂ seems to be tolerated in patients who have undergone ABMT (134,135,137). A recent randomized prospective trial of chimeric anti-GD₂ antibody with GM-CSF and IL-2 is under way in the COG. Patients in remission after high-dose therapy and HCT were randomized to receive either 13-*cis*-retinoic acid alone or the retinoid along with chimeric anti-GD₂ antibody (Ch14.18), GM-CSF, and IL-2. The randomization was stopped early due to the significant improvement in EFS at 2-years post transplant shown with the antibody arm. With median follow-up of 2.1 years, EFS ($p = 0.01$) and OS ($p = 0.02$) were significantly higher for patients randomized to immunotherapy, with 2-year estimates of $66\% \pm 5\%$ versus $46\% \pm 5\%$ for EFS, and $86\% \pm 4\%$ versus $75\% \pm 5\%$ for OS (139).

Further attempts at immunotherapy are being tested in phase I trials using a fusion protein of the humanized form of the antibody Hu14.18 and IL-2. This immunocytokine has the advantage of working simultaneously through both antibody-dependent cytotoxicity and natural killer cell mechanisms. A murine NB model showed superior activity of the immunocytokine to the physical mixture of the antibody and cytokine (140,141).

Other approaches to MRD in the future may use genetically engineered vaccines to generate immune response (142). Another possible avenue would use antiangiogenic therapy after transplantation. Angiogenesis appears to play a major role in progression of NB in that multiple proteins associated with angiogenesis have been shown to be associated with more advanced disease or worse prognosis (143).

SURGERY

Surgery has both a diagnostic and a therapeutic role. If the diagnosis has not been established by bone marrow aspirate, biochemical testing, or skin biopsy, surgery provides histologic confirmation of malignancy. Even in the presence of a clear, nonsurgically determined diagnosis of NB, a tissue sample is important for biologic analysis.

As previously stated, 20–40% of children present with localized disease. In children without evidence of metastatic disease, an attempt at resection is warranted if substantial morbidity (sacrifice of vital structures) can be avoided. Complete gross excision of the primary tumor in localized disease is associated with a very high likelihood of cure irrespective of the patient's age. For patients with stage 1 or

2 disease, the cure rate exceeds 90% (70,96,144). If the tumor is localized but unresectable (INSS stage 3) because of its intimate relationship with major blood vessels or other characteristics, the proper extent of surgery may depend on tumor biology. In a study of 228 patients with stage 3 NB, for children who had elevated serum ferritin or tumors with unfavorable histopathology or *MYCN* amplification, the EFS was improved by complete gross resection, whereas the extent of resection did not appear to affect the children with biologically favorable tumors treated with standard dose chemotherapy (76). Similar results were shown by European groups in infants and older children with biologically favorable NB (145,146). The optimal timing of the surgery is still under debate; it is possible that the advantages of early resection are outweighed by a higher complication rate before chemotherapy reduction followed by delayed surgery (147). However, even when the primary tumor is unresectable, defining its extent remains important for staging and determining optimal additional local therapy with radiation.

Recurrence in the local or regional area of primary disease is a component of relapse in a large proportion of children with high-risk NB, at rates ranging from 20% to 80% in reports that often include local RT and myeloablative therapy. Both single-arm studies and one randomized study demonstrate the benefit of local control measures for children with advanced but nonmetastatic NB (76,78), but the impact of resection in stage 4 disease in the past were mixed; however, as therapy intensity has improved control of metastatic disease and survival, the importance of gross total resection and radiation therapy seems to have increased (148,149).

Second-look surgical procedures are commonly used in NB. Chemotherapy and irradiation may produce significant interval regression of a bulky primary tumor (149). For patients with residual tumor, surgery may then be performed to achieve a complete response. Children who have localized NB converted to a resectable status by interval therapy and who undergo complete excision have a better prognosis (76,78). Completely resecting the primary tumor also appears feasible for patients with advanced disease; eventual complete excision can be accomplished in up to 65% of patients (150). In this situation, resection after chemotherapy appears to be associated with fewer complications than resection before chemotherapy (151). The Italian Cooperative Group for Neuroblastoma has reported 145 patients with localized inoperable NB or primary tumor excised with a tumor residue more than 2 mL. Ninety-four of the 145 (65%) achieved a complete or partial response with chemotherapy, and 75 (52%) subsequently underwent complete resection (152).

Although the prognostic value of lymph nodes has been controversial, and nodes adherent to or removed with the primary tumor do not appear to predict prognosis, lymph nodes that are distinct (usually superior or inferior, but especially if bilateral or contralateral) from the tumor are ideally sampled for complete staging and later considerations for RT (55,69). However, this may be difficult for some patients with cervical or thoracic tumors or infiltrative unresectable abdominal primaries. The utility of other prognostic factors suggests that aggressive attempts to acquire this information are unwarranted. If RT is contemplated, clips should be used to mark the tumor.

If treated surgically, dumbbell tumors are dealt with by a two-stage procedure. The extraspinal component of the tumor

is removed at a first operation. The extradural, intraspinal portion of the tumor is removed later. However, if there is evidence of spinal cord compression and if surgery is used, the laminectomy is performed first. Osteoplastic laminotomy is preferable to minimize later deformity (51,52). Many institutions prefer to treat spinal cord compression with chemotherapy to try to minimize late deformities, as discussed elsewhere in this chapter.

On occasion, infants with a small primary tumor and extensive liver metastases (stage 4S) warrant special surgical considerations. The enlarging liver may compromise respiratory function from upward pressure on the diaphragm or compress the inferior vena cava or renal vein. If chemotherapy or local irradiation does not adequately reduce hepatic size, a silastic sheet may be inserted in the abdominal wall to allow room for liver expansion and reduce compression of vital structures. Resection of the primary tumor does not influence survival in stage 4S (77,153).

RADIATION THERAPY

Indications concerning the use of RT in children with NB continue to be refined by progress in devising effective chemotherapy and the desire to avoid unnecessarily aggressive treatment regimens in young children, all on the backdrop of the recalcitrant nature of NB in many children. NB cells in culture are generally radiosensitive (154), although radiation responsiveness of NB in patients is less predictable. In the prechemotherapy era, Lingley et al. (155) reported that irradiation to local residual disease in patients with stage 2 and 3 NB resulted in survival in 13 of 13 patients. In discerning the optimal use of RT in NB, reports must be interpreted cautiously because of the differences in staging systems and lack of information about tumor biology.

Low-Risk Disease

Postoperative RT is unnecessary in INSS stage 1 and 2 NB, since all recent cooperative studies have reported more than 90% survival with surgery alone or surgery with chemotherapy. Gross surgical excision cures the majority of these children, regardless of age, urinary VMA and HVA ratios, and histologic patterns, as mentioned in the section "Surgery" (70,96,144). A prospective POG study of 101 children with POG stage A disease treated with surgery alone demonstrated a 2-year disease-free survival of 89% and OS (with salvage therapy) of 97% (96). Most recurrences were noted within 1 year of diagnosis, and six of the nine children who relapsed were cured with chemotherapy. Matthay et al. (156) reported outcomes in 156 patients with INSS stage 2A. No significant benefit was associated with the use of chemotherapy or irradiation. The outcome for 75 patients treated with surgery alone was similar to that of 66 patients receiving RT with 6-year PFS of 89% versus 94%, respectively. For the subgroup of patients with residual (postsurgical) gross or microscopic disease, survival was not influenced by the use of irradiation. A subsequent prospective CCG study by Perez et al. (70) demonstrated more than 98% survival for 374 children with stage 1 and 2 NB with surgery alone as primary therapy. Thus, cooperative group studies of localized NB dictate surgery as the primary treatment modality. Chemotherapy is generally reserved for recurrent or progressive tumors that cannot be resected successfully. RT is reserved for the very rare in-

stances of local recurrence in spite of surgery and chemotherapy or for instances in which function is threatened, such as in spinal cord compression or in respiratory insufficiency caused by hepatomegaly.

Stage 4s and Hepatomegaly

Stage 4S NB was initially proposed as separate from stage 4 in light of the observation that infants with a localized primary NB with metastases to liver, bone marrow, or skin without cortical bone involvement had a surprisingly good outcome compared with other infants with metastatic disease and might need little or no therapy (157). In fact, patients with stage 4S NB who have favorable biology have an excellent prognosis, with 85–90% needing little or no therapy (77,153). Therefore, RT should be reserved for palliation of life-threatening conditions such as marked, symptomatic hepatomegaly (158). The indication for radiation must be balanced against the need for such therapy and the risk of late sequelae of irradiation in infancy (159,160). Certainly, routine RT is inappropriate in stage 4S disease and should be instituted only when disease progression threatens vital organ function. This occurs most commonly in infants 1–2 months old, a risk factor for death in several series (77,153,158). An enlarging liver may induce respiratory compromise from upward pressure on the diaphragm, produce inferior vena cava obstruction, compromise renal perfusion, and occasionally result in gastrointestinal compromise or disseminated intravascular coagulation. When symptoms are early, low-dose chemotherapy can be attempted for symptom reduction. However, often in very young infants the progression is too rapid and local irradiation in stage 4S NB is indicated for acute reduction of hepatic enlargement (77,153,158). A radiation of 2–6 Gy is usually sufficient to reduce hepatic tumor burden and is well within the accepted limit of hepatic radiation tolerance.

Intermediate-Risk Disease

For children with regional NB on the less favorable end of the spectrum (i.e., INSS stage 3), several reports support a survival advantage from the use of RT (Table 6.8). Unfortunately, because of the previous multiple staging systems, many

reports have combined INSS stage 2B and INSS stage 3, making it difficult to discern whether radiation is beneficial in both of these groups. As noted above, recent studies suggest that INSS stage 2B disease does not necessitate RT, despite older reports showing improved survival with RT. Patients with stage 3 disease who are more than 1 year old with MYCN amplification or unfavorable pathology need additional treatment. For these children EFS is only 50–60%, even with aggressive multimodality therapy (76). Well before the period of biologic staging, Koop and Johnson (166) found that in patients with stage III disease, postoperative irradiation improved survival (six of seven vs. one of nine patients alive with and without postoperative irradiation, respectively). Only one randomized study of RT has clearly delineated results for unresectable nonmetastatic disease. This POG study randomized patients more than 1 year old with stage C NB to receive postoperative chemotherapy or chemotherapy with regional RT (24–30 Gy, 16–20 fractions) (167). Of 62 eligible patients, in the chemotherapy arm 45% and 31% achieved complete remission and remained disease-free, respectively, at a median of 35 months, and in the chemotherapy and RT arm 67% and 58% achieved complete remission and remain disease-free, respectively, at a median of 23 months. Unfortunately, the chemotherapy used in this 10-year study was much less dose intensive than current protocols, and there were no biologic risk factors reported, rendering these results nearly impossible to interpret in the context of current therapy (162). However, current reports seem to support the importance of local control in biologically unfavorable high-risk stage 3 disease, although no further randomized trials have been performed (78). All current protocols prescribe RT for residual disease after chemotherapy, with the exception of infants and children with favorable biology (nonamplified MYCN, favorable histology, hyperdiploid).

In Evans stage III or with positive lymph nodes (POG stage C), a body of evidence suggests that RT may increase the probability of survival and local tumor control. However, the most recent available trials indicate that patients with MYCN nonamplified and favorable ploidy do reasonably well with surgery and chemotherapy. Patients with amplified MYCN clearly need

Table 6.8

Effect of Radiation in Local Control of Advanced (INSS 3 and 4) Neuroblastoma

Reference	Local Relapse Rate		Local Radiation	Total Body
	With Local EBRT (%)	Without Local EBRT (%)	Dosage Median (Range), in Gy	Irradiation (%)
161	32	81	12–37.5	None
162	24	54	24–30	None
98			Intra-abdominal: 10 Other sites: 20	10 (3.33 q.d.)
163	15	NA ^b	21 (1.5 b.i.d.)	None
164	10	21	10 (8–24)	12 (2 b.i.d.)
165	10	NA ^b	21 (1.5 b.i.d.)	None
150	22 ^a	35	Intra-abdominal: 10	10 (3.33 q.d.)
CC			Other sites: 20	

ABMT, autologous bone marrow transplantation; CC, continuation chemotherapy; EBRT, external beam radiation therapy.

^aEBRT administered only to patients with residual disease at primary site.

^bAll patients received EBRT.

improved methods of local and systemic control. It remains to be determined whether more aggressive irradiation will help these patients. Until prospective data are available based on INSS staging, no unequivocal recommendations can be made regarding the efficacy of RT in children with stage 3 disease.

The most recently completed COG study for intermediate-risk disease (A3961), including stage 3 with favorable biology and infant stage 4, used surgery to provide diagnostic material at diagnosis and to attempt maximal safe resection of the primary tumor after chemotherapy. Chemotherapy included cyclophosphamide, doxorubicin, carboplatin, and etoposide. The duration of chemotherapy was based on the biologic risk factors. RT was limited to situations in which there was clinical deterioration despite chemotherapy and surgery or persistent tumor after chemotherapy and second-look surgery. This treatment resulted in >90% survival for this group.

High-Risk Disease

Nearly half of all patients diagnosed with NB present with high-risk disease. Despite concerted clinical and scientific efforts, the prognosis of children with high-risk NB remains poor. Less than 30% of patients with high-risk disease who are more than 1 year old survive more than 5 years. Historically, early attempts to use radiation to cure children with advanced NB focused on large-volume RT, "segmental" or "sequential" fields administered as fractionated or single doses (168). Mixed results in the face of significant toxicities diminished enthusiasm for such radiation approaches, and they ultimately fell out of favor.

Although large-field RT has not proven efficacious, the concept of aggressive systemic therapy has prevailed and has proven successful at improving outcomes for high-risk patients. The randomized CCG 3891 trial showed superior clinical outcomes for patients with high-risk NB who were treated with myeloablative chemotherapy and TBI with transplantation of purged autologous bone marrow (90). Indeed, TBI has played a prominent role in many myeloablative regimens. Table 6.7 summarizes studies that use autologous or allogeneic BMT either with or without TBI as a component of their preparatory regimens. For most reports EFS rates are on the order of 20–40%, although mortality continues to increase as follow-up lengthens. As with older TBI protocols, trends in conditioning regimens for stem cell transplantation have favored omitting TBI because it limits dosages of myeloablative chemotherapy that can be administered and because of the increase in late effects in young children.

Although the use of TBI for NB is nearly obsolete, an enlarging body of evidence supports the use of local RT to the primary site and bulky metastatic sites. Disease recurrence after BMT for NB is most common at previous sites of disease. Local irradiation delivered either in preparation for the transplant or afterwards appears to reduce the risk of relapse at these sites (150,164,169). Indeed, the current standard of care dictates that patients with high-risk disease receive radiation to the primary disease site regardless of the extent of surgical resection and to sites of metastatic disease that display persistent ¹³¹I-MIBG avidity on the pre-stem cell transplant scans.

Several reports have specifically tackled the role of radiation to the primary tumor site in uniform cohorts of patients with advanced NB. Such results strongly support the administration of radiation to the primary site in high-

risk disease. These single-institution and small consortium studies have reported excellent local control rates after treatment regimens that consist of induction chemotherapy, delayed primary surgery with attempted resection of primary and bulky metastatic lesions, external beam radiation to the primary tumor site and persistent metastatic areas, myeloablative chemotherapy, and infusion of stem cells. A report from Japan describes a program of intensive chemotherapy and treatment of primary disease with surgery and radiation for a group of children more than 1 year old with stage 4 disease, although a few patients with stage 3 disease and children younger than 1 year were included. The 5-year EFS was 39% (110). CCG protocol 321P3 used a dose-intensive combination of four chemotherapeutic agents followed by autologous purged BMT and enrolled 99 children more than 1 year old with stage 4 and high-risk stage 3 disease. The 4-year PFS was 40% (107). Despite TBI and local RT to residual disease, the primary site was involved in more than 50% of the relapses (98). Better primary control was seen at Memorial Sloan-Kettering Cancer Center in patients with stage 4 NB, who received higher-dose local radiation to primary tumor sites regardless of resection and had an actuarial locoregional control rate of 84% at 5 years (169). An update of this single-institution experience reported a 10.1% probability of primary site failure among 99 patients, 92 of whom had no evidence of disease in the primary site at the time of irradiation (165). Children received 1.5 Gy twice a day to 21 Gy to the prechemotherapy, presurgery primary tumor volume and regional lymph nodes. Among seven patients with disease at the primary site at the time of irradiation, three had disease that recurred locally. A similar treatment regimen was used by the German multicenter NB trial in which 14 of 26 patients with advanced disease had disease that relapsed, with 4 (29%) including the primary sites (163). Comparable regimens have resulted in decreased local relapse rates, ranging from 0% to 17% (164,170).

Although favorable local control rates have been reported in single-institution and small consortium studies, large multi-institutional studies have lower rates of complete total resections and differing chemotherapy regimens that limit direct comparisons of clinical results. Therefore, it is not surprising that large, modern multi-institutional trials report higher rates of local relapse. The CCG trial (CCG 3891) showed superior EFS for patients with high-risk NB who were treated with myeloablative chemotherapy and TBI with transplantation of purged autologous bone marrow, followed by treatment with 13-*cis*-retinoic acid. External beam RT (EBRT) was prescribed for all patients with gross residual disease after induction chemotherapy and surgery. Patients randomly assigned to the transplantation arm received additional TBI as a component of the ablative regimen (90).

In CCG 3891, recurrence at the primary disease site was a major component of relapse. Among 539 patients, 349 had recurrences, including 31 with isolated locoregional relapses, 148 with simultaneous local and distant recurrences, and 150 with distant relapses. At 5 years, the estimated regional recurrence rate was 51% $\pm$ 5% among patients who received continuation chemotherapy and 33% $\pm$ 7% among patients who received transplantation. The difference in local relapses between the continuation chemotherapy and ABMT groups was most pronounced in patients with *MYCN*-amplified tumors.

Among patients with *MYCN* amplification, the estimated 5-year local recurrence rate was $70\% \pm 10\%$ for those who received continuation chemotherapy and $25\% \pm 15\%$ for patients who received ABMT (150).

Although CCG 3891 did not examine the benefit of local EBRT in a randomized fashion, some conclusions were evident from an analysis of RT administered in this trial. For patients who received 10 Gy of EBRT to the primary site, the addition of 10 Gy of TBI and ABMT resulted in lower local recurrence rates than continuation chemotherapy. The benefit of RT was particularly evident when systemic treatment was optimized with myeloablative therapy and 13-*cis*-retinoic acid (150). For patients with high-risk NB, we recommend EBRT to the primary tumor site in the context of a myeloablative regimen that does not include TBI but incorporates post-transplant therapy for MRD.

CNS Metastases

Some controversy exists regarding whether increasingly aggressive multimodality therapy for stage 4 disease has altered patterns of metastatic sites. Some metastatic sites, although perhaps rare in NB patients, pose unique therapeutic challenges, exemplified by CNS metastases. The incidence of CNS metastases in children with high-risk stage 4 NB varies widely in the literature, with crude values of 2–25% reported (61,171).

In a COG study, all 648 patients with stage 4 NB in CCG 3881 and 3891 were analyzed for sites of metastases. At diagnosis, the most common sites of metastases were bone marrow, bone, lymph nodes, and liver. The distribution of metastatic sites differed between patients at diagnosis and those at first progression. Whereas the frequencies of bone, bone marrow, liver, lymph nodes, and skin metastases were lower at first progression than at diagnosis, frequencies of adrenal, lung, and CNS metastases exhibited the opposite propensity. Whereas CNS involvement was almost never seen at diagnosis, at first progression, CNS metastases were more common in all age groups. Of all patients with stage 4 disease and relapse, 11% of children younger than 1 year and 3% of children 1 year or older had CNS metastases at relapse. Although the number of patients with CNS metastases was small, a few trends were evident. All patients with CNS metastases were more than 1 year old, died within 1 year of diagnosis, and had both *MYCN* amplification (among those tested) and unfavorable Shimada histopathology. Among patients with CNS metastases at diagnosis and those younger than 1 year who progressed with CNS metastases, hematogenous spread to parenchymal sites was nearly absent. In contrast, for patients older than 1 year, CNS metastases at progression appeared to result from hematogenous routes of spread (61).

A similar analysis at the Institute Curie and Institute Gustave-Roussy confirmed that CNS metastases at diagnosis are extremely rare but revealed an estimated 3-year risk of CNS recurrence of 8% among patients with stage 4 disease, a rate that was stable over 15 years (172). Patients with CNS recurrences were equally distributed among those with parenchymal lesions, those with only meningeal involvement, and those with a combination thereof. Of note, ^{131}I -MIBG scans did not reliably identify CNS recurrences, detecting lesions in only 43% of those with known CNS metastases (172).

In contrast to the aforementioned studies, investigators at Memorial Sloan-Kettering Cancer Center found more CNS metastases associated with increased intensity of curative protocols for patients with stage 4 disease (173). In patients treated with earlier N4–5 protocols, 2% recurred in the CNS, whereas in those treated with more intensive N6–7 protocols, 12% experienced CNS metastases, perhaps reflecting the longer median survival times in patients treated on N6–7. As patients live longer, metastases to sanctuary sites such as the CNS may become more evident.

Although prospective head CT or MRI scans may better quantify the true incidence of CNS metastases, the infrequent occurrence of such metastases does not justify routine CNS imaging. Furthermore, although most studies do not support an increase in frequency of CNS metastases in the past two decades, it is unclear whether the movement away from TBI for stage 4 NB will result in increased metastases to sanctuary sites such as the CNS. The rarity of CNS metastases does not justify prophylactic CNS radiation; however, for a patient with CNS recurrence the appropriate field of radiation remains unclear.

CNS parenchymal or meningeal metastatic relapse has portended a very short survival in prior studies, with median survival of 3–6 months. However, with aggressive surgery and local radiation, survival may be extended in some instances. In addition, experimental targeted radiation with ^{131}I -labeled antibody administered intrathecally suggests another way to improve disease control in a phase I study (174).

Metastatic Disease Treated with Palliative Intent

Most children with NB have metastatic disease at presentation, which may occasionally threaten function, such as an orbital metastasis affecting vision, an epidural metastasis causing cord compression, or severe pain caused by bone lesions. RT is effective in palliating symptoms secondary to bone and soft tissue metastases, although in a newly diagnosed, chemotherapy-naïve patient, systemic treatment usually is initiated first, except in extreme circumstances. A Duke study assessed the value of palliative RT for NB by retrospectively studying 40 irradiated bony sites. Pain completely or partially responded at 65% of treated sites. A subsequent recurrence of pain was seen in 23% of initially responding sites. Complete or partial palliation of soft tissue mass effect was seen in 67% of treated sites. A subsequent relapse of mass effect was seen in 28% of initially responding sites (175). Palliative RT for pain or other symptoms in the refractory relapsed patient can generally be administered rapidly with good relief. There are also extensive phase I and II data concerning palliative treatment of metastatic disease with ^{131}I -MIBG (176,177).

ADOLESCENT AND ADULT NEUROBLASTOMA

NB occurs only rarely in adolescents and adults. More than one-third of patients are diagnosed before the age of 1 year, whereas fewer than 5% of patients present after the age of 10 years (80). NB in adolescents and adults presents unique challenges that necessitate distinct analyses and therapeutic approaches.

NB in adolescents and adults is characterized by an indolent course, persistent disease, multiple recurrences, and poor outcome. In studies examining patients who were diagnosed with NB between the ages of 15 and 75 years, fewer than 5% of patients are long-term survivors, without evidence of disease (178–180). Most aspects of clinical presentation are similar to those of younger patients. For example, sites of metastatic disease are similar in adolescents and younger children, most commonly found in bone marrow, lymph nodes, bone, and liver. However, distinct differences occur between younger patients and adolescents with NB. Such differences in tumor histology and secretion of catecholamine metabolites may reflect the unique entity of NB in adolescents and adults. The lower frequency of MYCN amplification and secretion of catecholamine metabolites probably go hand in hand with the more chronic nature of the disease in this age group (178,181).

Franks et al. (178) reported the experience of the CCG with NB in adults and adolescents. This study examined 16 patients from the University of California, San Francisco (UCSF), and 38 patients registered in the CCG, all 13 years or older. They found that older patients experienced multiple recurrences; chronic, prolonged courses; and poor outcome regardless of stage or site of disease. For example, although 25% of patients in the UCSF series had pelvic primaries, a site that in younger patients is associated with more favorable outcome, pelvic primaries were associated with outcomes as poor as those for adults and adolescents with other primary sites (178). The indolent, chronic nature of NB in adults and adolescents was reflected with a long median time to progression of 32 months. Although stage IV disease recurred within a year from diagnosis in most patients, late recurrences were observed, as long as 83 months after diagnosis. Furthermore, although younger patients with stage IV NB have only a 3- to 4-month median survival after their first recurrence, similarly staged adolescents experienced multiple recurrences and persistent disease after their first recurrence. After their first recurrence, adolescents and adults had a median survival of 17 months, with a significant proportion surviving more than 4 years after recurrence (178).

Whereas the CCG and UCSF experiences demonstrate poor outcome for all adolescents, regardless of stage, the French Society of Pediatric Oncology found that patients with stage I–II disease fared well and had survival rates comparable to those of younger patients with early stage disease (86). None of six patients with stage I–II disease experienced recurrence. In contrast, adolescents with stage III disease experienced multiple recurrences, with prolonged and chronic clinical courses. This is reflected in discordant PFS and OS rates at 5 years, which were 28% and 86%, respectively. Adolescents with metastatic NB had low PFS and OS rates of 18% and 27%, respectively, and exhibited poor responses to intensive chemotherapy (86).

The poor outcome for adults and adolescents, even with localized disease, calls into question the usual risk-based treatment in this age group. Aggressive multimodality therapy may be appropriate even for patients with low-stage disease but certainly for patients with INSS stage 3 and 4 disease. Specifically, higher radiation dosages are appropriate. Dosages to the primary tumor site should be maximized, tailored to the individual disease sites, and constrained by tolerance of adjacent normal tissues. For example, abdominal primary tumors

should be treated with 45 Gy, which constitutes small bowel tolerance, as long as the dosage to the kidneys can be kept within tolerance. Given the poor clinical outcome for adults and adolescents with NB, creative approaches are warranted in the treatment of such patients, including immunotherapy, differentiating agents, targeted RT using ¹³¹I-MIBG, and biologic agents.

RADIOTHERAPEUTIC MANAGEMENT

Volume

The volume for irradiation of regional NB is determined by imaging studies and by the operating surgeon's description. If lymph node involvement is suspected or proven, a wide field that covers the primary tumor site and nodal drainage areas is appropriate. If the field must cover a portion of the vertebral body, the full width of the bone should be encompassed. This will reduce the severity of subsequent scoliosis and ensure coverage of the regional lymph nodes (175). Some controversy surrounds the issue of whether next-echelon lymph nodes (i.e., mediastinal lymph nodes with an upper abdominal primary tumor) need to be irradiated. Relapse in nonirradiated next-echelon nodes can occur, albeit usually in conjunction with local or distant failure. In the Duke experience of 33 patients with stage A to C, 12 relapsed. Only 1 of the 21 irradiated patients (5%) experienced an in-field failure, whereas 7 of the 12 not receiving RT (58%) experienced local failures at the time of recurrence ($p = 0.001$). Routine next-echelon nodal irradiation was not given. Five of the 12 patients who suffered a relapse had next-echelon nodal failure as a component of relapse; only one case was an isolated next-echelon nodal failure (182). Extensive nodal fields may contribute to late morbidity and limit the ability to give chemotherapy, so most radiotherapists cover only the primary tumor volume and adjacent nodal groups. With a dumbbell-shaped tumor, careful attention must be paid to the intraspinal and extravertebral components of the tumor to ensure full coverage.

As previously discussed, RT may be used for INSS stage 4S-associated hepatomegaly that is symptomatic. The entire liver need not be irradiated to induce tumor regression. The therapist may use portals designed to avoid the kidneys and, in girls, the ovaries. One may use two lateral fields, parallel opposed or slightly angled anteriorly, to treat the majority of the liver but spare the kidneys. Placing the posterior border of the lateral field at the anterior aspect of the vertebral body accomplishes this objective. The ovaries are generally avoided by keeping the inferior border of the field at or above the superior iliac crest. Irradiation dosages for stage 4S hepatomegaly are low, usually 2–6 Gy in two to four fractions, so it could be argued that the kidneys are in little danger of chronic injury and that the liver could be treated with parallel, opposed anterior and posterior fields or a single anterior field. Although these are acceptable field arrangement options, the infant kidney is more sensitive to irradiation than kidneys in older children (183). Children with stage 4S disease have high likelihood of survival and, if possible, should not be subjected to the risks of lifetime reductions of glomerular filtration rates. Stage 4 NB with hepatomegaly may also be treated for palliation with ports designed to cover the entire liver, using the anterior–posterior parallel, opposed beams. NB metastases occur in a wide variety of locations. Bone and soft tissue sites are irradiated with moderate margins.

Dosage

Classic radiobiologic analyses reflect the relative radiosensitivity of NB cell lines *in vitro* but produce conflicting results regarding the most appropriate fractionation schedules. The D_0 for most mammalian tumor cell lines is between 1.3 and 1.5 Gy. The n is usually between 1.5 and 10. The n is the extrapolation number and measures the width of the survival curve shoulder. The D_0 describes the final slope of the cell survival curve and is the dose required to reduce survival from 0.1 to 0.037. Collated data on 11 NB cell lines derived from 7 patients indicate moderate cellular radiosensitivity beyond that seen for many other mammalian tumors. The median n for NB is 1.36, and the D_0 is 1.04 Gy (154,184). This low repair capacity for radiation damage implies that little sparing would result from dose fractionation. Wheldon et al. (185) used human NB grown as multicellular tumor spheroids (MTS) to confirm this hypothesis. There was no significant difference in the killing ability of single-dose and split-dose irradiation. The absence of substantial interfraction repair capacity of MTS may provide a radiobiologic rationale for treating NB with multiple fractions per day. Some NB cell lines have a rapid doubling time. This would also suggest that the overall treatment time of a fractionated course of radiation should be kept short to prevent tumor repopulation between fractions. However, Deacon et al. (186) performed *in vitro* split-dose irradiation of an NB cell line and found a small but finite capacity for sublethal damage repair. There may be intrinsic variability in repair capabilities between NB cell lines.

Although NB is radiosensitive in the laboratory, its clinical response to irradiation is variable, and in-field recurrences, although rare, do occur. Possible reasons for this discrepancy include the following. First, the *in vitro* data may not indicate clinical NB because cell culture techniques may select more radiosensitive cell lines (187). Second, NB, characterized by certain microscopic and biochemical characteristics, may actually be a spectrum of diseases. Genomic amplification of *MYCN* has been correlated with the stage and prognosis of NB, suggesting that *MYCN* may have a role in determining the aggressiveness of human NB. Perhaps clinical variability in radiosensitivity reflects the variation in oncogene amplification in NB (187). In defining the role of radiation for high-risk NB, adequate dosages have been defined empirically. Studies on patients now known not to have the needed radiation shaped standard radiation dosages that were then translated into dosages adequate for high-risk disease. Historically, RT was administered to most patients with NB, with the exception of those with stage I tumors. Radiation dosages ranged from 10 to 45 Gy and were dictated by patient age rather than stage of disease (188). In this era, in which patients with early-stage disease received radiation, two studies examined the radiation dosage of NB (189,190). Dosages below 20 Gy were deemed sufficient to achieve local control. However, the majority of patients included in both studies probably would not receive RT in the current era. Nonetheless, the adequacy of dosages of less than 20 Gy was adopted for all stages of disease.

Emerging data suggest that although 20 Gy may be adequate for controlling completely resected tumors, gross residual disease may necessitate higher dosages. Joint Center for Radiation Therapy analyzed radiation dosage and local control and concluded that higher dosages are necessary for local control of NB in older patients (161). The protocol design of CCG 3891 also allowed a limited dose-response analysis, suggesting

that the combined effect of external beam radiation and TBI improved local control (150).

Whereas the majority of patients on CCG 3891 had mediastinal and intra-abdominal tumors and therefore received 10 Gy to the primary site, a subgroup of patients received 20 Gy delivered to extra-abdominal primary tumors. Of 36 patients with extra-abdominal primaries, 6 patients received 20 Gy EBRT (2 also received TBI) and 30 patients received no EBRT (10 of these received TBI). Local relapse rates at 5 years were $0\% \pm 0\%$ and $44\% \pm 15\%$ for patients with and without EBRT, respectively ($p = 0.09$). Thus the data suggest a dose-response relationship for local EBRT, although the optimal dosage to primary tumor sites has not been established (150).

As a basic guide for patients with high-risk NB, a minimum dosage of 21 Gy, in either 1.8 Gy daily fractions or 1.5 Gy twice-daily fractions, should be delivered to the tumor volume present before surgical resection. This dosage should be adequate for patients with a complete surgical resection, but patients with incomplete surgical resections may benefit from higher radiation dosages directed at gross residual disease in an attempt to improve on poor local control rates reported in the literature.

Recent publications suggest that current local therapy for incompletely resected patients is inadequate. Wolden et al. reported on a series of patients with stage 4 NB receiving 1.5 Gy twice a day to 21 Gy to prechemotherapy, presurgery primary tumor volume and regional lymph nodes (169). The actuarial locoregional control rate at 5 years was 84%. A more recent update of this experience reported a 10.1% probability of primary-site failure among 99 patients, most of whom (92 patients) had no evidence of disease in the primary site at the time of irradiation (165). Among seven patients with disease at the primary site at the time of irradiation, three had disease that recurred locally. EBRT did not increase acute toxicity, except for increased total parenteral nutrition administration.

A recent abstract from the University Children's Hospital in Cologne, Germany, reported that 36 Gy of EBRT administered to patients with incompletely resected primary tumors could compensate for "the disadvantage of incomplete response to induction chemotherapy." In this report of the NB97 trial for patients 1 year of age or older with stage 4 NB, patients with isolated localized residual disease had improved outcome following EBRT (3-year-EFS 100%, 3-year-OS 100%) compared to those not receiving EBRT despite residual tumor tissue (3-year-EFS $20 \pm 18\%$, $p < 0.001$; 3-year-OS $20 \pm 18\%$, $p < 0.001$) (191).

Given high rates of local recurrence, particularly following an incomplete surgical resection, and tolerable side-effects of EBRT evident in multi-institutional trials, the current COG high-risk study is assessing whether a boost to residual primary tumor in patients with less than gross total resection will improve the 3-year local control rate compared to historical controls. Thus, patients enrolled on ANBL0532 who have an incomplete surgical resection of the primary tumor will receive 21.6 Gy EBRT to the postinduction chemotherapy, preoperative primary tumor volume and an additional boost of 14.4 Gy EBRT to the gross residual volume (total dose of 36 Gy to gross residual tumor volume). A dose of 36 Gy is well within normal tissue tolerance for most organs within the field of radiation, and kidneys and liver will likely prove to be the dose-limiting structures. It should be noted that the volume that receives 36 Gy is generally substantially smaller than the original preoperative tumor volume that receives

21.6 Gy. An example of a patient treated with such a radiation regimen is shown in Figure 6.10.

Several investigators have published recommendations for time and dose fractionation schedules for the irradiation of metastatic NB in bone or soft tissues with a wide range of daily fractions of 2–8.5 Gy and total dosages of 4–32 Gy. In a retrospective evaluation of palliative RT for NB at Duke, there was no evidence of a dose–response relationship (175). However, all total dosages used in this study were low. The clinician must avoid selecting too low a dosage for palliation of painful bony or soft tissue lesions. Although most children with stage 4 NB die from the malignancy, some live for 1 year or more after palliative local treatment. The dosage should be adequate to control the symptom for the remainder of the patient's lifetime yet not be so high as to have a significant likelihood of complications. Fractionation depends on volume. Small fields may be treated with 16–20 Gy in four or five fractions, whereas large volumes are better treated with 2–3 Gy per fraction to 20–30 Gy. In the preterminal case, where timely pain control is desired with minimal trips to the RT department, one may administer 6–8 Gy once or twice with moderate success.

Palliation of hepatomegaly in stage 4S disease usually can be accomplished by 2–6 Gy in two to four fractions. However, regression of the liver may be slow. It is occasionally necessary to repeat the dose. If possible, one should allow a 2- to 3-week interval to gauge response. If the dose is repeated such that the cumulative dosage reaches 12 Gy, the infant's kidney should be out of the field of irradiation.

TECHNIQUES OF IRRADIATION

Some abdominal and pelvic sites are best treated with parallel, opposed anterior and posterior portals. When possible, multiple fields should be used to spare normal tissues. We have often found three-dimensional (3D) reconstruction of bulky localized disease useful. After reconstruction of the tumor volume, conformal fields or intensity-modulated RT may be used. A key benefit of computer planning in the treatment of abdominal NB is related to the ability to localize the kidneys and liver in addition to the precise delineation of the areas at risk for recurrent disease. Field position and blocking are used to minimize the dosage to normal tissue. However, often

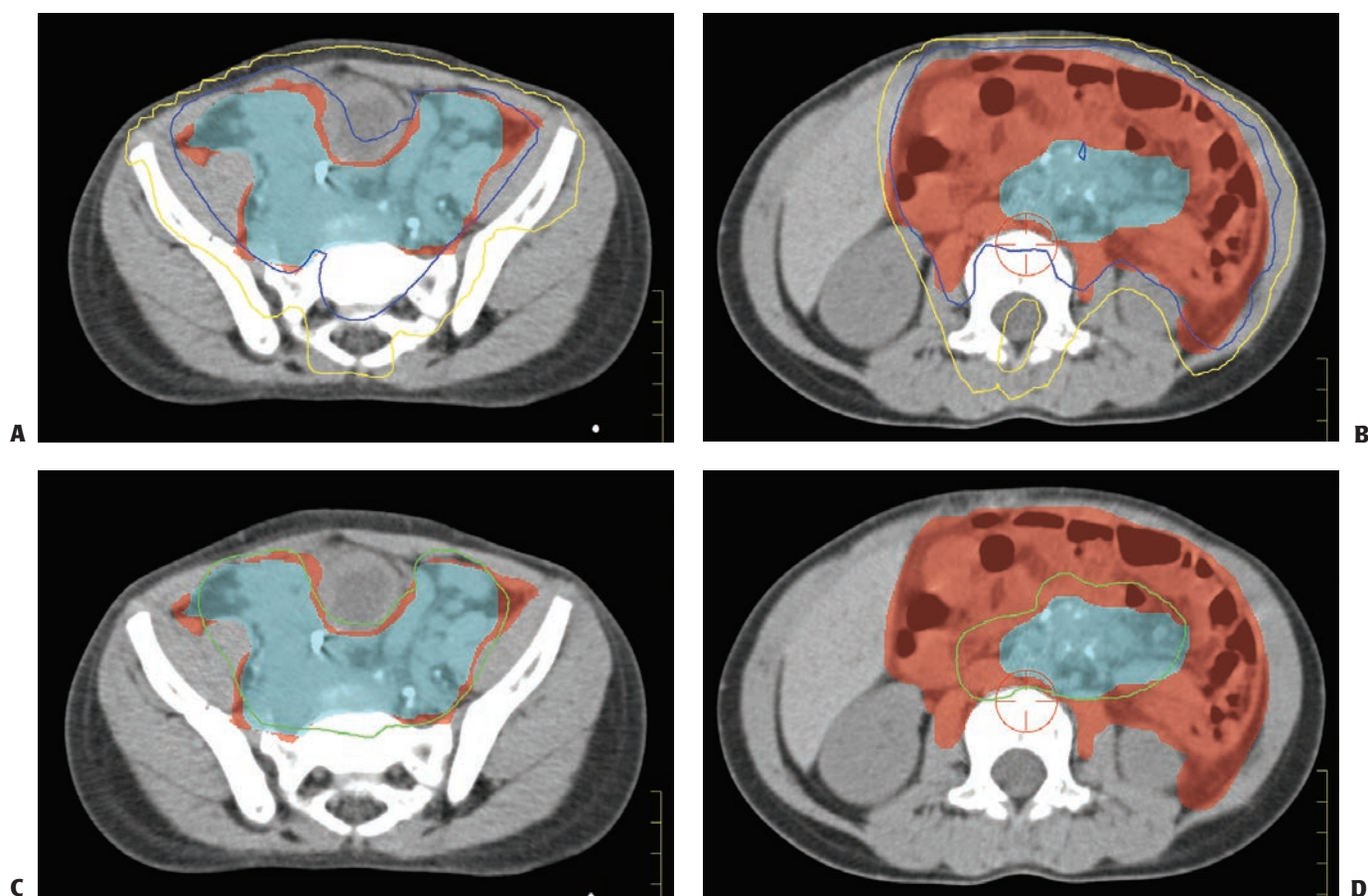


Figure 6.10 **A:** Two axial sections demonstrating dose distributions to the primary tumor volume (shown in red). CTV shown in red represents the postinduction chemotherapy, preoperative tumor volume that received 21.6 Gy; CTV shown in light blue is the postoperative residual disease that, per the COG ANBL0532 protocol, received a boost of 14.4 Gy for a total dose of 36 Gy. An IMRT plan was used and the isodose lines shown are 21.6 Gy (dark blue) and 18.0 Gy (yellow) highlighting the relative sparing of the bony pelvis as well as liver and kidneys. (With gratitude to Tarek Halabi, PhD, Hospital Physicist.) **B:** Two axial sections demonstrating isodose lines encompassing the gross residual postoperative tumor volume that received an additional boost of 14.4 Gy to a total dose of 36.0 Gy, as per the COG ANBL0532 protocol. The isodose line shown is 14.4 Gy (green) and shows the volume that received a total dose of 36.0 Gy. This child is without evidence of disease 2 years after radiation therapy.

anteroposterior/posteroanterior or minimally obliques fields prove to be best.

Improved imaging technology, specifically MRI and CT, and biological, metabolic imaging such as radiolabeled MIBG have improved delineation of tumor and surrounding critical structures. Novel techniques capitalize on an improved definition of tumor volumes, allowing clinicians to decrease the dosages delivered to critical structures while maintaining or increasing the dose to tumor. 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. Intensity-modulated radiotherapy (IMRT) has the potential to reduce morbidity (e.g., spare liver, kidneys).

CT images are analyzed jointly by radiation oncologists, diagnostic radiologists, pediatric oncologists, and pediatric surgeons. Once target volumes and critical structures are defined, beam geometry and weighting are defined and dose distribution is calculated. Selection of beam angles can be done by referencing axial images or by using beam's eye view (BEV). BEV allows visualization of the relationship of tumor volumes to the volumes 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 finally to optimize the 3D plan.

The last decade has seen rapid development of novel technical approaches to RT and its application to pediatric malignancies in general and NB in particular. These include 3D conformal RT (3D-CRT), IMRT, proton beam RT, intraoperative RT, and radiosurgery. In particular circumstances, such cutting-edge technical innovations can be of great help, as exemplified in Figure 6.11. Shown is a paravertebral mass with extension into the spinal canal that recurred locally after prior radiation therapy. Radiosurgery using the CyberKnife allowed sparing of the previously irradiated spinal cord.

Paulino et al. compared the use of conventional techniques to IMRT specifically for treatment of primary abdominal NBs. They found that although IMRT was superior to parallel, opposed anteroposterior/posteroanterior fields prescribed to midplane with respect to kidney doses, this advantage was at a cost of higher mean doses to the liver, stomach, and spleen. Furthermore, IMRT was not found to be superior to conventional anteroposterior/posteroanterior field arrangements for lateralized tumors (192). Thus, although IMRT has advantages of dose conformity that are particularly appealing in the treatment of children, each case must be individualized and the best plan be utilized for each individual patient. Excellent conformity is shown in Figure 6.12 in which IMRT allowed sparing of ears and contralateral eye while treating a maxillary sinus metastasis.

INTRAOPERATIVE RADIATION THERAPY

Patients with high-risk disease often present with large abdominal primary tumors, abutting or invading many dose-limiting normal tissues. External beam radiation to these tumors often entails treatment of a large volume of normal tissue, including bowel, liver, kidney, bony structures, and spinal cord. RT to NB occurring at other primary sites, including the thorax and pelvis, similarly exposes normal tissues to the risk of long-term side effects. Long-term toxicities associated with EBRT are particularly severe in children (160,182,193–196). Furthermore, EBRT may decrease renal function, resulting in diminished tolerance to high-dose chemotherapy with stem cell transplant.

Although EBRT plays a key role in NB treatment, several institutions have explored intraoperative RT (IORT) (Table 6.9) as an effective radiation modality that may minimize acute and long-term side effects. In contrast to EBRT, IORT allows treatment of high-risk areas at the time of primary resection. Critical structures can be directly visualized and manipulated at the time of surgery, allowing their exclusion from the radiation field

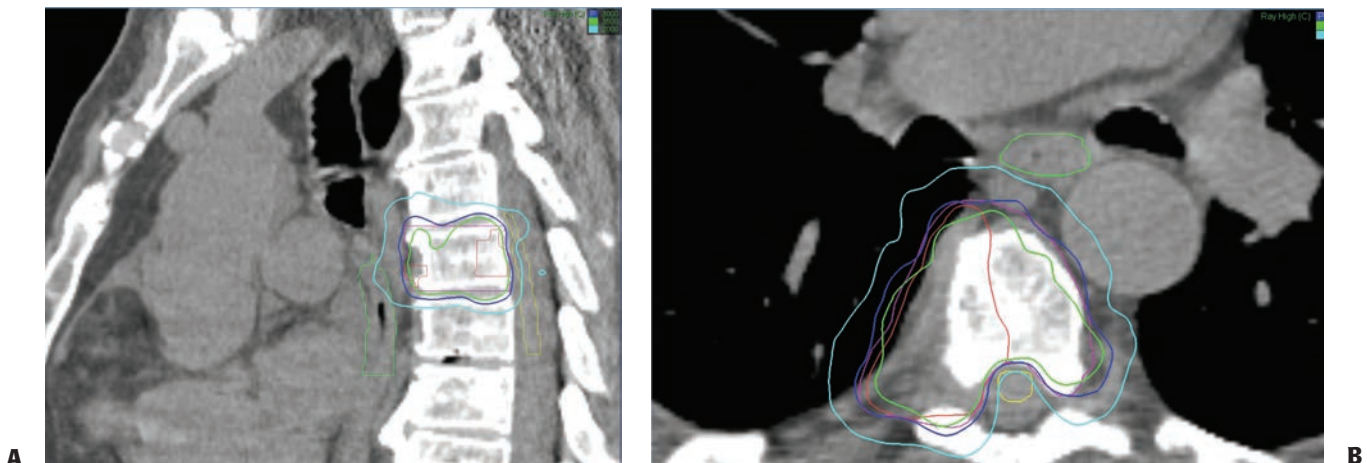


Figure 6.11 CyberKnife isodose lines and plan for the treatment of a paravertebral mass with extension into the spinal canal. Red line denotes the tumor volume shown on (A) sagittal, (B) axial, and (C) coronal sections. This locally recurrent mass after prior radiation therapy required sparing of the spinal cord that was achievable by CyberKnife treatment planning, as shown in the figure. A total dose of 30 Gy in five 6 Gy fractions was prescribed to the dark blue isodose line. The light blue and green lines denote the 20 and 35 Gy isodose lines, respectively.

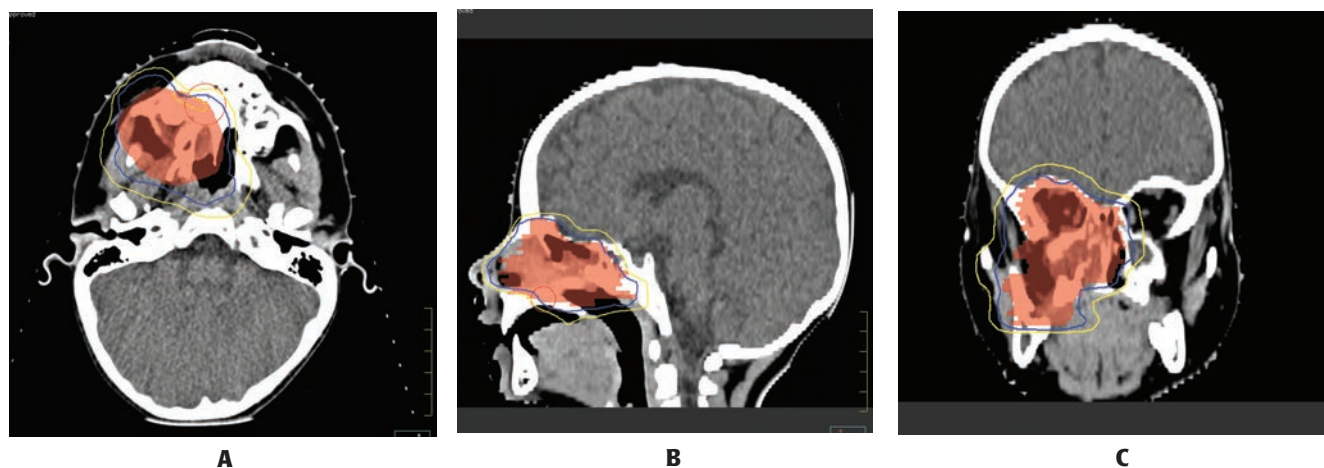


Figure 6.12 Axial, coronal, and sagittal sections showing the dose distribution for a right maxillary sinus metastasis that showed persistent ^{131}I -MIBG uptake on the pretransplant MIBG scan and therefore received 21.6 Gy. Radiation was administered using an IMRT plan. Isodose lines, 21.6 Gy in blue and 18.0 Gy in yellow, demonstrate excellent conformity with the tumor volume (shown in red) while sparing of the ears and contralateral eye. (With gratitude to Tarek Halabi, PhD, Hospital Physicist.)

if they are at low risk for microscopic disease. A high radiation dosage can be delivered to residual tumor and areas at high risk for microscopic disease with minimal radiation dosage to nearby normal tissues. A small number of studies have established the potential for IORT as a treatment modality in infants and children, including patients with NB (87,197–201). IORT in these studies is extremely well tolerated and may improve local disease control.

UCSF reported on a cohort of 28 consecutive patients treated with IORT for newly diagnosed high-risk NB. With follow-up ranging from 19 to 200 months (median 45 months), none of the 20 patients who had gross total resections experienced local recurrences. In contrast, three of eight patients who had subtotal resections experienced local recurrence, despite the addition of 20 Gy of EBRT to the primary site post-operatively (200). A more recent report focused on a historical cohort of 31 consecutively accrued patients with high-risk NB treated with IORT at UCSF (202). The 3-year estimate of local control, PFS, and OS rates were 85%, 47%, and 60%, respectively. Only 1 of 22 patients who had undergone gross total resection developed recurrence at the primary tumor site. Side effects attributable to either the disease process or multimodality treatment were observed in seven patients who developed either hypertension or vascular stenosis. These late complications resulted in the death of two patients; however, additional analysis is needed to determine the relative contributions of the disease process and specific components of the multimodality treatment to these adverse events.

IORT at the time of primary resection achieves excellent local control in patients with high-risk NB and is well tolerated. IORT achieves control and survival rates comparable to those of historical controls while avoiding the use of systematic EBRT. Additional therapy with EBRT may not be warranted in high-risk patients with gross total resection treated with IORT who have only microscopic residual disease, although more conclusive evidence requires larger patient numbers and longer follow-up. Higher local failure rates in patients with high-risk NB after incomplete resections or multiple positive lymph nodes warrant additional therapy with EBRT.

COMPLICATIONS

Patients with high-risk NB often present with large abdominal primaries, abutting or invading many dose-limiting normal tissues. EBRT to these tumors often entails treating a large volume of normal tissue, including bowel, liver, kidney, bony structures, and spinal cord. RT to NB occurring at other primary sites, including the thorax and pelvis, similarly exposes normal tissues to the risk of long-term side effects. Long-term toxicities associated with radiation are particularly severe in children (193–196,203). Furthermore, EBRT may decrease renal function, resulting in diminished tolerance to high-dose chemotherapy with stem cell transplant.

Acute side effects during RT depend on the precise normal tissues included in the radiation field. In the treatment of most primary tumors, whether thoracic or abdominal, radiation to the gastrointestinal tract, particularly the small bowel, may cause nausea and vomiting. Antiemetic medications are very effective in ameliorating such symptoms. Diarrhea and abdominal pain occur less often, and dietary counseling is generally sufficient to control such side effects. Some primary tumors and metastatic sites necessitate the inclusion of significant regions of bone marrow, resulting in a fall in blood counts that necessitates regular monitoring.

Long-term sequelae of radiation are of particular concern because most patients with NB are very young and prone to such toxicities (193–196,203). Dosages of approximately 20 Gy to bones produce only minimal deficits, although specific effects depend on the type of bone growth: radiation to epiphyses of tubular bones leads to bone shortening, whereas radiation to diaphyses impairs bone modeling and thickness. Effects on bone are highly dependent on patient age and radiation dosage (160). Substantial impairment in bone growth has been reported for dosages greater than 30 Gy, and although dosages of 10–20 Gy probably affect all cell types in maturing bones, such lower dosages probably will produce more subtle clinical sequelae. For all patients, regardless of delivered dosage, shielding of bone growth centers will minimize potential growth arrest and skeletal abnormalities. When one is treating regions close to vertebrae, irradiation of

Table 6.9
Intraoperative Radiotherapy for Neuroblastoma

Reference	Stage	Local Control/Total Patients	IORT Dosage Median (Range), in Gy	EBRT Given (n)	IORT for Persistent or Recurrent Disease	IORT Toxicity
197	III: 7					
	IV: 18	18/25	10 (10–15)	8	25	None identifiable
198	2B: 1					
	3: 2					
	4: 5	7/8	10 (3–15)	4	0	None identifiable
199	II: 2					
	III: 12					
	IV: 10	13/24	10 (7–15)	6	10	Transient pancreatitis (1) Postoperative intussusception (2)
200	3: 6					
	4: 17	6/23	10 (7–16)	3	3	Narrowing of abdominal aorta (1)

EBRT, external beam radiation therapy; IORT, intraoperative radiotherapy.

the entire vertebral bodies reduces the risk of scoliosis and other musculoskeletal abnormalities.

A high incidence of spinal deformity has been seen in long-term survivors of NB. Among the most common abnormalities are postsurgery or postirradiation kyphosis or scoliosis (51,175,204,205). The incidence of these abnormalities in 5-year survivors of NB with paraspinal tumors ranges from 25% to 50%. Factors associated with development of spinal deformity include irradiation at a very young age, orthovoltage irradiation, asymmetric irradiation of the spine, epidural spread of tumor, and laminectomy. In young children, a laminectomy may result in growth abnormality, gibbus formation, and instability of the spine. Therefore, the young child with a dumbbell-shaped tumor is at risk for spinal deformity, and every effort should be made to minimize this and other late sequelae with the use of chemotherapy when possible as first-line treatment for cord compression or surgical decompression using osteoplastic laminotomy rather than traditional laminectomy (51,52,205,206).

In addition to musculoskeletal toxicities, local radiation may cause organ dysfunction if tolerance dosages are exceeded. Whole organ tolerance levels generally are presented as dosages that cause a severe complication rate of 5% within 5 years of radiation completion. These include the lungs (17.5 Gy), kidneys (20 Gy), liver (30 Gy), small bowel (40 Gy), ovaries (10 Gy), and testes (2 Gy). These tolerance dosages are general guidelines and may be lower in children and in patients who are also receiving chemotherapy. Skull and orbital metastases are common in NB, often necessitating irradiation of normal brain tissue. The risks of neurocognitive dysfunction and endocrine abnormalities increase with higher dosages of radiation, larger volumes of irradiated normal brain, and younger age at time of radiation. Lens tolerance is as low as 10 Gy, and dosages to the lens should be minimized to prevent cataract formation.

Permanent alopecia is extremely rare after dosages of 21 Gy or less, but permanent hair thinning may occur in a small proportion of children.

Investigators at Memorial Sloan-Kettering Cancer Center have described the spectrum of long-term complications in a population of survivors of advanced-stage NB (195). The study included 63 survivors with a median age at diagnosis of 3.0 years and a median follow-up from diagnosis of 7.06 years. All patients had surgery and received chemotherapy, 89% received RT, 62% immunotherapy, and 56% autologous stem cell transplant. The vast majority of survivors (95%) experienced late complications that included hearing loss (62%), primary hypothyroidism (24%), ovarian failure (41% of females), musculoskeletal (19%), and pulmonary (19%) abnormalities. As would be expected based on known toxicities of specific drugs, survivors who received cisplatin were at greater risk for developing hearing loss, and greater total doses of cyclophosphamide were associated with ovarian failure. Although the majority of complications were moderate, 4% were deemed life-threatening.

Another recent manuscript investigates potential post-treatment complications of aortic growth inhibition and Middle Aortic Syndrome in patients with NB. These investigators used CT to analyze effects of RT on the growth of the aorta in NB patients. Abdominal CT scans of 31 patients with intra-abdominal NB (stage II–IV), treated with RT ($n = 20$ IORT/EBRT, $n = 11$ EBRT alone), were analyzed retrospectively. The diameter of the abdominal aorta was measured before and after RT in 31 patients with intra-abdominal NB (stage II–IV) ($n = 20$ IORT/EBRT, $n = 11$ EBRT alone). These data were compared to normal, predicted aortic diameters of children and to a control group of children who did not undergo irradiation. They found that mean aortic diameters pre-RT and post-RT and the growth of the aorta were significantly lower than expected for patients with NB and when compared to the growth in a control group with normal and nonirradi-

ated aorta. However, among the irradiated patients, there was no difference due to the type of RT—IORT/EBRT versus EBRT alone. Seven patients from the IORT ± EBRT group developed vascular complications that included hypertension, middle aortic syndrome, death due to mesenteric ischemia, and critical aortic stenosis that required aortic bypass surgery. These finds led the authors to recommend that CT evaluations of RT-treated NB patients should include not only reports of changes in tumor extension, but also documentation of perfusion, size, and growth of the aorta and its branches over time (207).

Whereas side effects of local radiation depend on the exposed normal structures, TBI carries inherent toxicities that, like local radiation, worsen with increasing radiation dosage and decreasing patient age. Long-term side effects of TBI include risks of impaired growth, chronic interstitial lung disease, cataracts, neurocognitive deficits, chronic renal insufficiency, dental disturbances, and endocrinopathies (193,195,196,167,208–211). After fractionated TBI, a majority of patients experience diminished height and endocrine deficits, most commonly manifest by delayed puberty, but only a minority of patients experience other major organ toxicities.

Both local RT and TBI carry the risk of second malignancies. Reliable risk estimates of second malignancies after RT for NB are not available. In the treatment of a malignancy with guarded prognosis such as high-risk NB, the risk of death from recurrent disease clearly outweighs the risk of death from a second malignancy. One may extrapolate from a large body of literature in pediatric Hodgkin disease survivors and assume that children who are cured after receiving radiation for NB will develop additional cancers 10–20 years later (212). Common radiation-related malignancies include breast cancer, sarcomas, lymphomas, and other solid tumors. Long-term survivors of NB need lifelong screening for late sequelae of RT.

TARGETED RADIONUCLIDES

Targeted radioisotope therapy using anti-GD2 antibody or MIBG for delivery of radiation in the form of ^{131}I has also been tested in clinical trials in relapsed and newly diagnosed NB (213,214). Although responses were reported, this has not advanced into cooperative or phase III trials, possibly due to the myelosuppression and the lack of an available commercialized form of the antibody. MIBG is a guanethidine derivative that is structurally similar to norepinephrine and therefore concentrates in the neurosecretory granules of catecholamine-secreting cells. Radiolabeled MIBG provides very sensitive and specific visualization of primary and metastatic NB in 90% of tumors by scintigraphy. In an attempt to deliver higher dosages of tumor-specific RT and avoid normal organ toxicity, ^{131}I -MIBG therapy has been used in pilot trials since the mid-1980s, with more than 500 children reported in the literature. Initially, it was shown to induce a 30–40% response rate in highly refractory relapsed patients, without significant non-hematologic toxicity (215,216). At low and moderate dosages, up to 12 mCi/kg of ^{131}I , the main toxicity has been thrombocytopenia, usually self-limited. Phase I dosage escalation studies showed that higher dosages, up to 18 mCi/kg, could be administered with bone marrow or peripheral blood stem cell support to mitigate the neutropenia and thrombocy-

topenia, but still without other organ toxicity, excepting a 10–15% incidence of hypothyroidism caused by an uptake of some free iodide by the thyroid gland (177). There are a few reports of patients with secondary leukemia developing after MIBG therapy, but the estimated risk of this problem at 5 years after therapy is only 4%, lower than with some chemotherapy regimens (217,218). Recent studies are investigating the use of low-dose ^{131}I -MIBG at diagnosis before surgical resection (219) or in combination with standard (220) or high-dose myeloablative chemotherapy (120,221,222). The response rate in 22 patients was 27%, and there were 5 patients surviving more than 3 years (120). A phase II study on the use of ^{131}I -MIBG with myeloablative chemotherapy and stem cells for refractory patients has been completed in a multi-institution consortium, New Approaches to Neuroblastoma Therapy (NANT), and a pilot COG study (ANBL09P1) will open this year to test this concept in newly diagnosed high-risk patients. Additional investigations are needed to determine the optimal timing and use of this targeted approach.

MOLECULARLY TARGETED AGENTS

Novel agents directed at genetic aberrations in NB have entered clinical trials. One example is histone deacetylase inhibitors (HDACIs) that have emerged as a new concept in cancer therapy. Among HDACIs, vorinostat is furthest along in clinical development and is the first agent in its class to be approved by the Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma. Several studies have shown that HDACIs, including vorinostat, have radiosensitizing functions in a variety of cancer models (223). The underlying mechanism for radiosensitization is not fully understood but studies show that vorinostat inhibits expression of double-strand break repair enzymes like Rad51 and Ku87.

Consortium studies, including those within COG, have examined vorinostat as a single agent and in combination with additional agents (e.g., combined with isotretinoin in the COG study) (224). These trials have demonstrated favorable safety profiles in adults and children. Recent research lends considerable enthusiasm to combining vorinostat and ^{131}I -MIBG therapy for the treatment of NB. This study finds that not only does vorinostat sensitize NB cells to radiation in vitro and in vivo, but also it increases expression of the norepinephrine transporter (NET), which in turn enhances MIBG uptake by NB cells in a dose-dependent fashion. Based on such promising results, NANT has opened a phase I clinical trial (NANT 2007-03) in which vorinostat will be combined with ^{131}I -MIBG therapy for resistant/relapsed NB. Other targeted agents under investigation include inhibitors of specific activated genetic pathways, including ALK, Trk B, PI3 kinase, IGF1R, Aurora A kinase, and mTor.

FUTURE INVESTIGATIONS

Current treatment regimens for NB are risk based; that is, the biologic characteristics of the tumor are considered together with traditional clinical prognostic factors in determining the optimal therapy. As data are accumulated, the most powerful independent prognostic determinants will be clarified. Areas of active investigation include the following:

- Efforts to develop chemotherapeutic agents with new mechanisms of action.
- Megatherapy (high-dose chemotherapy with or without RT) followed by hematopoietic stem cell rescue.
- Targeted therapy using radiolabeled MIBG or monoclonal antibodies.
- The use of biologic response modifiers or immunotherapy, such as IL-2, IL-12, or dendritic cells and vaccines. The retinoids, such as 13-*cis*-retinoic acid and fenretinide, can decrease tumor cell proliferation, morphologic differentiation, expression of N-myc, or apoptosis.
- Targeted inhibitors of activated critical genetic pathways.
- Clinical studies are in progress to assess the potential benefit of these agents.

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Hodgkin Lymphoma

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Pediatric Hodgkin lymphoma (PHL) presents a challenge to continue making progress in its curability while diminishing the risk for the morbidities that compromise quality of life and survival. The history of PHL is, of course, the history of Hodgkin lymphoma (HL). In 1832, Thomas Hodgkin (1) described seven patients with enlarged absorbent (lymphatic) glands not thought to result from inflammation. At the turn of the century, Sternberg and Reed each described the multinucleated giant cell characteristic of HL (2). Shortly after the discovery of x-rays in 1902, Pusey (3) demonstrated the radioresponsiveness of HL. In the 1930s, Gilbert (4) laid the foundation for its definitive treatment with radiotherapy (RT), and Peters (5) provided additional definition of important principles. During World Wars I and II, the lympholytic effects of nitrogen mustard were recognized (6), and over the next two decades progress in safely combining multiple chemotherapeutic agents to treat HL led to DeVita's (7) report on the use of nitrogen mustard, vincristine (Oncovin), procarbazine, and prednisone (MOPP) chemotherapy. Kaplan (2) systematically studied the role of RT for HL during these decades. Concurrently, advances were made in identifying different pathologic subtypes, determining staging criteria, improving diagnostic imaging capabilities, and developing effective chemotherapeutic regimens. When the clonality of the Hodgkin-Reed-Sternberg (HRS) cell was finally established in the 1960s, controversy over the malignant or inflammatory nature of HL abated (8).

Although the biology and natural history of HL in children are similar to that in adults, when irradiation techniques and dosages suitable for controlling disease in adults were translated to the pediatric setting, substantial morbidities (primarily musculoskeletal growth inhibition) were produced (9,10). It is in this context the new strategies for the treatment of pediatric HL were developed by Donaldson and others (11–19). Historically, children were thought to have a worse prognosis than adults (2). It is now apparent that the converse is true (20–22).

BIOLOGY

For many years, the rarity and distribution of malignant cells in pathologic material precluded elucidation of the origin and evolution of the HRS cell. Advances in immunohistology and molecular biology subsequently revealed that the HRS cell and its variants most commonly derive from a neoplastic clone that originates from B lymphocytes in lymphoid germinal centers. Clonality can be demonstrated at diagnosis and relapse through detection of unique nucleotide sequences, which molecularly fingerprint the HRS cell clone; these

sequences represent rearrangements of immunoglobulin variable-region (V) genes, which are B-cell derived (23,24). Complicating this scenario is the finding by Kanzler et al. (24) that flawed V genes, which would be lethal for normal B cells, are present in HRS cells and prevent them from expressing immunoglobulin. Such cells would be expected to die of apoptosis. Therefore, the genesis of classic HL (CHL) probably involves evasion by the HRS cell of the apoptotic pathway. Deregulation of the nuclear transcription factor (NF- κ B) in the HRS cells has been hypothesized as a mechanism that prevents apoptosis (25). Epstein-Barr virus (EBV) and genes that monitor cell damage, such as *p53*, may play a role in the rescue and repair of the HRS cells (24,26). EBV genome fragments can be found in HRS cells in 30–50% of HL specimens, most commonly in the mixed-cellularity HL (MCHL) subtype and rarely in the lymphocyte-predominant HL (LPHL) (27,28). The EBV genome is temporally stable because it can be found at diagnosis and relapse. Finally, the HRS cell can also have characteristics of T lymphocytes and the interdigitating reticulum cell. Such evidence of a multilineage origin of the HRS cell may be explicable by postulating that the HRS cell is a hybridoma resulting from fusion of different cell lines, provoked by a virus or other agent. Cytogenetic data also show an unexpected frequency of B-cell translocation (14:18) and *bcl-2* gene involvement in HL, but these may derive from bystander normal lymphocytes rather than the HRS cell (29). The complexity of elucidating the etiology of HL continues to unfold, and is illustrated by recent data that not only support the association of infectious mononucleosis with EBV-positive HL, but also suggest that EBV-negative HL has a different etiology (30). A pathogenetic model for HL is depicted in Figure 7.1, which suggests that the HRS cells arise in a germinal lymphoid center from a clone of antigen-stimulated B cells and through genetic changes achieve immortality and malignant properties (31).

A curious characteristic of HL is the rarity (about 1%) of the malignant HRS cell in specimens and the abundant reactive cellular infiltrate of lymphocytes, macrophages, granulocytes, and eosinophils. The histologic features and clinical symptoms of HL have been attributed to the numerous cytokines secreted by the HRS cells, which include interleukin (IL)-1 and IL-6, and tumor necrosis factor (TNF) (32,33). IL-5 could be responsible for the eosinophilia in MCHL, and transforming growth factor β could be responsible for the fibrosis in the nodular sclerosis subtype. These cytokines also enable the cells to evade immunologic surveillance and promote their own replication (32).

Evidence that HL comprises a family of diseases includes the observation that HRS cells can rarely be

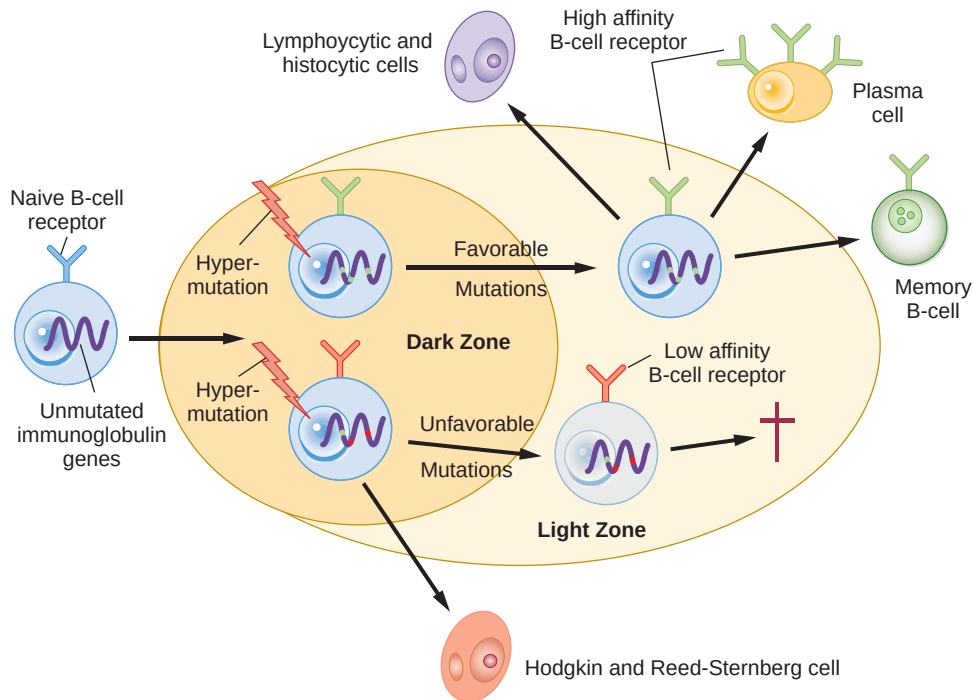


Figure 7.1 The derivation of Hodgkin and Reed-Sternberg cells in classic Hodgkin's lymphoma and lymphocytic and histiocytic cells in nodular lymphocyte-predominant Hodgkin's lymphoma. (From Thomas RK, Re D, Wolf J, et al. Part 1: Hodgkin's lymphoma— molecular biology of Hodgkin and Reed-Sternberg cells. *Lancet Oncol* 2004;5:11–18.)

derivatives of cytotoxic T cells and that nodular lymphocyte-predominant HL (NLPHL) is a distinctive and uncommon lymphoproliferative disorder. The lymphocytic and histiocytic (L&H) cells characteristic of NLPHL have folded and lobate nuclei among small lymphocytes and histiocytes. The L&H cells are also B cell-derived but harbor V gene alterations, which differ from those in HRS cells; whether the L&H cells are monoclonal is unclear (34,35). The clinical characteristics of NLPHL differ from those of the subtypes of CHL by virtue of its indolence, excellent prognosis, epidemiology, and response to chemotherapy. The Revised European–American Classification of Lymphoid Neoplasia (REAL) has devised a schema that reflects the distinction of NLPHL from CHL (36).

Several aspects of the biology of HL continue to unfold, and many have prognostic applicability. For example, loss of CD15 expression may be a prognostic factor for PHL clinical outcomes, although CD15 expression has been inconsistent possibly due to biologic or technical variability (37,38). A high proliferative index (PI) may suggest chemoresponsiveness and, as a result, a low pre-treatment PI may be associated with poor outcomes (37,38).

EPIDEMIOLOGY

HL makes up 6% of childhood cancers. A striking male:female predominance is found among children, with a ratio of 4:1 for 3- to 7-year-olds, 3:1 for 7- to 9-year-olds, and 1.3:1 (a ratio more similar to that of adults) for older children (20,39,40). The age-specific incidence curves for HL in the United States and other developed countries are bimodal, peaking in the 20s and then again after the age of 50 (41). The disease is uncommon

before age 5 and, among children, is most common in adolescence. Not only does the incidence of PHL vary in younger children versus adolescence, but the histologic subtypes and associations with EBV also vary (42).

Although evidence that HL is infectious or contagious was suggested by reports of case clusters (43), confirmatory data are lacking. However, the role of EBV in its pathogenesis of EBV-positive HL is well established (30). EBV early RNA1 is expressed in HRS cells in 58% of childhood cases, most commonly in those with mixed-cellularity histology (44). Of particular interest, expression was age-dependent: 75% of children under the age of 10 years compared with 20% of older children. In addition, a history of infectious mononucleosis increases the risk for HL, and anti-EBV titers are elevated before diagnosis of HL.

In a large population-based study, infectious mononucleosis was associated with an increased risk of EBV-positive HL with an odds ratio of 3, but did not increase risk for EBV-negative HL (30). EBV latent membrane protein (LMP-1) is expressed in CHL and has been correlated with serum IL-10 levels (45). LAG-3 expression, a marker for regulatory T cells, is also associated with EBV positivity and related to impairment of LMP-1 function (46). Several reports have suggested that EBV positivity is most common in the MCHL subtype (47–49). There has been conflicting evidence as to whether latent EBV infection carries prognostic significance. LMP-1 positivity has been associated with inferior survival in patients with nodular sclerosis cellular subtype Bennett II and those with advanced-stage disease despite a lack of influence on failure-free survival. LMP-1 emerged as an independent prognostic factor for overall survival (OS) on multivariate analysis in a study by Claviez et al. Latent EBV infection has also been

associated with inferior OS in patients greater than the age of 50 years when adjusting for stage, sex, and B symptoms, although it was not associated with inferior disease-specific survival (48). Analysis of the database of the International Hodgkin Study Group revealed no significant differences associated with EBV positivity in failure-free survival or OS after adjustment for stage and age (45,49). Understanding the pathogenesis and prognostic implications of EBV-associated HL may help to improve immune-directed therapeutic strategies.

Evidence of a genetic predisposition exists and is relevant when counseling families. The incidence of HL is two to five times higher in the siblings of affected children and nine times higher in same-sex siblings than in the general population. Parent–child associations have been reported (41,50). Mack et al. (51) reported a 99-fold increased risk in monozygotic twins of patients but no increased risk in dizygotic twins. The status of the immune system in patients with HL also deserves comment. A complex deficiency in cellular immunity exists, which includes a deficiency in naive T cells and an elevated sensitivity of effector T cells to suppressor monocytes and T-suppressor cells (52). Of interest is that radiation results in a long-term dysregulation of T-cell subset homeostasis. Finally, it is unclear whether HL is more common in patients with either congenital (e.g., ataxia–telangiectasia) or acquired immunodeficiency states, including acquired immunodeficiency syndrome (43,53), but HL is rarely seen as a second malignancy. In patients with the human immunodeficiency virus, the disease more commonly presents in an advanced stage with systemic symptoms, extranodal involvement, and a poor response to therapy (54).

CLINICAL PRESENTATION

HL appears to be unifocal in origin, with 90% of patients presenting in a pattern that suggests contiguous lymphatic spread (2,55). Most children are diagnosed on the basis of supradiaphragmatic lymph nodes, with painless cervical adenopathy in 80%. The nodes are generally firm and may be tender. Mediastinal involvement occurs in 76% of adolescents but in only 33% of 1- to 10-year-olds. Mediastinal disease may produce symptoms such as dyspnea, cough, and superior vena cava syndrome. Axillary adenopathy is less common (2). Associations exist between the mediastinum and the neck, the neck and the ipsilateral axilla, the mediastinum and the hilum, and the spleen and abdominal lymph nodes (55). Isolated mediastinal or infradiaphragmatic HL is rare, occurring in fewer than 5% of patients. About one third of the patients have systemic “B” symptoms, as defined in Table 7.1 (2,56).

PATHOLOGIC CLASSIFICATION

The HRS cell is the essential malignant cell in HL (Fig 7.2). It is large, with abundant cytoplasm, two or three nuclei, and a prominent nucleolus. However, its frequency in pathologic specimens is greatly variable because of the presence of numerous reactive cells including lymphocytes, eosinophils, and plasma cells. Moreover, the HRS cell, particularly its mononuclear variant, is not pathognomonic for HL because cells simulating it can be found in other disorders that are reactive, infectious, or malignant (57). The diagnosis of HL must be established by lymph node biopsy. Aspiration cytology alone is not recommended because of the lack of stromal tissue, the

Table 7.1	
Ann Arbor Staging System with Cotswold Modifications for Hodgkin Lymphoma	
Stage	Description
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, the Waldeyer ring, or single extralymphatic site [IE])
II	Involvement of two or more lymph node regions on the same side of the diaphragm or localized contiguous involvement of only one extranodal organ or site and lymph node region on the same side of the diaphragm (IIE). The number of anatomic sites is indicated by a subscript (e.g., II ₃)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by involvement of the spleen (III _S) or by localized contiguous involvement of only one extranodal organ site (III _E) or both (III _{SE})
III ₁	With or without involvement of splenic hilar, celiac, or mesenteric nodes
III ₂	With involvement of para-aortic, iliac, or mesenteric nodes
IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement
Designations applicable to any stage	
A	No symptoms
B	Fever (temperature >38°C), drenching night sweats, unexplained loss of >10% of body weight in the preceding 6 months
X	Bulky disease (a widening of the mediastinum by more than one third or the presence of a nodal mass with a maximal dimension >10 cm)
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site
CS	Clinical stage
PS	Pathologic stage (as determined by laparotomy)

Modified from Kaplan H. *Hodgkin's Disease*. Cambridge, MA: Harvard University Press; 1980; and Grufferman S, Delzell E. Epidemiology of Hodgkin's disease. *Epidemiol Rev*. 1984;6:76–106, with permission.

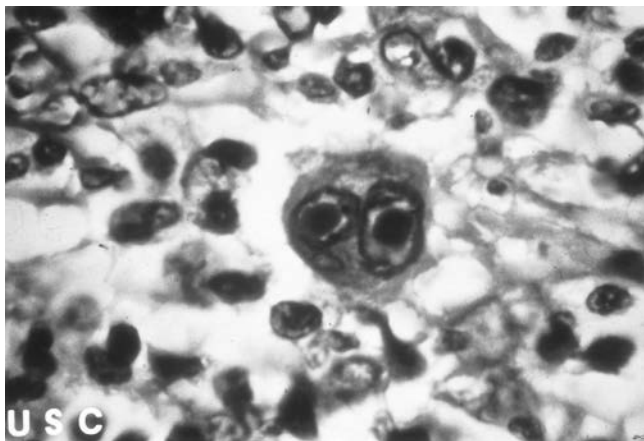


Figure 7.2 Reed–Sternberg cell.

small number of cells present in the specimen, and the difficulty of classifying HL into one of the four categories of the Rye classification. The Rye classification subcategorizes HL into nodular sclerosing (NSHL), MCHL, LPHL, and lymphocyte-depleted (LDHL) types. With modern treatment the prognostic significance of these subtypes has diminished, although the presenting characteristics and natural history remain evident, particularly for the nodular subtype of LPHL. The importance of distinguishing NLPHL from the other types has led to the REAL classification (Table 7.2) (39). The clinicopathologic characteristics are the same as those in adults and are briefly described here.

- NLPHL (58): The distinctive cell is the L&H “popcorn” cell, which is CD20 (B-lymphocyte marker) positive and CD15 negative. Classic HRS cells (which are usually CD15 and CD30) are rare, as is the detection of EBV. Progressive transformation of the germinal centers of lymph nodes is often seen, and, in fact, can occur in the absence of NLPHL. Therefore, it is important to distinguish these entities. NLPHL has a long natural history, in its time to diagnosis and to relapse, reminiscent of that of indolent non-Hodgkin lymphomas (NHL). It is more common in young children (33% of all patients are younger than 15 years), has a high male:female ratio (4:1), and commonly involves a single lymph node region with sparing of the mediastinum (59).
- Lymphocyte-rich (classic) HL: HRS cells (CD15) are identifiable against a background predominantly of lymphocytes. Clinical behavior is similar to that of MCHL.

- Mixed-cellularity (classic) HL: HRS cells (CD15) are common against a background of abundant normal reactive cells (lymphocytes, plasma cells, eosinophils, histiocytes). This subtype can be confused with peripheral T-cell NHL. MCHL is less common in children, often accompanied by “B” symptoms, and more often involves infradiaphragmatic nodes.
- Nodular sclerosis (classic) HL: This subtype is distinctive because of the presence of collagenous bands that divide the lymph node into nodules, which often contain an HRS cell variant called the lacunar cell. NSHL often occurs in children, involves supradiaphragmatic nodes, and spreads in an orderly manner along contiguous nodal chains.
- Lymphocyte-depleted (classic) HL: This subtype is rare and commonly confused with NHL, particularly of the anaplastic large cell type. HRS and pleomorphic variants are common relative to the number of background lymphocytes. LDHL often is advanced at diagnosis and has a poor prognosis.

Although the pathologic and immunohistochemical characteristics of HL generally are sufficiently clear to establish a diagnosis, confusion with select subtypes of NHL is problematic. In particular, CHL and NLPHL can be confused with anaplastic large cell NHL, and LPHL can be confused with T cell–rich B-cell NHL (32,39). NHL, and LPHL can be confused with T cell–rich B-cell NHL (32,39).

The relative distribution of the subtypes in younger children differs from that in adolescents and adults, as reported from Stanford University (20). LPHL is more common (13%) in younger children (younger than 10 years), whereas LDHL is exceedingly rare. Although NSHL is the most common subtype in all age groups, it is more common in adolescents (77%) and adults (72%) than in younger children (44%). Conversely, MCHL is more common in younger children (33%) than in adolescents (11%) or adults (17%).

STAGING

Using anatomic groups of regional lymph nodes, the staging system was designed for all age groups, according to a modification of the system devised at the 1970 Ann Arbor Symposium. This was subsequently revised at the Cotswold’s Meeting, although not all suggestions from those recommendations are consistently used (56). In this system patients are assigned a clinical stage, and if staging laparotomy is performed, the patient is assigned a pathologic stage (Table 7.1) (2).

A weakness of the Ann Arbor system is its failure to consider disease bulk (either dimension or number of involved sites) or specific patterns of involvement. For this reason,

Table 7.2 Comparison of Revised European–American Classification of Lymphoid Neoplasia (REAL) and Rye Classification of the Hodgkin Disease	
REAL Classification	Rye Classification
Lymphocyte predominance, nodular	Lymphocyte predominance, nodular (most cases)
Classic Hodgkin disease	
Lymphocyte-rich	Lymphocyte predominance, diffuse (most cases)
Nodular sclerosing	Lymphocyte predominance, nodular (some cases)
Mixed cellularity	Mixed cellularity
Lymphocyte depletion	Lymphocyte depletion

Modified from Klein G. Epstein–Barr virus–carrying cells in Hodgkin’s disease. *Blood*. 1992;80(2):299–301, with permission.

subclassifications of the Ann Arbor staging system have been proposed, particularly for patients with large mediastinal adenopathy (LMA) or stage IIIA disease. LMA, most commonly defined as a mass exceeding one third the transverse diameter of the chest (intrathoracic width measured at the dome of the diaphragm) on a standard upright posteroanterior chest radiograph, places a patient at a greater risk for disease recurrence after radiation alone. Patients with pathologic stage (PS) III disease limited to the spleen or splenic, celiac, or portal nodes are denoted anatomic substage III1 and considered to have a more favorable prognosis than patients with involvement of para-aortic, iliac, or mesenteric nodes, denoted as III2 (60). However, this system has not proven useful in some centers.

The distribution of stages observed in children is somewhat different from that observed in adults. Table 7.3 summarizes the demographic and clinical features of children, adolescents, and young adults presenting with HL (61). Among 3571 consecutive patients with HL treated at three pediatric centers, 18.1% were younger than 10 years and 81.4% were 11–16 years old. Stage I or II disease was present in 65.8% of children.

DIAGNOSTIC EVALUATION

After pathologic confirmation, the patient undergoes an extensive clinical staging. This begins with a detailed history of systemic symptoms and evidence of cardiorespiratory compromise or organ dysfunction. The physical examination carefully records the location and size of all palpable lymph nodes. An evaluation of Waldeyer ring, cardiorespiratory status, and organomegaly is vital. *Laboratory studies* include complete blood count with platelets and biochemical evaluation of renal and liver function. Acute phase reactants, including erythrocyte sedimentation rate, serum copper, and ferritin, may be elevated at diagnosis and can be used as nonspecific marker of disease activity. Elevated serum CD30 and CD25 have been correlated with advanced stage, the presence of constitutional symptoms, and poor prognosis; however, these studies have not been widely used to stage and monitor patients during therapy (62,63). C-reactive protein, another acute phase protein produced in the liver, holds promise as a diagnostic and prognostic index for both Hodgkin and cardiovascular

Table 7.3

Demographic and Clinical Characteristics at Presentation of Pediatric Hodgkin Disease

Age Range	Childhood HL ≤14 years	AYA HL 15–35 years	Adult HL ≥35 years	Older Adult HL ≥55 years
Prevalence of HL Cases	10–12%		50.00%	35.00%
Gender				
Male:Female	2–3:1		1:1–1.3:1	1.2:1–1:1.1
Histology				
Nodular sclerosis	40–45%		65–80%	35–40%
Mixed cellularity	30–45%		10–25%	35–50%
Lymphocyte-depleted	0–3%		1–5%	2–6%
NLPHL	8–20%		2–8%	7–10%
EBV-associated	27–54%	20–25%	34.00–40%	50–56%
	Risk factors: male, younger age, mixed-cellularity histology, economically disadvantaged countries			
Other risk factors	Lower SES Increasing family size	Higher SES Smaller family size		
Stage at presentation	30–35 % with stage III or IV disease 25% with B symptoms	Early birth order 40% with stage III or IV disease 30–40% with B symptoms		55% with stage III or IV disease 50% with B symptoms Trend to less bulky disease, less mediastinal mass but more advanced stage with higher IPS scores
Relative survival rates at 5 years	94% (<20 years)	90% (<50 years)		65% (>50 years)

SES, socioeconomic status

From Punnett A, Tsang R, Hodgson DC. Hodgkin lymphoma across the age spectrum: epidemiology, therapy, and late effects.

In: Constine, LS, ed. Cancer genesis, treatment, and late effects across the age spectrum. *Seminars in Radiation Oncology*. 2010;20(1):30–44.

diseases (64). Patients with “B” symptoms or stage III–IV disease should undergo bone marrow biopsy (65). The low yield of a bone marrow evaluation in asymptomatic patients with localized disease (stage I and II) does not support routine use of the procedure.

Imaging studies of the thorax should include a chest radiograph with a posteroanterior and lateral view. It should be noted that the LMA ratio, if based on computed tomography (CT) scan measurements, would increase the frequency of patient’s LMA since a mediastinal mass will splay bilaterally in a reclined child. CT scans are essential for delineation of the status of intrathoracic lymph node groups (including the hila and cardiophrenic angle), lung parenchyma, pericardium, pleura, and the chest wall, demonstrating abnormalities in about one half of patients with unremarkable chest radiographs (22,66). Definition of disease involvement of intrathoracic tissues by CT often dictates more aggressive therapy than would otherwise have been administered. Distinguishing normal (or hyperplastic) thymus from nodes in children can be problematic.

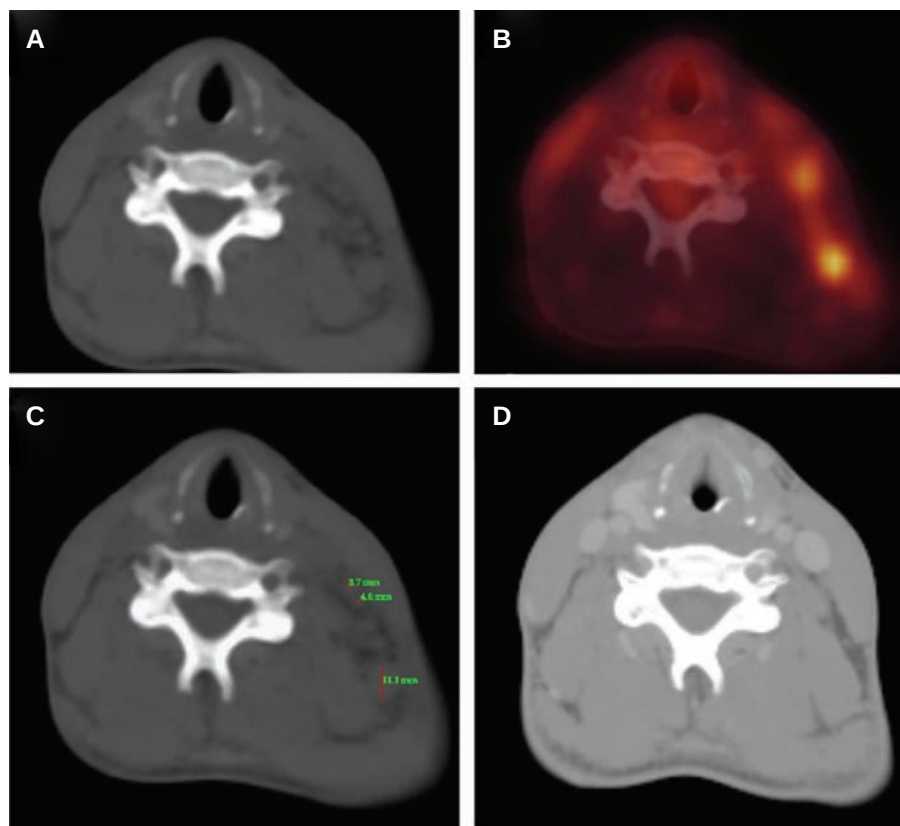
Imaging of the abdomen and pelvis may involve an abdominal and pelvic CT scan or magnetic resonance imaging (MRI). If CT is used, oral and intravenous contrast administration is needed to accurately distinguish retroperitoneal and pelvic lymph nodes from other infradiaphragmatic structures. In cases with suboptimal contrast resolution of the bowel, MRI may provide a better evaluation of the fat-encased retroperitoneal nodes (67). In previous German and Pediatric Oncology Group (POG) trials using CT or MRI for staging, the size of abdominal and pelvic lymph nodes was used to define the disease involvement. Abdominal nodes less than 1.5 cm in diameter and pelvic nodes less than 2 cm were considered negative, whereas abdominal nodes more than 2 cm in

diameter and pelvic nodes more than 3 cm were considered positive. Nodal biopsies were undertaken in equivocal nodes falling in between these sizes.

HL involving the liver and spleen is suggested by CT or MRI findings of organomegaly with areas of abnormal density. Organ size alone does not reliably predict lymphomatous involvement because tumor deposits may be less than 1 cm in diameter and not visualized by diagnostic imaging studies. In a POG analysis of 216 children, intrinsic spleen lesions and abnormal portohepatic and celiac nodal areas were highly predictive CT findings but were infrequently observed (68). Therefore, only histologic assessment can definitively evaluate the liver and spleen, but the indications for surgical staging of these organs are limited.

Nuclear imaging with gallium-67 was widely used to stage and monitor treatment response in children with HL. However, gallium has limitations because of its low resolution and physiologic biodistribution, which cause difficulties in evaluating abdominal and pelvic lymph nodes and necessitates delayed imaging. Positron emission tomography (PET) is now recognized as an integral staging modality for lymphoma (Fig. 7.3) (69–71). Uptake of the radioactive glucose analog fluorodeoxyglucose (FDG) correlates with proliferative activity in tumors undergoing anaerobic glycolysis. FDG-PET has advantages over gallium-67 because the scan is a 1-day procedure with higher resolution, better dosimetry, and less intestinal activity, has quantitation potential, and can provide better anatomic localization when combined with CT scan. Gallium-67 and FDG-PET both provide full-body imaging in which areas of abnormal avidity have been correlated with treatment outcomes. Both also have limitations in the pediatric setting (e.g., tracer avidity in nonmalignant thymic

Figure 7.3 **A:** A few poorly identifiable lymph nodes in the left cervical area on an axial CT slice without IV contrast before chemotherapy. **B:** FDG-PET image of the same area. **C:** Measurements of the largest lymph nodes (3.7, 4.6 and 11.1 mm). **D:** The left cervical area after chemotherapy.



rebound commonly observed after completion of therapy for HL).

Improved sensitivity and specificity of FDG-PET relative to CT/MRI and gallium scanning in PHL have been noted. Although FDG-PET and gallium were similar for staging, both response assessment and relapse identification were improved with FDG-PET in a study by Mody et al. (72). PET and gallium scans were performed at diagnosis, at early response assessment, and off therapy in HL patients at St. Jude Children's Research Hospital. PET had increased sensitivity relative to gallium. PET upstaged four patients and changed response assessment in two patients although these findings only changed management in one patient. Gallium scanning did not change stage in any patient. PET and gallium scanning sensitivity were similar in the neck and mediastinal regions at diagnosis but the sensitivity of gallium is limited in infradiaphragmatic regions due to decreased resolution as a result of gallium excretion in the bowel. Neither positive PET nor gallium scan at early response predicted relapse. In this study, the negative predictive value (NPV) for PET at the end of therapy was 89.3% compared to 83% for gallium while the positive predictive value for PET was 28.6%. The predictive power of PET scans for early response and end of therapy evaluation requires further investigation with larger pediatric cohorts.

PROGNOSTIC FACTORS

As the treatment of HL has improved, characteristics that influence outcome have diminished in importance. However, several factors continue to influence the success and certainly the choice of therapy. These factors are interrelated in the sense that disease stage, bulk, and biologic aggressiveness often are codependent. Also complicating the determination of prognostic factors is that relevant variables often depend on staging evaluation and treatment. Most data are based on reports that include primarily adults.

The *disease stage* persists as the most important prognostic variable. Patients with advanced-stage disease, especially stage IV, have a worse outlook than those with early-stage disease (73).

The bulk of disease is reflected by the disease stage and is determined more specifically by the volume of distinct areas of involvement and the number of disease sites. LMA places a patient at a greater risk for disease recurrence. While OS remains high due to the effectiveness of salvage chemotherapy (2,22,74), patients with LMA have a somewhat lower survival rate in most, but not all series (2,22,75). Patients (at least those staged only clinically) with several sites of involvement, generally defined as more than three sites, fare less well (22). Patients with stage IV disease who have multiple organs involved fare especially poorly.

Nonwhite pediatric patients presented more frequently with advanced-stage disease based on a study population derived from two South African hospitals although white children had a lower OS (76). In this report, nonwhite pediatric patients had better survival when compared to white pediatric patients of the same stage. However, in a recent study from St. Jude Children's Research Hospital, black pediatric patients had lower event-free survival (EFS), but equivalent 5-year OS to white pediatric patients (77). The impact of race on prognosis remains unclear particularly given the potential impact of socioeconomic, cultural, and environmental differences between white and black populations that may play a role in clinical outcomes.

Systemic ("B") symptoms, which result from cytokine secretion, reflect biologic aggressiveness and confer a worse prognosis. The constellation of symptoms appears to be relevant to this observation. That is, patients with night sweats only (at least among patients with PS I and II disease) appear to fare as well as patients with PS I-IIA, and those with both fever and weight loss have the worst prognosis (78).

Laboratory studies/biologic markers, including the erythrocyte sedimentation rate, serum ferritin, hemoglobin level, serum albumin, and serum CD8 antigen levels, have been reported to predict a worse outcome (62,63,78,79). This could reflect disease biology or bulk. Other investigational serum markers associated with an adverse outcome include soluble vascular cell adhesion molecule-1 (80), TNF (81), soluble CD (28,82), β_2 -microglobulin (83), transferrin, and serum IL-10 (84). High levels of caspase 3 in HRS cells have been correlated with a favorable outcome (85). Serum vascular endothelial growth factor (VEGF) levels may also have prognostic implications. VEGF is a pro-angiogenic molecule involved in neovascularization of tumors. Increased microvessel density associated with increased VEGF level expression has been demonstrated in HL progression (86) and VEGF expression has been identified in HRS cells (87). Pretreatment levels of angiogenic factors have been found to be significantly elevated in HL patients compared to controls and high levels of VEGF have been associated with poor survival (88). Serum VEGF levels have also been associated with treatment response in children with HL (89). In a study by Ben Arush et al., serum VEGF levels correlated with treatment response in seven of nine children with HL. A significant reduction in serum VEGF level was identified in patients with a partial or complete response based on an assessment using PET-CT. The identification of angiogenic factors that play a role in the clinical course of HL may have therapeutic implications for the use of anti-angiogenic agents in the future. Other biologic factors that may enable prognostic modeling continue to be discerned (90,91). A recent study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA) prospectively analyzed the prognostic value of TNF, soluble receptors TNF-R1 and TNF-R2, IL-10, IL1-RA, IL-6, and sCD30 in patients with an initial diagnosis of CHL. Five-year EFS probability was predicted by segregating combinations of serum marker levels into four prognostic classes, suggesting that a plasma cytokine signature may predict clinical outcomes in CHL (91).

Histologic subtype is relevant but may differ in children versus adults. For example, adults with clinical stage I or II MCHL have a higher frequency of subdiaphragmatic relapse, and which (indirectly) influences survival (22). Grade 2 NSHL histology has conferred poor outcome in some but not all studies (92). Patients with LDHL fare poorly. A recent report from the United Kingdom Children's Cancer Study Group assessing the relevance of histology in 331 children is revealing. Fewer than 1% had LDHL, obviating any meaningful assessment of its prognostic significance. For patients with other histologies treated with combined therapy, no difference in outcome was observed (93). As previously discussed, patients with NLPHL have distinctive differences in disease-free survival and OS.

Age is a significant prognostic factor in some studies. Survival rates for children with HL approach 95%. In a report from Stanford, the 5- and 10-year survival rates for children younger than 10 years with HL are 94% and 92%, respectively, compared with 93% and 86% for adolescents (11–16 years old)

and 84% and 73% for adults (20). Although children younger than 4 years with HL are uncommon, even these children appear to have an excellent prognosis (21).

The rapidity of response to initial therapy is an important prognostic variable in many forms of cancer, including HL. In some trials, the rapidity of response to chemotherapy is used to determine subsequent therapy (94). Early response to therapy as measured by gallium-67 or FDG-PET imaging is under investigation as a possible marker of prognosis. The NPV of PET was recently evaluated in the GHSG HD15 trial. After patients received BEACOPP-based chemotherapy, PET was used to assess residual disease measuring greater than or equal to 2.5 cm in diameter. Progression-free survival was significantly improved in PET negative patients (96%) as compared to PET positive patients (86%) ($p = 0.011$). Although survival outcomes are not yet available due to the length of follow-up, response-adapted therapy proved promising with an NPV of 94% for PET in this study (95). In the setting of stem cell transplant for refractory/recurrent HL, pretransplant functional imaging response has been found to predict outcome. Patients with positive PET or gallium scans prior to undergoing high-dose chemotherapy with autologous stem cell transplant had a significantly lower 3-year PFS and OS rates than patients with negative functional imaging (96).

Although prognostic factors will continue to be influenced by choice of therapy, parameters such as disease, bulk, number of involved sites, and systemic symptoms are likely to remain relevant to outcome. Nonetheless, as therapy becomes increasingly tailored to prognostic factors and therapeutic response, overall outcome should become less affected by those parameters.

SELECTION OF THERAPY

HL is one of the pediatric malignancies that has an adult counterpart with a similar natural history and biology. However, devising the optimal therapeutic approach for children with this disease is complicated by their greater risk for adverse effects. In particular, RT dosages and fields used in adults can cause profound musculoskeletal retardation, including intraclavicular narrowing, shortened sitting height, decreased mandibular growth, and decreased muscle development in the treated volume (see Chapter 19) (9,10). Therefore, whereas adults with early-stage HL were historically treated with full-dose radiation as a single modality (22), in prepubertal children, despite a similar success rate, this approach produced unacceptable sequelae (10,19,74,97). Additionally complicating the treatment of children are sex-specific differences in chemotherapy-induced gonadal injury. The desire to cure young children with minimal side effects has stimulated attempts to reduce staging procedures, the intensity and types of chemotherapy, and the radiation dosage and volume. Because of the differences in the age-related developmental status of children and the sex-related sensitivity to chemotherapy, no single treatment method is ideal for all children.

Important studies using chemotherapy and low-dose radiation in children to effect cure with tolerable sequelae were first undertaken at Stanford University. These trials used chemotherapy in combination with lower dosages of RT for young children with early-stage disease (2,11,12). Although growth deformity was decreased, full-course MOPP is associated with a high risk of sterility and secondary leukemia (discussed in

Chapters 19 and 20). Therefore, alternative regimens were used subsequently (14,16,51,98).

An important sequence of studies performed by the German-Austrian Pediatric Hodgkin's Disease Study Group progressively refined the extent of staging and the intensity of chemotherapy and radiation (14,16,98). The nature and results of these studies (HD-82, HD-85, HD-87, HD-90, and HD-95) are summarized in Tables 7.4 and 7.5. Stage-dependent chemotherapy and radiation dosage and volume were used and these studies served as the paradigm for the risk-adapted treatment approach that is currently used at most pediatric treatment centers.

In general, the use of radiation and chemotherapy broadens the spectrum of potential toxicities while reducing the severity of individual (drug- or radiation-related) toxicities. The volume of radiation and the intensity and duration of chemotherapy are risk adapted, or determined by prognostic factors at presentation, including presence of constitutional symptoms, disease stage, and bulk. Results for patients with early (favorable) and advanced (unfavorable) HL are summarized in Tables 7.4 and 7.5, and our therapeutic recommendations are summarized in Table 7.6.

COMBINATION CHEMOTHERAPY

MOPP was the standard chemotherapy regimen used in the United States for many years after DeVita et al.'s 1972 report (124). The major toxicities include an associated risk of acute myeloid leukemia, azoospermia in more than 90% of boys treated at any age, and a risk of sterility in girls, which increases with age (125,126). Subsequently, the effectiveness of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) as front-line chemotherapy was established (113,114,127). Second malignancies and sterility were less common with ABVD than with MOPP (128). The predominant adverse effects of ABVD are pulmonary toxicity related to bleomycin and cardiovascular toxicity secondary to adriamycin. These side effects may be exacerbated by the addition of mediastinal or mantle irradiation (120). Consequently, ABVD and MOPP were combined with the aim of improving disease control and reducing the risk of leukemogenesis and sterility related to the alkylating agents in the MOPP regimen. This alternating combination proved to be more effective than MOPP chemotherapy alone (18,114,110). Its use in pediatric patients also diminished the risk of cardiopulmonary dysfunction predisposed by the anthracycline and bleomycin in the ABVD regimen. Over the years, the MOPP and ABVD regimens have undergone a variety of modifications, but the majority of the chemotherapeutic regimens used today are derived from these two combinations.

COMBINED MODALITIES VERSUS CHEMOTHERAPY ALONE

The current era of risk-adapted response-based therapy for PHL presents several critical issues regarding the role of RT.

- For patients with PHL, is chemotherapy alone adequate without administering excessive amounts or using overly aggressive combinations in terms of potential morbidities? Embedded in this question are the relative toxicities of curative chemotherapy versus less chemotherapy plus RT.

Table 7.4

Treatment Results for Early, Favorable Pediatric Hodgkin Disease

Group or Institution	Patients (n)	Stages	Chemotherapy	Radiation (Gy), Field	Survival (%)		Follow-Up Interval (Years)	Reference
					Overall	DFS, EFS, or RFS		
Radiation therapy alone								
Joint Center/Harvard	50	PS I, IIA	None	36–44, IF	97	82	11	10
Bart's/GOS	28	CS I, II	None	35–40, IF	95.5	79	10	97
Stanford	48	PS ^a I, II	None	40–44, IF	86	82	10	97
Toronto	8 (EF)	CS, PS I	None	35, IF	95	87	10	19
	23 (IF)							
Royal Marsden	42 (EF)	PS IIA, IIIA	None		85	45	10	
	99	CS I	None	35, IF	92	70	10	93
Combined-modality trials								
Stanford	27	PS ^a I, II	6 MOPP	15–25, IF	100	96	5	12
St. Jude	58	CS II and III	4–5 COPP/3–4 ABVD	20, IF	96/100	96/97	5	99
Stanford St. Jude	110	CS I and II ^b	4 VAMP	15–25.5, IF	96	89	10	100
Dana Farber Consortium								
U.S. CCG	294	CS IA/B, IIA	4 COPP/ABV	21, IF	100	97	3	101
Germany–Austria HD-82	100	IA/IB–IIA	2 OPBA	35, IF	100	98	9	98
	53	IIB–IIIA	2 OPBA/2 COPP	30, IF	96	94	9	
Germany–Austria HD-85	53	IA/IB–IIA	2 OPA	35, IF	98	85	6	98
	21	IIB–IIIA	2 OPA/2 COMP	30, IF	95	55	6	
Germany–Austria HD-90	275	IA/IB–IIA	2 OEPA/OPPA	25, IF	99	94/95	5	15, 16
	124	IIB–IIIA	2 OEPA/OPPA + 2 COPP	25, IF	97	90/96	5	
Germany–Austria HD-95	326	I, IIA	2 OEPA/OPPA	20–35, IF for PR;	97	91	3	102
	224	IIB, IIIA	2 OEPA/OPPA + 2 COPP	no RT if CR	97	94	3	
Royal Marsden	46	I–III	8 VEEP	30–35, IF	93	82	5	103
Royal Marsden SFOP MDH-82	125	II	6–10 ChIVPP	35, IF	92	85	10	93
	79	CS I–IIA	4 ABVD	20–40, IF		90	6	104
	67	CS I–IIA	2 MOPP/2 ABVD	20–40, IF		87	6	
	31	CS IB–IIB	3 MOPP/3 ABVD	20–40, EF	92		6	
(continued)								

(continued)

Table 7.4

Treatment Results for Early, Favorable Pediatric Hodgkin Disease (continued)

Group or Institution	Patients (n)	Stages	Chemotherapy	Radiation (Gy), Field	Survival(%)		Follow-Up Interval (Years)	Reference
					Overall	DFS, EFS, or RFS		
SFOP MDH-90	171	I-II	4 VBVP, good responders 4 VBVP + 1-2 OPPA, poor responders	20, IF	97.5	91	5	105
	27	I-II		20, IF		78	5	
AEIOP MH-83	83	Group 1 IA	Group 1 3 ABVD	Group 1 20-40, IF	95	86	7	106
	83	IIA (M/T < 0.33)	3 ABVD	20-40, R				
		Group 2 IIA (M/T ≥ 0.33)	Group 2 3 MOPP/3 ABVD	Group 2 20-40, R	81		7	
		IIIA	3 MOPP/3 ABVD	20-40, EF				
Florida-POG	51	CS I-IIIa	4 DBVE	25.5 IF	98	91	6	107
POG 8625	81	CS I-IIIa	4 MOPP/ABVD	25.5 IF	97	91	8	108
Chemotherapy alone								
USA-CCG	106	CS IA/B, IIA	4 COPP/ABV	None	100	91	3	101
Uganda	18	CS I-IIIa	6 MOPP	None	75	75		109
POG 8625	78	CS I-IIIa	6 MOPP/ABVD	None	94	83	8	108

^aSome patients were clinically staged.

^bMediastinal thoracic ratio <0.33; lymph node <6 cm.

ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; AEIOP, Italian Association of Hematology and Pediatric Oncology; Bart's/GOS, St. Bartholomew's Hospital/Great Ormond Street; CCG, Children's Cancer Group; ChIVPP, chlorambucil, vinblastine, procarbazine, and prednisolone; COMP, cyclophosphamide, vincristine (Oncovin), methotrexate, and prednisolone; COPP, cyclophosphamide, vincristine (Oncovin), prednisone, and procarbazine; COPP/ABV, cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone, adriamycin, bleomycin, and vinblastine; CR, complete response; CS, clinical stage; CVPP, cyclophosphamide, vinblastine, procarbazine, and prednisone; DBVE, doxorubicin, bleomycin, vincristine, and etoposide; DFS, disease-free survival; EF, extended field; EFS, event-free survival; GATLA, Grupo Argentino de Tratamiento de Leucemia Aguda; HD, Hodgkin disease; IF, involved field; MDH, multicenter trial; MH, multicenter Hodgkin trial; MOPP, nitrogen mustard, vincristine (Oncovin), procarbazine, and prednisone; M/T, mediastinal/thoracic ratio; OEPA, vincristine (Oncovin), etoposide, prednisone, and adriamycin; OPA, vincristine (Oncovin), prednisone, and adriamycin; OPPA, vincristine (Oncovin), procarbazine, prednisolone, and adriamycin; PR, partial response; PS, pathologic stage; R, regional; RFS, relapse-free survival; RT, radiotherapy; SFOP, French Society of Pediatric Oncology; VAMP, vinblastine, adriamycin, methotrexate, and prednisone; VBVP, vinblastine, bleomycin, etoposide (VP-16), and prednisone; VEEP, vincristine, etoposide, epirubicin, and prednisolone.

Table 7.5

Treatment Results for Advanced, Unfavorable Pediatric Hodgkin Disease

Group or Institution	Patients (n)	Stages	Chemotherapy	Radiation (Gy), Field	Survival (%)		Follow-up Interval (Years)	Reference
					Overall	DFS, EFS, or RFS		
Combined-modality trials								
Germany–Austria HD-82	50	II _E B, III _E A/B, IIIB, IVA/B	2 OPFA/4 COPP	25, IF	85	86	9	98
Germany–Austria HD-85	24	II _E B, III _E A/B, IIIB, IVA/B	2 OPA/4 COMP	25, IF	100	49	9 6	15,16
Germany–Austria HD-90	179	II _E B, III _E A/B, IIIB, IVA/B	2 OEPA/OPPA + 4 COPP	20, IF	98/89	83/91	6 5	15,16
Germany–Austria HD-95	280	II _E B, III _E A/B, IIIB, IVA/B	2 OEPA/OPPA + 4 COPP	20–35, IF for PR; no RT if CR	97	84	3	102
Gustave–Roussy SFOP MDH-82	60	I–IV	3–6 MOPP	40, IF	93	86	5	17
AEIOP MH-83	40	CS III	3 MOPP/3 ABVD	20–40, EF		82	6	104
	21	CS IV	3 MOPP/3 ABVD	20–40, EF		62	6	
	49	Group 3	Group 3				7	106
		IIIB–IV	5 MOPP/5 ABVD	20–40, EF	60			
Royal Marsden	24	I–IV	CCOPP/CAPTe	30–40, IF		83	5	
	80	III	6–10 ChIVPP	35, IF	84	73	10	93
	27	IV	6–10 ChIVPP	35, IF	71	38	10	
Royal Marsden	8	IV	8 VEEP/ChIVPP	30–35, IF	50	44	5	103
			if NR or PR to VEEP					
Toronto	57	CS IIA–IV	6 MOPP	25–30, EF	85	80	10	19
U.S. POG	62	CS/PS IIB, IIIA ₂ , IIIB, IV	4 MOPP/4 ABVD	21, TLI	91	77	3	110
U.S. POG	80	CS/PS IIB, IIIA ₂ , IIIB, IV	4 MOPP/4 ABVD	21, EF	87	80	5	111
Stanford	28	III–IV	6 MOPP	15–25.5, IF	78	84	7.5	12
St. Jude	27	CS IV	4–5 COPP/3–4 ABVD	20 Gy, IF	86	85	5	99
Joint Center/Harvard	83	IA–IIIB	6 MOPP	25–40	95	77	11	10

(continued)

Table 7.5

Treatment Results for Advanced, Unfavorable Pediatric Hodgkin Disease (continued)

Group or Institution	Patients (n)	Stages	Chemotherapy	Radiation (Gy), Field	Survival (%)		Follow-Up Interval (Years)	Reference
					Overall	DFS, EFS, or RFS		
Stanford, St. Jude, Dana Farber	56	CS I/II bulky (n = 26), CS III/IV (n = 30)	6 VEPA	15–25.5, IF	81.9	67.8	5	112
U.S. CCG	64	PS III–IV	12 ABVD	21, R	89	87	3	113
U.S. CCG	54	PS III–IV	6 ABVD	21, EF	90	87	4	114
U.S. CCG	394	CS I/II ^a , CS IIB, CS III, CS IV	6 COPP/ABV	21, IF	95	87	3	101
	141	CS IV	COPP/ABV + CHOP + AraC/VP-16	21, IF	100	90	3	
St. Jude, Stanford, Dana–Farber, Maine Children's	159	CS IB/IIB or bulky >6 cm	6 VAMP/COP	15 IF if CR	93	76	5	115
COG–P9425	216	CS IB, IIA/IIIA ₁ with bulky mediastinum or IIIA ₂ 5 ABVE-PC for SER	3 ABVE-PC for RER	25.5 IF if PR 21 IF	95	86	5	116
Chemotherapy alone		CS	21 IF		84			
UKCCSG	67	IIB/IIIB/IV	6–8 ChIVPP	None ^b	80.8	55.2	5	117
Australia/ New Zealand	53	CS IV	6–8 MOPP or 6 ChIVPP	None	94	92	4	118
Australia/ New Zealand	53	CS I–IV	5–6 VEEP	None	92	78	5	119
Uganda	10	CS IIB, IV	6 MOPP	None		60	5	109
The Netherlands	21	CS I–IV (<4 cm node)	6 MOPP	None	100	91	5	120,121, 122
	17	CS I–IV	6 ABVD		94	70		
	21	CS I–IV	3 MOPP/3 ABVD		91	91		

(continued)

Table 7.5
(Continued)

Group or Institution	Patients (n)	Stages	Chemotherapy	Radiation (Gy), Field	Survival (%)		Follow-Up Interval (Years)	Reference
					Overall	DFS, EFS, or RFS		
U.S. CCG	57	PS III/IV	6 MOPP/6 ABVD	None	84	77	4	114
U.S. CCG	394	CS I/II ^a , CS IIB, CS III CS IV	6 COPP/ABV	None	100	83	3	101
	141		COPP/ABV + CHOP AraC/VP-16	None	94	81	3	
U.S. POG	81	CS IIB, III ₂ A, IIIB, IV	4 MOPP/4 ABVD	None	96	79	5	111
Rotterdam-HD-84	23	CS I-IIA	6 EBVD	None	100	96	10	123
	23	CS IIB-IV	3–5 EBVD/MOPP	None	91	87	10	123

^aPresence of adverse features = (t)hila, >4 nodal sites, bulk.

^bTwelve patients received 20 to 35 Gy; IF; two received whole-lung irradiation.

ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; ABVE-PC, adriamycin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide; AEIOF, Italian Association of Hematology and Pediatric Oncology; AOPE, adriamycin, vincristine (Oncovin), prednisone, and etoposide; AraC, cytosine arabinoside; CAPTe, cyclophosphamide, adriamycin, prednisone, and teniposide; CCG, Children's Cancer Group; CCOPP, CCNU, vincristine (Oncovin), procarbazine, and prednisone; ChIVP, chlorambucil, vinblastine, procarbazine, and prednisone; CHOP, cyclophosphamide, hydroxydaunomycin, vincristine (Oncovin), and prednisone; COMP, cyclophosphamide, vincristine (Oncovin), methotrexate, and prednisone; COPP, cyclophosphamide, vincristine (Oncovin), prednisone, and procarbazine; COPP/ABV, cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone, adriamycin, bleomycin, and vinblastine; CR, complete response; CS, clinical stage; CVPP, cyclophosphamide, vinblastine, procarbazine, and prednisone; DFS, disease-free survival; EBO, epirubicin, bleomycin, and vincristine (Oncovin); EF, extended field; EFS, event-free survival; EVAP/ABV, etoposide, vinblastine, cytarabine, cisplatin, adriamycin, bleomycin, and vincristine; GATLA, Grupo Argentino de Tratamiento de Leucemia Aguda; HD, Hodgkin disease; IF, involved field; MDH, multicenter trial; MH, multicenter Hodgkin trial; MOPP, nitrogen mustard, vincristine (Oncovin), procarbazine, and prednisone; NR, no response; OEPA, vincristine (Oncovin), etoposide, prednisone, and adriamycin; OPA, vincristine (Oncovin), prednisone, and adriamycin; OPFA, vincristine (Oncovin), procarbazine, prednisone, and adriamycin; POG, Pediatric Oncology Group; PR, partial response; PS, pathologic stage; R, regional; RFS, relapse-free survival; RT, radiotherapy; SFOP, French Society of Pediatric Oncology; TLI, total lymphoid irradiation; UKCCSG, United Kingdom Children's Cancer Study Group; VAMP, vinblastine, doxorubicin, methotrexate, and prednisone; VEEP, vincristine, etoposide, epirubicin, and prednisone; VEPA, vinblastine, etoposide, prednisone, and adriamycin.

Table 7.6
Treatment Recommendations in Pediatric Hodgkin Disease

Clinical Presentation	Stages	Recommended Treatment Approach
Early (favorable): localized disease involving less than four nodal regions in absence of “B” symptoms, bulk, or extranodal extension	IA, IIA	Recommended therapy: two to four cycles non-cross-resistant chemotherapy without alkylators (ABVD or derivative) plus low-dose, involved-field radiation (1500–2550 cGy) Other considerations: six cycles non-cross-resistant chemotherapy alone (alternating COPP and ABVD or derivative) In clinical trial setting only: four cycles of chemotherapy alone
Localized unfavorable (intermediate): localized disease involving ≥ 3 nodal regions in presence of bulky lymphadenopathy (mediastinal ratio $\geq 33\%$; lymph node mass ≥ 610 cm)	IA, IIA, IIB ^a , IIIA	Recommended therapy: four to six cycles (three to five compacted, dose-intensive cycles) non-cross-resistant chemotherapy (alternating COPP and ABVD or derivative with or without etoposide) plus low-dose, involved-field radiation (1500–2550 cGy) Other considerations: six to eight cycles (five compacted, dose-intensive) non-cross-resistant chemotherapy alone (alternating COPP and ABVD or derivative with or without etoposide)
Advanced (unfavorable): stage II disease with constitutional symptoms of fever or weight loss and any disease	IIB ^a , IIIB, IV	Recommended therapy: six to eight cycles (five to seven compacted, dose-intensive cycles) of non-cross-resistant advanced chemotherapy (alternating COPP and ABVD or derivative with or without etoposide) plus low-dose, involved-field radiation (1500–2550 cGy) Other considerations: eight cycles (six to seven compacted, dose-intensive cycles) non-cross-resistant chemotherapy alone (alternating COPP and ABVD or derivative with or without etoposide)

^aPatients with stage IIB disease have been variably treated as having intermediate or unfavorable risk. Some studies use associated factors (e.g., weight loss, bulk disease, or extranodal extension) for further risk stratification.

ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; COPP, cyclophosphamide, vincristine (Oncovin), prednisone, and procarbazine.

- Can the rapidity and the completeness of the response to chemotherapy define the use of RT, and will functional imaging enhance the precision of this approach?
- When RT is administered, then what is the appropriate target volume? Can RT be restricted to initially involved lymph nodes rather than chains (or regions) of nodes? In what settings should RT be directed to areas of initial bulk disease or residual postchemotherapy disease? Should involved organs, such as the liver, lung, and heart, ever be irradiated?
- If we use RT, what is the appropriate dose? Should this be dependent on the initial or postchemotherapy extent of disease, bulk of disease, organ at risk, and age of the patient?

Inherent in these questions is the recognition that RT is effective in locally controlling PHL but provokes a dose-dependent spectrum of toxicities. Most profound are musculoskeletal growth inhibition, coronary artery disease and

cardiomyopathy, pulmonary fibrosis, infertility, and subsequent malignancies. However, eliminating RT necessitates more toxic chemotherapy (either agents or amounts). Discerning the ideal balance will maximize cure while minimizing toxicity. We address these questions in upcoming sections.

The arguments that favor treatment with chemotherapy alone for all stages propose that this treatment approach obviates surgical staging and avoids the dysmorphic and carcinogenic consequences of irradiation. The disadvantages of the use of chemotherapy alone are the risks of treatment-related fatality, cardiopulmonary toxicity, infertility, and leukemogenesis caused by the higher cumulative dosages of anthracyclines, alkylating agents, and bleomycin (118) and a greater likelihood of disease recurrence in sites of bulk disease (129). Generalization of treatment outcomes after these trials has been limited because most studies include small numbers of patients assigned to treatments in a nonrandom fashion. Also,

long-term follow-up related to disease control and late treatment sequelae has not been reported.

Early chemotherapy trials used MOPP or similar regimens derived from MOPP and prescribed 6–12 months of chemotherapy (109,118,121,122). In an effort to avoid treatment complications associated with alkylating agent chemotherapy, contemporary chemotherapy-alone trials have alternated MOPP-type regimens with ABVD or similar derivatives or used combinations without alkylating agents (101,114,119,122,123). Across all stages, EFS rates after treatment with 6–12 months of alternating MOPP and ABVD chemotherapy alone range from 77% at 4 years to 91% at 10 years; several of these investigations included pathologic staging to confirm eligibility for reduced therapy (114,111,130). The use of ABVD or ABVD-derivative chemotherapy combinations produced unsatisfactory outcomes in advanced-stage patients treated with six cycles of ABVD chemotherapy alone (71% 8-year disease-free survival) and five or six cycles of vincristine, etoposide, epirubicin, and prednisolone (VEEP) chemotherapy alone (78% 5-year disease-free survival) (119,122).

Few randomized controlled trials have prospectively compared chemotherapy alone with combined-modality therapy in children and adolescents with HL (101,111,114). The Children's Cancer Group (CCG) compared 12 cycles of alternating MOPP and ABVD with 6 cycles of ABVD and low-dose (21 Gy) radiation. The trend in EFS and OS suggested a survival advantage for the combined-modality group (90% 4-year EFS) over the chemotherapy-alone group (84% 4-year EFS), but this difference was not statistically significant (114). The POG evaluated the benefit of adding low-dose radiation to four cycles each of MOPP and ABVD (111); the addition of RT did not improve disease-free survival or OS. However, statistical and quality assurance issues complicate interpretation of this data (131). Long-term follow-up will be necessary to assess the toxicity from these trials, but cardiopulmonary and neoplastic sequelae were observed in early follow-up and could potentially increase with the cumulative dosages of alkylating agent chemotherapy, anthracyclines, and bleomycin.

In an important CCG trial reported by Nachman et al. (101), chemotherapy alone using the COPP and ABV hybrid regimen was compared with combined-modality therapy including low-dose involved-field radiation treatment (IFRT). Treatment assignment was risk-adapted based on the presence of clinical features including the presence of “B” symptoms, hilar adenopathy, mediastinal and peripheral lymph node bulk, and the number of involved nodal regions. Patients with favorable disease presentations received four cycles of COPP and ABV; those with unfavorable risk features received six cycles of COPP and ABV. Patients with stage IV HL received sequential cycles of high-dose cytarabine and etoposide, COPP and ABV, and cyclophosphamide, vincristine, doxorubicin, and methylprednisolone. Patients achieving a complete response to chemotherapy were eligible for randomization to receive low-dose IFRT or no further therapy. The trial was terminated prematurely because results indicated a significantly higher number of relapses among patients treated with chemotherapy alone. The 3-year EFS estimates according to patient randomization were 92% for patients treated with combined-modality therapy and 87% for those treated with chemotherapy alone; the benefit of IFRT

remained significant in the as-treated analysis. The difference was most marked in patients with stage IV disease, who had 90% EFS if randomized to receive IFRT and 81% if randomized to receive chemotherapy alone. Because of successful salvage therapy after relapse, estimates of OS do not differ between the randomized groups in early follow-up. However, other investigations of long-term outcomes after treatment for PHL implicate retrieval therapy after relapse as a significant risk factor for neoplastic complications and early mortality (132,133). In the German-Austrian Pediatric Hodgkin's Disease Study Group (GPOH) HD-95 trial, relapse-free survival rates were higher for patients treated with RT after partial response (93%) than for those without RT after complete response (89%) (102). The difference was significant for patients treated for advanced-stage but not early-stage disease.

Patients with stage I, IIA, or IIIA HL were randomized in a study conducted by the POG to six courses of alternating MOPP/ABVD or four courses of MOPP/ABVD and IFRT to 25.5 Gy. At a median follow-up of 8.25 years, there were no significant differences in EFS or OS rates between either arm. Eight-year EFS rates were 83% for chemotherapy alone and 91% for combined-modality therapy ($p = 0.151$) while 8-year OS rates were 93.6% for chemotherapy alone and 96.8% for chemotherapy and radiation ($p = 0.785$) (108). Patients with early response to therapy had a significantly better outcome, which supports the paradigm of response-based treatment.

In summary, numerous investigations have confirmed that chemotherapy alone is an effective treatment approach for PHL. However, the higher cumulative dosages used in these protocols predispose survivors to greater risks of acute and late toxicity associated with alkylating agents, anthracyclines, and bleomycin. Conversely, these protocols avoid radiation-associated treatment complications including musculoskeletal growth impairment, cardiopulmonary dysfunction, and solid tumor carcinogenesis. Current information suggests that children with advanced and unfavorable symptomatic or bulky disease at presentation have better outcomes using a combined-modality approach. Identifying the prognostic features of patients who need radiation to optimize disease control is a focus of many ongoing pediatric trials.

RISK-ADAPTED THERAPY

Numerous investigations published in the 1990s supported the use of a risk-adapted treatment assignment based on clinical features at disease presentation (14,16,59,98,100–102,104–106,111,112). Parameters have varied according to individual studies, but those used most often in risk assessments include the presence of “B” symptoms, mediastinal and peripheral lymph node bulk, extranodal extension of disease to contiguous structures, hilar lymph node involvement, number of involved nodal regions, and Ann Arbor stage. These studies uniformly evaluated treatment outcomes using a lower number of multiagent chemotherapy cycles in clinically staged patients with favorable clinical presentations (Tables 7.5 and 7.6). Novel treatment approaches have been explored in patients with intermediate- and high-risk features in an effort to improve long-term disease control and reduce late therapy-related complications. The results of these studies are summarized in Tables 7.4 and 7.5.

Revised International Workshop Criteria have also recently been proposed for response assessment to incorporate

imaging with PET in addition to CT given the increased specificity and sensitivity of PET compared to CT (134,135). A recent study conducted by Brepoels and colleagues compared these revised criteria incorporating PET versus the criteria using CT alone to predict clinical outcome and found that the revised criteria predicted response more accurately (136).

Treatment of Early-Stage Disease

Early-stage disease may present with favorable or unfavorable features. A favorable clinical presentation is typically defined as localized (stage I or II) nodal involvement in the absence of “B” symptoms and nodal bulk. The presence of extranodal extension to contiguous sites, hilar lymphadenopathy, or involvement of more than three nodal regions typically moves the patient into an intermediate- or high-risk group. Children and adolescents with early-stage, favorable presentations of HL are excellent candidates for reduced therapy. Several multiagent regimens and a variety of nonalkylator regimens have proven effective (Table 7.4) (10,12,14,16,59,93,97,98,100,101,104–106,109,111,137). Treatment for patients with a favorable clinical presentation typically involves two to four cycles of chemotherapy and low-dose IFRT. In some regimens, the radiation dosage has been reduced based on a favorable response to chemotherapy.

The German pediatric Hodgkin lymphoma investigators pioneered the use of risk- and sex-adapted therapy featuring the OPPA regimen (16,98). The recent GPOH HD-95 trial investigated whether RT could be omitted in patients achieving a complete response to chemotherapy. Early results (median follow-up time of 38 months) indicate a 94% EFS for favorable-risk patients and no difference in outcome in favorable-risk patients treated with chemotherapy alone or combined-modality therapy (102). Notably, bulky lymphadenopathy is not used in the GPOH risk assessment because bulk has not influenced outcome in the German trials, which prescribe a 5- to 10-Gy boost in cases with an insufficient remission after chemotherapy (138).

Several North American investigators have observed excellent treatment results in combined-modality trials for favorable-risk HL. Pediatric Hodgkin's Consortium investigators from Stanford, St. Jude Children's Research Hospital, and Dana Farber Cancer Institute have reported treatment results using a novel nonalkylator regimen, vinblastine, adriamycin, methotrexate, and prednisone (VAMP), for children with clinical stage I or II, nonbulky HL (100,139). Patients received four cycles of VAMP chemotherapy and IFRT; the radiation dosage was determined by early response after two cycles of chemotherapy. Patients achieving a complete response received 15 Gy, and those achieving a partial response received 25.5 Gy. At a median follow-up of 9.6 years, 5- and 10-year EFS were 92.7% and 89.4%, respectively; 5- and 10-year OS were 99.1% and 96.1%, respectively. Long-term toxicity has been limited to 42% of irradiated patients with hypothyroidism, one patient with cardiac dysfunction, and two malignant tumors (139). Patients were also able to maintain fertility with 17 healthy babies born to 106 patients.

Very good early treatment results have also been observed by POG investigators using response-based doxorubicin, bleomycin, vincristine, and etoposide (DBVE) chemotherapy and low-dose (25.5 Gy) IFRT (140). Two-year EFS for the entire cohort is 91%, with 93% EFS for rapid early responders treated with two cycles of DBVE and 89% EFS for slower responders treated with four cycles of DBVE. Tebbi and colleagues

evaluated the feasibility of combined-modality therapy using four courses of DBVE followed by involved-field radiation to 25.5 Gy to treat stage IA, IIA, and IIIA HL. After a median follow-up of 8.4 years, 6-year OS and EFS rates were 98% and 91%, respectively, with all patients achieving remission after completion of therapy. Four recurrences were noted thus far and no significant cardiopulmonary toxicities were identified (107).

Treatment of Advance and Unfavorable Disease

In risk-adapted treatment regimens, early disease presenting with unfavorable features sometimes is treated similarly to advanced-stage disease. Alternatively, an intermediate designation is given in some risk categorizations to patients with localized (stage IA or IIA) disease presentations that have one or more of the unfavorable features and to patients with stage IIIA disease. For example, the GPOH studies prescribe four cycles of chemotherapy (two OPPA or two OEPA and two COPP) for patients with intermediate risk (designated as stage IIEA, IIB, or IIIA) and six cycles (two OPPA or two OEPA and four COPP) for patients with unfavorable and advanced disease (16,102). In this study, with a median follow-up of 38 months, the EFS for intermediate- and high-risk patients was 91% and 84%, respectively (75). The criteria for unfavorable clinical presentations vary between investigations but typically include the presence of “B” symptoms, bulky lymphadenopathy, hilar lymphadenopathy, involvement of three or more nodal regions, extranodal extension to contiguous structures, or advanced stage (IIIB–IV). Chemotherapy used for this group includes MOPP and ABVD or derivative combinations that incorporate etoposide in many cases. As illustrated in Table 7.5, RT for unfavorable and advanced HL is variable and protocol dependent. Although IFRT remains the standard in patients treated with combined-modality therapy, restricting RT to areas of initial bulky disease (generally defined as larger than 5 cm at the time of disease presentation) or postchemotherapy residual disease (generally defined as larger than 2 cm, or residual PET avidity) is under investigation (10,12,15–17,19,93,98,99,101–104,106,109–114,117–119,122,141,142).

Hudson and colleagues evaluated the combined-modality regimen of VAMP/COP followed by response-based involved-field radiation in advanced or unfavorable HL patients. Patients achieving a complete response received 15 Gy and patients achieving a partial response after two cycles of chemotherapy received 25.5 Gy. Five-year OS and EFS rates were 92.7% and 75.6%, respectively. Given the low rates of EFS, combined-modality therapy with VAMP/COP and response-based involved-field radiation was not considered efficacious for unfavorable PHL patients (115).

The Children's Oncology Group conducted a study evaluating early-response adapted therapy using ABVE-PC chemotherapy with 216 eligible patients less than 22 years old who presented with intermediate or high risk HL. ABVE-PC is advantageous in the pediatric population as the cumulative chemotherapy doses are below the doses typically associated with long-term toxicities. In this study, patients with a rapid early response to three cycles of ABVE-PC received 21 Gy of regional field radiation (mantle, para-aortic, or pelvis). Slow early responders received an additional two cycles of ABVE-PC and then received involved-field radiation to 21 Gy. The five-year EFS was 86% for rapid early responders and 83% for

slow early responders ($p = 0.85$) and the five-year OS was 95%. This protocol has provided encouraging clinical outcomes using risk-adapted therapy in a high-risk group of patients (116).

Two primary treatment approaches have been used for patients with unfavorable and advanced disease presentations. A conventional treatment approach prescribes chemotherapy on a twice-monthly schedule for 6–8 months (102,112). An alternative strategy administers treatment over 3–5 months to increase dosage intensity and reduce the risk of developing resistant disease (101,140). This is accomplished by alternating myelosuppressive and nonmyelosuppressive agents in a weekly schedule and using colony-stimulating factor to support neutrophil recovery. A summary of treatment results of published trials is provided in Table 7.5, which demonstrates EFS rates ranging from 70% to 90%. Long-term follow-up is not yet available to determine whether the abbreviated, dose-intensive treatment approach is superior to a conventional treatment administration in maintaining disease control.

SUMMARY RECOMMENDATIONS FOR PRIMARY DISEASE

Optimal treatment planning involves a multidisciplinary approach beginning at diagnosis. This is best accomplished if the pediatric and radiation oncologist can meet to review staging studies after examining the patient. The treatment approach should consider host factors, such as age and sex, which may increase the risk of specific treatment complications, and disease factors (e.g., presence of “B” symptoms, bulky lymphadenopathy, and stage). Recommended treatment approaches for favorable localized, intermediate, and advanced unfavorable disease presentations are summarized in Table 7.6.

REFRACTORY AND RELAPSED DISEASE

HL may still be cured even after initial treatment programs fail. Relapse usually occurs within 4 years, and usually in 1–2 years but late relapse is not rare (116). The choice of therapy for such patients depends on the initial treatment and the disease characteristics at the time of relapse. A spectrum of

treatment options exist, including those outlined below (143). This section focuses on the role of radiation in the setting of refractory or relapsed therapy.

- Standard-dose chemotherapy with either the same initial regimen or an alternative regimen, which could be third line (depending on previous regimens). If possible, RT can be added.
- RT alone.
- High-dose chemotherapy (with or without RT), followed by stem cell support. The source of the stem cells can be allogeneic or autologous bone marrow or peripheral stem cells.
- Experimental therapy (e.g., radiolabeled antiferritin, immunotherapy).
- Palliative therapy.

For the rare patients who were initially treated with RT alone, salvage chemotherapy is effective, increasing disease-free survival and OS in 55–80% (14,145). If RT can be safely added to chemotherapy as salvage treatment, the outcome may be superior (143). Factors that independently predict a more favorable outcome include the following:

- Site of relapse (nodal better than extranodal)
- The stage that could be assigned at relapse (early better than advanced)
- The histology (LPHL and NSHL better than MCHL)

For children who relapse after treatment that includes chemotherapy, conventional (standard-dose) salvage chemotherapy regimens are of limited success, increasing disease-free survival and OS in only 10–50% (143,145). Fortunately, other strategies can be effective. The selection of the most appropriate salvage regimen is based on several considerations, including the following:

- Did the patient achieve a complete remission, or was the disease refractory?
- If a complete response was achieved, was it durable (longer than 1 year)?
- Did the relapse occur in nodal or extranodal sites, and, as a corollary, was the stage at relapse early or advanced?

The patients with the most favorable prognosis are those who have disease recurrence only at a prolonged interval after an initial complete response and in a limited nodal pattern. RT alone can cure some of these patients, often administered as standard-dose total lymphoid irradiation (TLI) (Fig. 7.4)

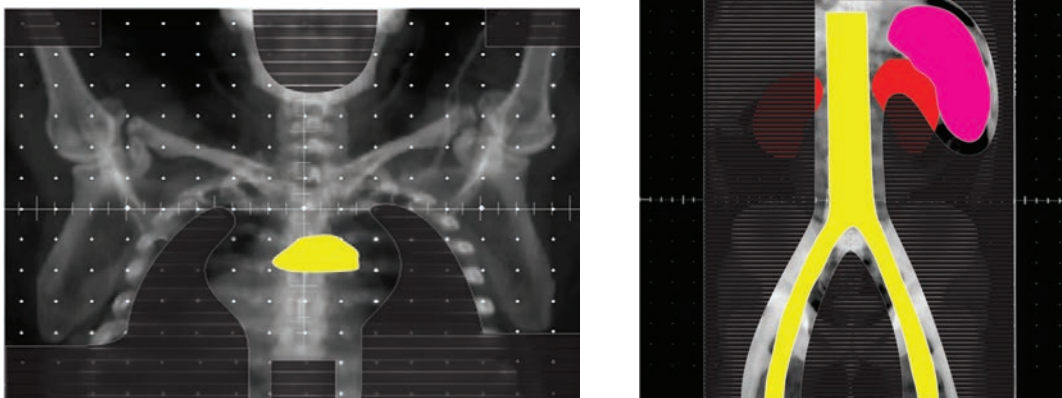


Figure 7.4 Digitally reconstructed radiograph depicting total lymphoid irradiation.

(146,147). However, this approach would be rare in children due to unacceptable morbidity. In fact, these patients may have a superior outcome (EFS as high as 80%) if treated with high-dose chemotherapy and autologous stem cell rescue (148,149). On the opposite end of the spectrum are patients who have chemotherapy-refractory disease and are never cured by conventional salvage chemotherapy.

Patients who relapse after regimens that include chemotherapy have been treated with high-dose chemotherapy and hematopoietic stem cell rescue (143,148,150). Three- to 5-year survival probabilities of 25–80%, depending on characteristics at relapse, have been reported (primarily in adults) after such treatment (149,151,152). Only one prospective study randomizing refractory or relapsed patients with HL to high-dose chemotherapy and stem cell rescue or conventional-dose chemotherapy has been performed. The British National Lymphoma Investigation Group randomized 40 patients to carmustine (BCNU), etoposide, cytarabine (arabinosylcytosine), and melphalan (BEAM) with stem cell support or lower-dose (mini) BEAM (153). Progression-free survival at 3 years was 53% and 10%, respectively. Data specific to children with recurrent HL are limited. However, an analysis of 81 pediatric patients with HL who underwent

ABMT and were reported to the European Bone Marrow Transplant Group demonstrated a similar outcome to a case-matched group of adults similarly treated (154). Claviez et al. found an increased risk of relapse and lower progression-free survival beyond 9 months when pediatric patients received reduced intensity compared to a myeloablative conditioning regimen prior to undergoing allogeneic stem cell transplant, although OS was not different between the two groups (Fig. 7.5) (155). The United Kingdom Children's Cancer Study Group performed a review of 51 pediatric patients with relapsed or refractory HL who underwent autologous stem cell transplant and 78 patients who underwent conventional salvage treatment without stem cell transplant. There were no statistically significant differences in OS between the two cohorts including those patients who had a short initial remission after primary therapy (156). Prognostic factors for unfavorable outcome include the duration of initial response to chemotherapy, "B" symptoms at relapse, disseminated pulmonary or bone marrow disease at relapse, and more than minimal disease at the time of transplantation (149,152). Patients with poor prognostic factors have a reported 5- to 10-year OS of 20–25% (157). Female sex, lactate dehydrogenase level ratio (the absolute LDH level divided by the upper limit

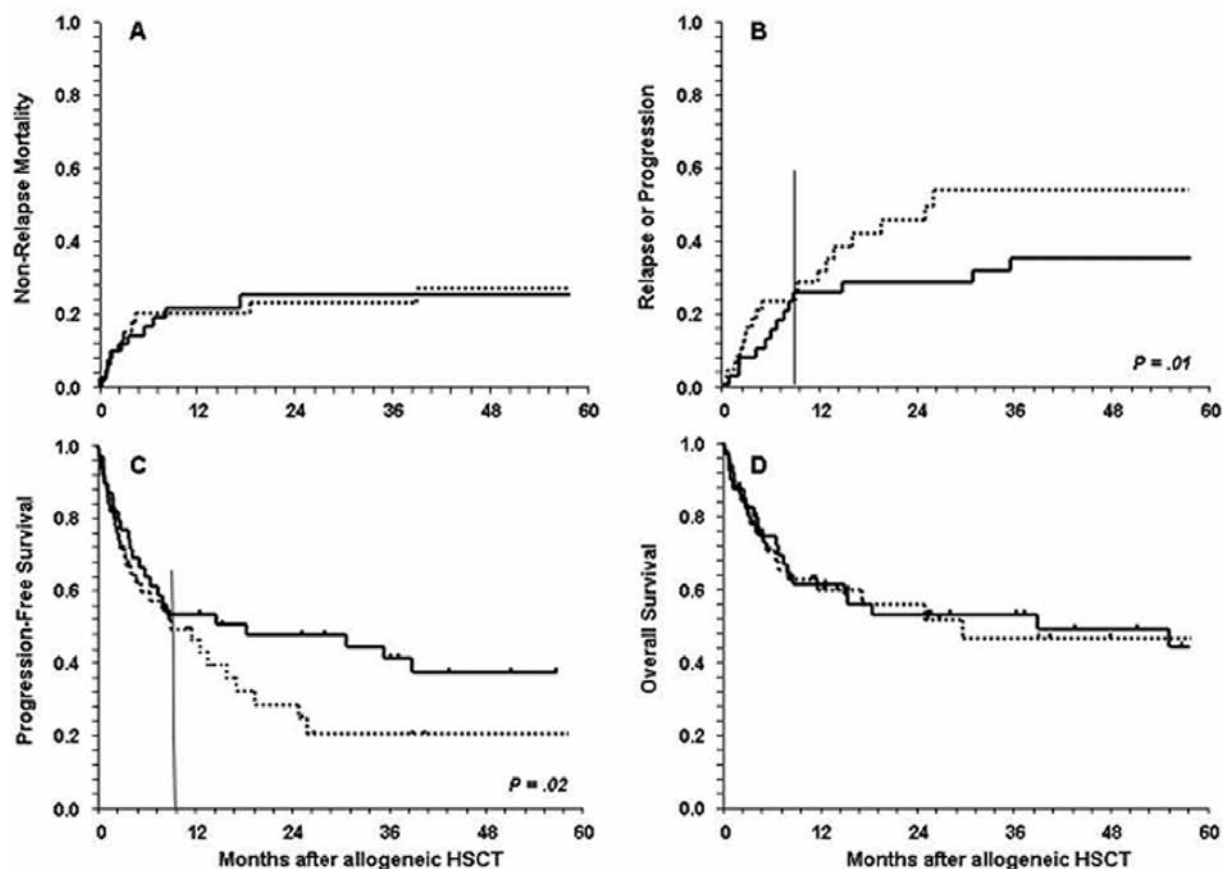


Figure 7.5 Outcome following allogeneic hematopoietic stem cell transplant (HSCT) for PHL by conditioning regimen (myeloablative [solid line] vs. reduced intensity [dotted line]). **A:** Cumulative incidence of nonrelapse mortality. **B:** Relapse rate that is significantly increased after a reduced intensity regimen ($p = 0.01$) from 9 months forward. **C:** Progression-free survival that is significantly lower ($p = 0.02$) from 9 months forward after reduced intensity regimen. **D:** Overall survival that is not significantly different between either regimen. (From Claviez A, Canals C, Dierickx, et al. Allogeneic hematopoietic stem cell transplantation in children and adolescents with recurrent and refractory Hodgkin's lymphoma: an analysis of the European Group for Blood and Marrow Transplantation. *Blood*. 2009;114(10):2060–2067, with permission. [Epub ahead of print]).

of the laboratory normal value) of greater than one and short interval from diagnosis to autologous stem cell transplant (≤ 15 months) have also been reported as negative predictive factors in pediatric patients (158). A variety of preparative regimens provide similar outcome (150,159).

What are the possible roles for RT in the setting of high-dose chemotherapy and stem cell rescue for HL? The basis for including RT is twofold: These aggressive salvage programs still fail to cure a large proportion of patients, and ample data show that many patients with progressive, recurrent HL after chemotherapy do not exhibit a cross-resistance to radiation (143,146,147). Moreover, most patients relapse in sites of previous involvement, mostly nodal (149,160,161). RT can be administered, in combination with chemotherapy conditioning regimens, as total body irradiation (TBI), IFRT, and TLI. Typical preparative regimens that include TBI or TLI are cyclophosphamide with or without etoposide (143,162). The rationale for TBI (e.g., 12–14 Gy in 4–5 days at 1.5–2.5 Gy twice daily) or TLI (e.g., 18 Gy in 2 weeks at 0.9 Gy twice daily) is the associated tumor cell kill and immunosuppressive effects. However, TBI and TLI programs for patients who have previously been treated with mediastinal RT are associated with a significant increase in pulmonary complications (162,163). Pneumonitis and pulmonary alveolar hemorrhage often are fatal. Because there appears to be no difference in relapse-free survival between TBI or TLI preparative regimens it is reasonable to avoid TBI or TLI if prior mediastinal irradiation has been given or is contemplated as boost treatment.

In considering the role of IFRT in the setting of high-dose chemotherapy and stem cell rescue, three essential questions must be answered: Does RT to sites of recurrent or refractory HL diminish relapse at these sites? If so, then what is the impact on freedom from relapse, EFS, and OS? Is the associated morbidity of IFRT acceptable? Data from several series support an affirmative answer to these questions (143,150,164,165).

In a Stanford report, patients with stage I–III disease at relapse who received ABMT and IFRT had a 3-year freedom from relapse of 100% and OS of 85%, compared with 67% and 60%, respectively, for patients not receiving IFRT (165). For patients not previously irradiated, IFRT was associated with an improved freedom from relapse of 85% and OS of 93%, in contrast to 57% and 55%, respectively, for those previously irradiated. Morbidity was similar to that of those not irradiated, although RT may have contributed to the peritransplant death of two patients.

Central issues relating to the use of IFRT are the dosage, target volume, and timing with respect to transplantation. RT dosages generally are 20–36 Gy, in 1.5- to 2.0-Gy fractions. This variation relates to potential normal tissue toxicity and the value of higher radiation dosages in patients with identifiable tumor that demonstrates radiation responsiveness (150). Radiation volume can vary and include treatment to all sites of initial disease, recurrent disease, persistent disease after salvage chemotherapy, persistent disease after the preparative regimen for transplantation, or all nodal sites (143,148,150). TLI administered before transplantation has been an effective program at Memorial Sloan–Kettering (162). IFRT can be administered before high-dose chemotherapy to place patients in a minimal disease state. RT can also be administered after high-dose chemotherapy to decrease the potential for disease progression elsewhere while

RT is being administered and for RT-related peritransplant morbidity such as esophagitis, pneumonitis, cardiomyopathy, and veno-occlusive disease. Possible disadvantages of this approach include the loss of the pretransplant cytoreductive effect and the theoretical carcinogenic effect of RT on the newly proliferating hematopoietic system (143,148,150).

Because of the historically high transplant-related mortality associated with allogeneic transplantation, autologous hematopoietic stem cell transplantation has been preferred for patients with relapsed HL. However, recent investigations of reduced-intensity allogeneic transplantation have demonstrated acceptable rates of transplant-related mortality (166). Nonmyeloablative conditioning regimens have varied, but most often they use fludarabine or low-dose TBI to provide a nontoxic immunosuppression. If successful, the procedure establishes a graft-versus-lymphoma effect and provides a platform for adoptive cellular immunotherapy. Evaluation of the effectiveness of this approach has been limited by reports describing treatment outcomes in small heterogeneous patient cohorts assigned to a variety of conditioning regimens in a nonrandom fashion. A longer follow-up period is needed to determine the efficacy of this approach.

RADIOTHERAPEUTIC MANAGEMENT

The curability of PHL, the complexity of current treatment approaches, and the vulnerability of the developing child to radiation and chemotherapy require the involved radiation oncologist to thoroughly understand the role of radiation and to deliver it with skill. As discussed earlier, most newly diagnosed children are treated with risk-adapted chemotherapy alone or combined-modality therapy including low-dose IFRT. In the past, fully-grown adolescents with favorable early-stage disease were considered for full-dose extended field RT using techniques that were standard for adults. This approach has been abandoned (in adults as well) because of concerns about cardiac toxicity and second malignant neoplasms, which are discussed in Chapters 19 and 20, respectively. Historically, the patterns of care studies (167,168) guided the definition of RT standards of practice. Results of treatment with RT alone were statistically better at institutions that treated a large number of patients with HL. Although different institutions and radiation oncologists may use slightly different treatment techniques, the underlying principles and most of the technical details remain constant (2,169). Because most children are treated in institutional (or multi-institutional) studies, the radiation oncologist should confirm all aspects of the diagnostic workup and staging and must also understand study requirements in order to deliver appropriate radiation. In a review of the DAL-HD-90 trial (German–Austrian pediatric multicenter trial), up-front centralized review of patients in the study altered the treatment approach in a large number of children (170). Unpublished data from the POG also support the superior outcome of children treated with appropriate radiation fields and dosages, in contrast to cases in which protocol violations occurred.

VOLUME CONSIDERATIONS

Most children with HL are treated with combined chemotherapy and low-dose IFRT. Meticulous and judiciously designed fields are necessary for optimizing disease control and tissue damage. The definitions of such fields depend on the anatomy

Table 7.7
Involved-Field Radiation Guidelines

Involved Nodes	Radiation Field
Cervical	Neck and/or supraclavicular ^a / infraclavicular
Supraclavicular	Supraclavicular/infraclavicular and lower neck
Axilla	Axilla with or without supraclavicular/infraclavicular
Mediastinum	Mediastinum, hila, and infraclavicular/ supraclavicular ^{a,b}
Hila	Hila, mediastinum
Spleen	Spleen with or without para-aortic
Para-aortic	Para-aortic with or without spleen
Iliac	Iliac, inguinal, femoral
Inguinal	External iliac, inguinal, femoral
Femoral	External iliac, inguinal, femoral

^aUpper cervical region is not treated if supraclavicular involvement is an extension of the mediastinal disease.

^bPrechemotherapy volume is treated except for lateral borders of the mediastinal field.

of the region in terms of lymph node distribution, patterns of disease extension into regional areas, and consideration for match line problems should disease recur. Involved fields typically should include not just the identifiably abnormal lymph nodes but the entire lymph node region containing the involved nodes (Table 7.7). The traditional definitions of lymph node regions can be helpful but are not necessarily sufficient. For example, the cervical and supraclavicular lymph nodes generally are treated when abnormal nodes are located anywhere in this area; this is consistent with the anatomic definition of lymph node regions used for staging purposes (Fig. 7.6) (171). However, the hila are irradiated when the mediastinum is involved, despite the fact that the hila and mediastinum are separate lymph node regions. Similarly, the supraclavicular volume often is treated when the axilla or the mediastinum is involved, and the ipsilateral external iliac nodes often are treated when the inguinal nodes are involved. However, in both these situations care must be taken to shield relevant normal tissues such as the breast in the former situation and ovaries in the latter. Moreover, it might be appropriate to treat the axilla or mediastinum without the supraclavicular volume and the inguinal nodes without the iliacs depending on the size and distribution of involved nodes at presentation. Field definitions often are protocol-specific, but excessively small fields usually are inappropriate. In a very young child (younger than 5 years), consideration may be given to treating bilateral areas (e.g., both sides of the neck) to avoid growth asymmetry. However, this is less of a concern with low radiation dosages, so unilateral fields usually are appropriate if the disease is unilateral. Every effort should be made to exclude unnecessary normal tissues (e.g., breast tissue in a child with isolated mediastinal disease and no axillary involvement). Treatment of involved supradiaphragmatic fields or a mantle field requires precision because of the distribution of lymph nodes and the critical adjacent normal

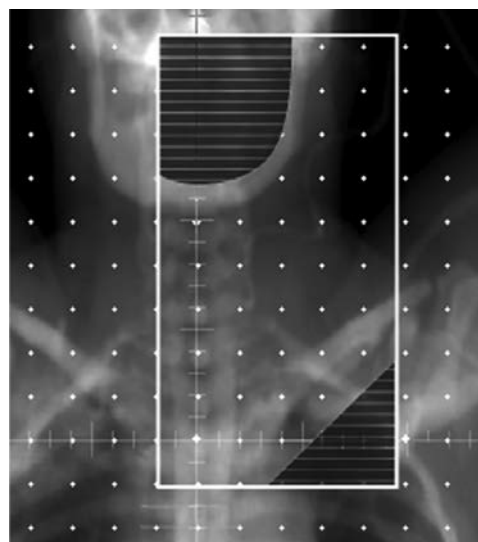


Figure 7.6 Digitally reconstructed radiograph depicting IFRT of the unilateral neck.

tissues. These fields can be simulated with the arms up over the head or down with hands on the hips. The former pulls the axillary lymph nodes away from the lungs, allowing greater lung shielding. However, the axillary lymph nodes then move into the vicinity of the humeral heads, which should be blocked in growing children. Therefore, the position chosen involves weighing concerns regarding lymph nodes, lung, and humeral heads (Fig. 7.7). Attempts should be made to exclude or position breast tissue under the lung and axillary blocking. When the decision is made to include some or all of a critical organ in the radiation field, such as liver, kidney, or heart, then normal tissue constraints, depending on the chemotherapy used and patient age, are critical.

Equally weighted anterior and posterior fields are used for daily treatment. Anteriorly weighted fields excessively irradiate the anterior heart, with associated cardiac morbidity (172). Dosage calculations should be based on the patient separation at the central axis. When a full mantle field is treated, nodes in the neck and axilla receive a higher dosage because the patient's body is thinner than at the midthorax. Therefore, separate axillary, neck, and low mediastinal dosimetry should be performed, and compensating filters or other modifications should be used to minimize inhomogeneity. Extended source-to-skin distances decrease dosage inhomogeneity in these different areas. Because of the increased dosage to the neck and cervical spinal cord, a posterior cervical spine block extending from the top of the field to below the level of the larynx may be added at a neck dosage of 20 Gy if midline disease is not present. Blocking the thoracic cord is not recommended because mediastinal nodes may be underdosed (169). Lung blocks should be carefully drawn, allowing adequate (1–2 cm) margins around mediastinal disease. If chemotherapy has been given, then the width of the field generally is based on the postchemotherapy residual disease, whereas the cephalad-caudad dimension respects the original disease extent (Fig. 7.8). As previously stated, humeral head blocks are appropriate unless bulky axillary adenopathy would thereby be shielded. Laryngeal and occipital blocks are also used unless disease is located in the vicinity of these structures; these blocks can be placed at the beginning of treatment or after some portion of it.

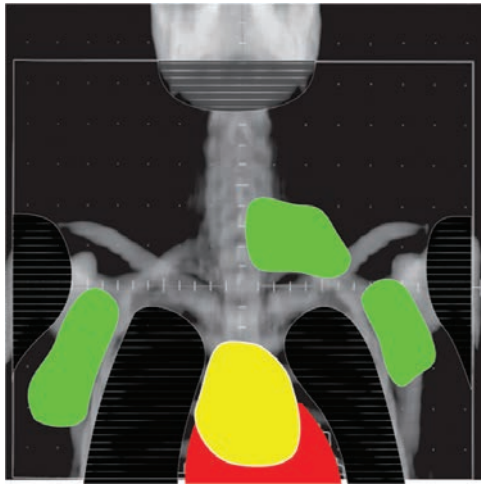


Figure 7.7 Digitally reconstructed radiograph of the mantle field demonstrating blocking of axillary nodes in the arms up versus arms down position.

Depending on the response of the disease to chemotherapy and the dosage administered, field reductions may be possible. Because 10- to 15-Gy dosages can cytorreduce HL, increasing the size of lung or cardiac blocks often is possible once or twice during the course of therapy; however, it is uncommon to use RT when large disease bulk has not already been treated with chemotherapy. The entire heart and lungs are rarely treated above dosages of 10–16 Gy, depending on the distribution of disease and chemotherapy used. More specifically, the indications for whole heart irradiation include pericardial involvement as suggested by a pericardial effusion or frank pericardial invasion with tumor; such patients generally receive combined-modality therapy and 10–15 Gy to the entire heart. Whole lung irradiation with partial transmission blocks is an option in the setting of overt pulmonary nodules or hilar involvement. Again, this is protocol dependent because some children treated for advanced-stage HL receive RT only to areas

of initial bulk disease or postchemotherapy residual disease. However, this approach remains investigational, and IFRT may remain the appropriate treatment approach. For children with pulmonary nodules at diagnosis, whole lung irradiation of 10–15 Gy is an option. A gap should be calculated in matching the para-aortic field (171).

When the subdiaphragmatic region is being treated, the spleen or pedicle must be included in patients who have splenic or para-aortic involvement, and the radiation dosage to the kidneys must be minimized. Usually the upper pole of the left kidney is within the irradiated volume. An intravenous pyelogram performed at the time of the simulation, a treatment planning CT, and diagnostic information obtained from the CT or MRI (coronal slices from a thoracic MRI will reveal the relationship of the spleen to the kidney) are helpful in drawing the blocks (Fig. 7.9). When the pelvis is being treated, special attention must be given to the ovaries and

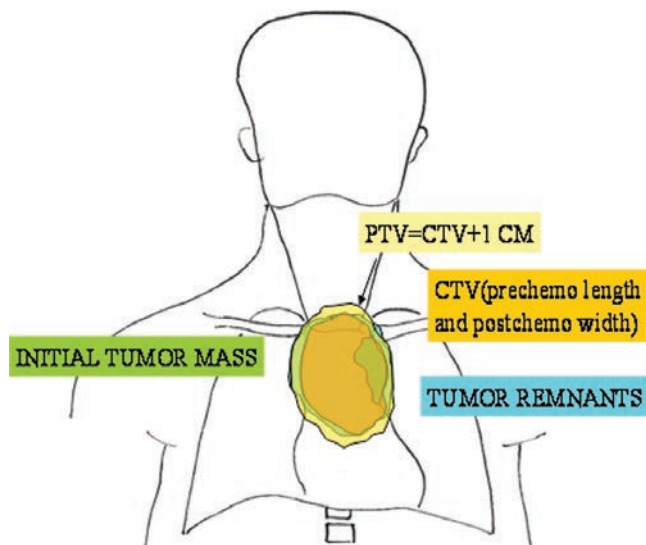


Figure 7.8 INRT based on CT contours of the mediastinum incorporating the prechemotherapy extent of disease in the superior and inferior direction and the postchemotherapy width of disease plus a margin to achieve the final PTV.

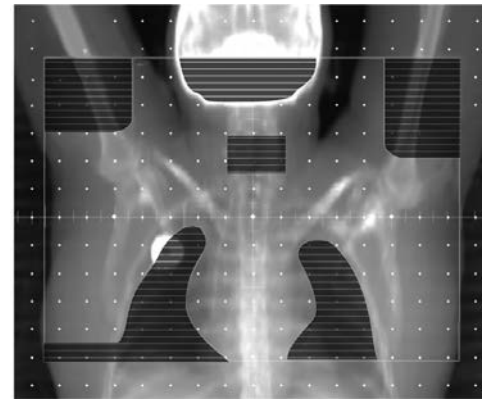


Figure 7.9 Digitally reconstructed radiograph of an involved para-aortic treatment field with CT-based contours of the involved para-aortic lymph nodes (red contour) and spleen (purple contour) with bilateral kidneys (blue and green contours, respectively) outlined.

testes. The ovaries should be relocated, marked with surgical clips, laterally along the iliac wings or centrally behind the uterus. In this manner, appropriate shielding may be used. The testes receive 5–10% of the administered pelvic dosage, which is sufficient to cause transient or permanent azoospermia, depending on the total pelvic dosage. The greatest shielding can be afforded to the testes if the patient is placed in a frog-legged position with an individually fitted testes shield. If multileaf collimation is available, the multileaf can be placed over the testes, additionally decreasing the transmitted dosage. Clearly, careful planning and judgment are necessary. As previously stated, RT for unfavorable and advanced HL is variable and protocol dependent. Although IFRT remains the standard when patients are treated with combined-modality therapy, restricting RT to areas of initial bulky disease (generally defined as larger than 5 cm at the time of disease presentation) or postchemotherapy residual disease (generally defined as larger than 2 cm or residual PET avidity) is under investigation.

Involved-Node Radiotherapy

Radiation treatment fields have been successfully reduced in size to include an involved field alone in combination with chemotherapy without sacrificing clinical outcomes. Smaller treatment fields are expected to decrease long-term toxicities given the increased sparing of normal structures. Patients with early-stage HL treated with chemotherapy alone most frequently relapse in the initially involved lymph node(s) (161). Therefore, an effort has been made to reduce treatment field size further to include only the initially involved lymph node(s). The EORTC-GELA has recently introduced the concept of involved-node radiotherapy (INRT) (173). This uses all available clinical information including pre- and postchemotherapy imaging with CT and FDG-PET scan to define the treatment field according to the prechemotherapy extent of disease. Based on the EORTC-GELA guidelines, any visualized lymph node after CRu should be included in the clinical target volume (CTV) and normal structures displaced by enlarged lymph nodes should not be included in the CTV. The margin of the planning target volume (PTV) should be 2 cm in the axial direction and 3 cm in the craniocaudal direction although may be reduced to 1–1.5 cm (174). Controversy still exists regarding the optimum margins for the application on INRT (174–176).

Given the high precision required to cover the full extent of disease using INRT, both pre- and postchemotherapy CT and FDG-PET scans should be performed. Contrast-enhanced imaging should be obtained with the patient in the treatment position and FDG-PET scans should be used to complement CT (176). In a study of early-stage HL patients by Girinsky and colleagues, PET identified 36% of involved lymph nodes that were radiographically occult on CT scan. Therefore, evaluation with FDG-PET scan prior to chemotherapy may help to delineate the complete extent of clinical disease (177). Initial clinical data with the use of INRT is emerging. Campbell and colleagues reviewed clinical outcomes of patients with limited stage HL treated with EFRT, IFRT, and INRT ≤ 5 cm. No marginal recurrences or locoregional failures occurred with INRT (178).

The application of INRT requires that all available clinical information is utilized to appropriately reduce treatment field size without sacrificing the excellent clinical outcomes that are attainable with standard therapy (Fig. 7.10).

PET/CT Radiation Planning

CT-based treatment planning has largely replaced conventional radiographic simulation, which is limited in its two-dimensional (2D) rendering of bony landmarks. CT simulation enables 3D visualization of the patient in the treatment position to allow increased precision for targeting tumor and normal structures. The Hounsfield units acquired from CT images are also proportional to electron density used to perform dose calculations. FDG-PET complements CT by providing functional information to help delineate the tumor volume and normal structures. FDG-PET and CT have been used in combination for radiation planning. Dedicated PET/CT scanners for simulation allow the immediate co-registration of FDG-PET and CT scan images while the patient is in the treatment planning position. An FDG-PET scan obtained separately can also be fused to a CT treatment planning scan obtained in a radiation oncology department. It is recommended that the patient be placed in the treatment planning position for both scans with an appropriate immobilization device to enhance reproducibility.

Several studies have specifically assessed the changes in tumor volume and management when PET is acquired at the time of simulation for adult patients with lymphoma (177,179,180). In a small study of thoracic lymphoma patients from the Royal Marsden Hospital, a decrease of 50% in dose to the lungs was achieved in two patients when PET-based planning was used in place of CT-based planning (179). Hutchings and colleagues studied 30 patients with early-stage HL who underwent a staging FDG-PET/CT. After a short course of ABVD, patients were treated with an involved field with tumor volumes delineated on the CT treatment planning scan. These patients were then replanned with incorporation of FDG-PET findings. The treated volume increased in seven patients and decreased in two patients. Given the potential expansion of the treated volume, the authors concluded that PET/CT treatment planning should be used with caution (180).

PET/CT treatment planning may have particular use in applying the INRT concept. Prechemotherapy CT and FDG-PET scans were performed in the treatment position using immobilization and fused to postchemotherapy CT planning scans for early-stage HL patients in a study performed by Girinsky and colleagues (177). FDG-PET was useful in identifying involved nodes in 36% of patients in whom lymph nodes were undetectable on CT scan. Therefore, PET may be a valuable adjunct to CT treatment planning, if treatment field size is reduced, to ensure adequate dose coverage to the tumor volume. In the clinical scenario where the use of conformal RT is being considered, the addition of PET to CT planning may enhance the accuracy of target volume definition. Given the potential for an increase in treatment volume with the use of PET/CT radiation planning, this technology should be used judiciously, enlisting the input of diagnostic specialists. Thus far, studies addressing the use of PET/CT for radiation treatment planning are few with small patient numbers and, therefore, further investigation is needed to understand how best to incorporate this technology.

CONFORMAL RADIATION PLANNING

Indications for conformal radiation approaches are increasing particularly with the widespread adoption of CT-based target localization. CT scan imaging enables 3D planning and

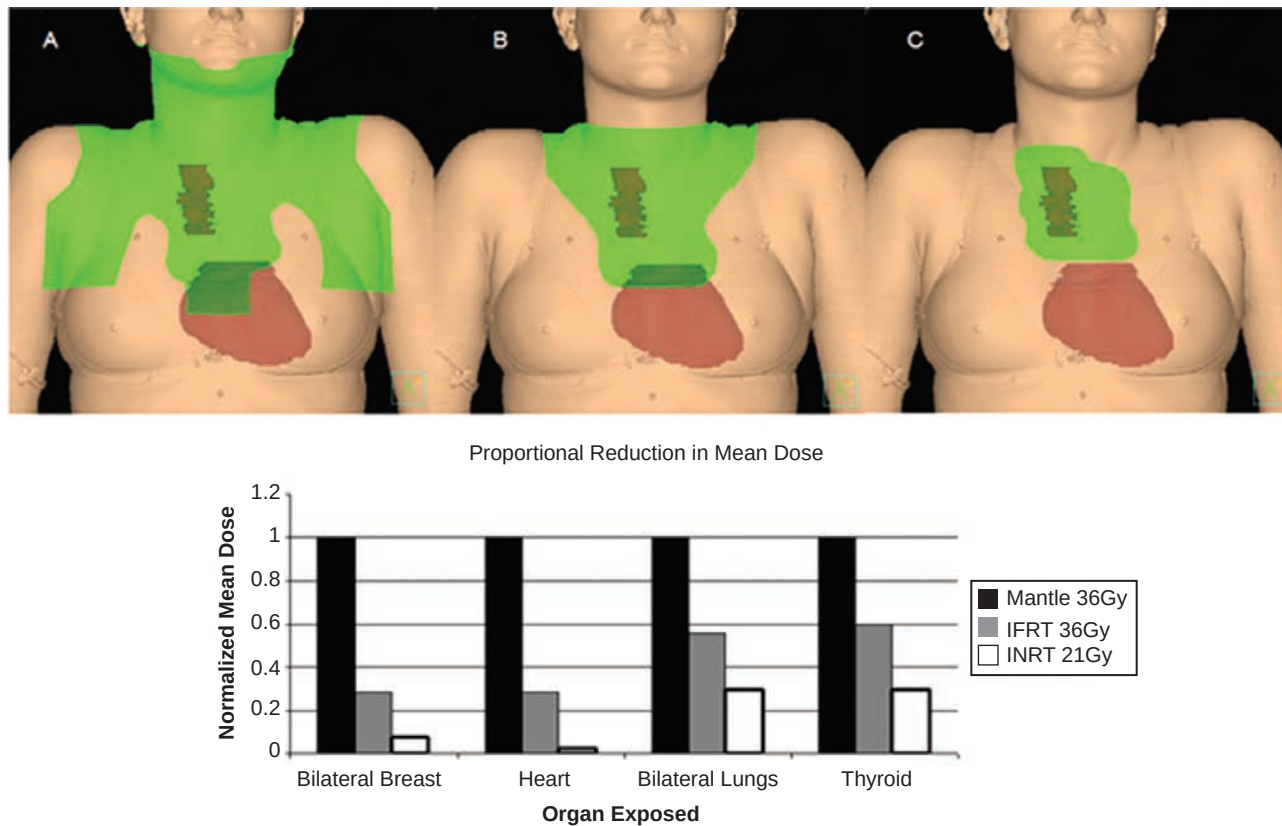


Figure 7.10 A: CT-based planning images depicting a historic mantle RT, compared to standard involved-field radiation treatment (IFRT), and involved-node RT (INRT) for a patient with stage I disease involving the mediastinum. The postchemotherapy volume of initially involved paratracheal nodes is depicted in dark red and the cardiac silhouette is also evident. B: Demonstration of the reduction in dose to breast, lung, heart, and thyroid for the female patient shown in (A). (From Hodgson DC, Hudson MM, Constine LS. Pediatric Hodgkin lymphoma: maximizing efficacy and minimizing toxicity. *Semin Radiat Oncol.* 2007;17(3):230–242, with permission.)

enhanced anatomic localization for treatment field design and dose calculations. Three-dimensional conformal radiation (3D-CRT) and intensity-modulated radiotherapy (IMRT) are methods used to deliver tightly conformal doses to the tumor volume. Steep dose gradients are achieved to spare normal structures, particularly for patients who are at risk for treatment complications. It is important to note that the use of conformal approaches is based on delineation of the appropriate volume to be irradiated, and not on anatomic definitions and structures as is true for traditional anterior/posterior (two-field) approaches. This requires the physician to identify all involved and uninvolved lymph nodes if an “involved field” versus an “involved lymph node” strategy is employed.

“Forward planning” is used to create 3D-CRT plans whereby the physician, physicist, or dosimetrist determines the nature of the radiation beams that will accomplish a desirable radiation dose distribution. Using “inverse planning,” the intensity of radiation beams can be varied across the treatment field. Optimization algorithms are used to create an intensity map based on a prespecified dose delivered to the target volume and normal structures. The intensity pattern for each field is determined using sophisticated software until the dose distribution most closely approaches the physician’s intent. IMRT allows the delivery of a tightly conformal radiation dose with a steep dose gradient to spare normal structures. It is particularly advantageous in its ability to create concavities to avoid treatment of surrounding tissues and

utilizes multiple treatment fields to accomplish this goal. Although an increased number of treatment fields improves conformality, the radiation dose is spread over a larger volume of tissue as a result. IMRT also requires additional monitor units to deliver treatment compared to conventional methods. Therefore, total body dose is increased due to increased leakage radiation.

The impact of IMRT in children is a special consideration. Children are known to be at higher risk for the development of secondary malignancies after radiation (ICRU 60). The use of multiple beams with IMRT results in a larger area of the body receiving a low dose compared to conventional techniques (“low-dose” bath effect). IMRT for the pediatric population remains controversial given the concerns for long-term toxicities including late growth disorders and the development of second malignancies. Increased radiation scatter may have a greater impact on oncogenic risk given the smaller body habitus of children as a result of the closer proximity of organs at risk and PTV compared to adults (181,182).

IMRT has been adopted as a standard treatment for various malignancies including prostate and head and neck cancer. However, the role of IMRT has been limited in the treatment of PHL due to the low doses required for treatment, the need to identify with certainty the target lymph nodes, as well as the limitations in the dosimetric advantage of IMRT when treating a large field. The use of IMRT may result in a dosimetric advantage in select cases particularly when applying the involved-field or

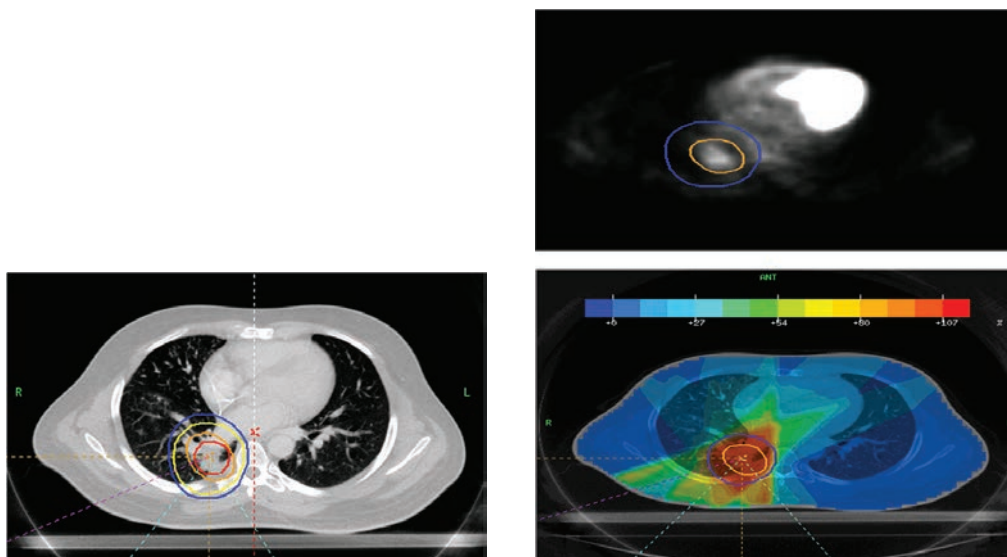


Figure 7.11 Reirradiation accomplished using IMRT for recurrent lymphoma in the mediastinum planned with PET/CT simulation. The GTV using CT alone is contoured in red, the GTV using PET/CT information is contoured in orange, the CTV is contoured in yellow, and the PTV is contoured in blue.

involved-node approach. For example, patients who are referred for IFRT before or after stem cell transplant may have received prior radiation or have higher risk for radiation pneumonitis. In a patient who has received prior radiation, IMRT may allow reirradiation of relapsed or refractory disease given the proximity of previously irradiated normal structures (Fig. 7.11). IMRT may also have a potential benefit in highly select patients with bulky mediastinal disease or after bleomycin administration for the sparing of lung and heart (Fig. 7.12).

Studies are ongoing to address the use of IMRT in lymphoma patients. At Memorial Sloan-Kettering Cancer Center, a study was conducted comparing conventional 2D radiation, 3D-CRT, and IMRT in patients with the Hodgkin or non-Hodgkin mediastinal disease who had received prior radiation or had large volume disease (183). PTV coverage was improved with the use of conformal treatment compared to conventional radiation. However, the volume of lung receiving at least 20 Gy (V20) was increased with IMRT. The probability for pneumonitis was assessed with a biologic model known as the fractional damage (Fdam) that evaluated damage to organ subunits. Both the Fdam and mean

lung dose were decreased with IMRT compared to conventional and 3D-CRT plans. Although Yorke et al. found that the Fdam and mean dose correlated significantly with the development of radiation pneumonitis in non-small cell lung cancer, these findings have not been verified in the lymphoma population (184). Reduced median heart and lung doses were achieved using IMRT in eight patients with mediastinal disease in a small study conducted by Nieder and colleagues (185). Girinsky and colleagues also compared IMRT, 3D-CRT, and conventional plans for HL patients presenting with mediastinal disease. Anteroposterior/posteroanterior (AP/PA) fields resulted in a minimally lower lung mean dose compared to 3D-CRT and IMRT plans. The V20 achieved with AP/PA fields was similar to an IMRT plan but lower than 3D-CRT. The median dose to the breast was lower using AP/PA fields although there was no difference in the breast V20. Studies evaluating dosimetric changes with the use of IMRT are few with small patient numbers. Given the possible advantages of IMRT in specific clinical scenarios, further study must be performed to understand the possible clinical applications of IMRT for lymphoma patients.

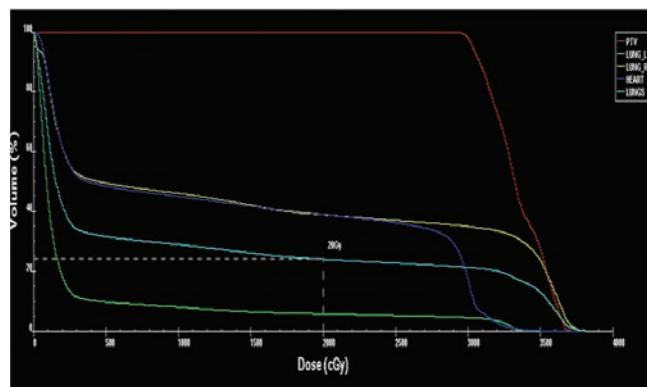


Figure 7.12 Dose-volume histograms of conventional and IMRT plans, respectively, in a patient with bulky mediastinal disease. A decrease in the lung V20 is accomplished with IMRT compared to conventional AP/PA fields.

IMRT can also modify the intensity patterns through a planned treatment volume to achieve escalated doses to specific regions. “Simultaneous integrated boost” IMRT (SIB-IMRT) or “dose painting” can deliver higher doses to areas of gross disease while delivering a lower dose to subclinical or microscopic disease. In this way, a boost treatment normally delivered after conventional therapy is integrated and treated simultaneously with a higher dose per fraction and an overall shorter treatment course. Dose painting may prove advantageous in the treatment of certain clinical sites such as the head and neck region but further investigation into the use of this technique in the pediatric population is warranted.

ENERGY

Megavoltage energies are necessary. A 4- to 6-MV linear accelerator should be used for supradiaphragmatic fields, thereby ensuring adequate dosages to the superficial nodes in the build-up region and to deep nodal areas such as the mediastinum. Higher-energy machines (8–15 MV) may be appropriate for treating para-aortic nodes. If high-energy machines must be used to treat the mantle field, some therapists use a beam spoiler or bolus on the neck and supraclavicular regions. Cobalt-60 units can underdose the field edge, and orthovoltage units are absolutely inappropriate. Distances of less than 80 cm are also contraindicated because of suboptimal depth-dosage characteristics.

DOSAGE CONSIDERATIONS

Kaplan (2) constructed a radiation dose–response curve for HL, but limitations of its current applicability include its use of kilovoltage data. Reports demonstrate that lower radiation dosages provide excellent local control, with variables including tumor size and fractionation schedule (167,168). In the absence of chemotherapy, subclinical disease is reliably (95%) controlled with 25–30 Gy, small bulk disease (variously defined but less than 5 cm in most reports) necessitates 30–35 Gy, and large bulk disease an additional 5–10 Gy. The dosages per fraction should be 1.5–1.8 Gy daily, five times a week. Patients treated with large volumes may tolerate only 1.5-Gy fractions. In the setting of combined therapy, certainly the intensity of the chemotherapy is important to consider in the choice of the radiation dosage and volume. However, dosages of 15–25 Gy are typical, with shrinking fields and boosts individualized. In Tables 7.4 and 7.5, the radiation dosages selected to complement the chemotherapy regimen are provided. In general, dosages of more than 25 Gy are uncommon in pediatrics. Of interest in this regard is the DAL-HD-90 trial, in which dosages of 20–25 Gy were administered in combination with OEPA or OPPA, with or without COPP. The radiation dosages administered were 20–25 Gy, with a local boost of 5–10 Gy for insufficient remission after chemotherapy. Tumor burden, indicated by bulky disease or number of involved nodes, proved not to be prognostically significant (138). Also of interest is the reported randomized trial by the German Hodgkin Lymphoma Group (186), in which adults with stage I–IIIA disease with intermediate prognosis received 20, 30, or 40 Gy to nonbulky or uninvolved sites after 4 months of chemotherapy. Bulky (larger than 7.5 cm)

disease always received 40 Gy. With this constraint, no difference was observed for the various dosages.

SEQUENCE OF THERAPY

The most effective sequence of therapy in the setting of combined chemotherapy and irradiation has not been established. However, chemotherapy usually is the first modality. This allows assessment of drug response, maximization of the amount of drug treatment, and shrinkage of disease and more limited fields of irradiation. Occasionally, focal irradiation before chemotherapy is necessary because of airway obstruction.

RESULTS

In assessing the results of therapy for HL, specific reports must be evaluated for the following:

- Definitions of survival (e.g., event-free, relapse-free, freedom from progression, overall)
- Characteristics of the patient population regarding evaluation and prognostic factors
- Treatment regimens and techniques, including chemotherapy dosage intensity
- Morbidity and mortality of therapy

The actuarial 10-year survival for children with early-stage disease is 85–95%, and for children with advanced-stage disease it is 70–90% (Tables 7.4 and 7.5). The data for early-stage patients (Table 7.4) indicate a similar OS for patients treated with full-dose RT, combined full-dose RT and chemotherapy, and low-dose RT and chemotherapy (97). However, the toxicities vary greatly between the treatment strategies, which underlie the recommendations present in Table 7.6. In fact, in the current era, essentially all patients will be treated with combined chemotherapy and radiation, or chemotherapy alone, with the rare exception of fully mature adolescents with very limited NLPD.

Although relapse-free survival and OS are excellent for patients with favorable, early-stage disease, patients with unfavorable disease continue to fare less well (Table 7.6). This is highlighted by the results from the GPOG HD-95 study of 830 children treated with two to six chemotherapy cycles and 20-Gy IFRT. The contrasting results for patients with favorable, intermediate, and unfavorable risk are depicted in Figure 7.13 (102).

It is critical to appreciate the extent to which death from causes other than recurrence of HL compromises OS. Several investigators have observed a greater risk of mortality in long-term survivors of PHL than in the general population (132,133,187). In the first 10 years after diagnosis, deaths were most commonly attributable to HL; with subsequent follow-up, subsequent cancers and cardiovascular disease contributed to higher mortality rates than in age- and sex-matched population control subjects. This is illustrated in Figure 7.14, which demonstrates the cumulative incidence functions for cause-specific deaths among survivors of PHL treated at St. Jude Children’s Research Hospital (132). Standardized incidence ratios in this cohort showed a 12-fold elevated risk for all second malignancies, 11-fold elevated risk for a second solid tumor, and 33-fold elevated risk of breast cancer in female patients. Standardized mortality ratios also indicated greater mortality from cardiovascular disease (22; 95% CI, 8–48) and infection

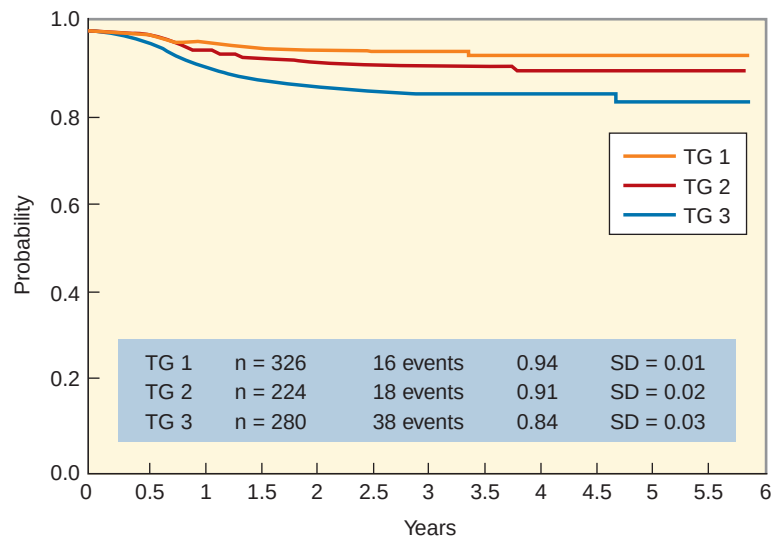


Figure 7.13 Comparison of treatment outcomes on the German pediatric oncology group HD-95 trial according to treatment risk group (TG) at a median follow-up time of 38 months. (From Wolden SL, Lamborn KR, Cleary SF, et al. Second cancers following pediatric Hodgkin's disease. *J Clin Oncol*. 1998;16(2):536–544, with permission.)

(18; 95% CI, 7–38). Importantly, HL consistently accounts for the majority of events in studies of long-term survivors; furthermore, relapse of HL is associated with a higher risk of subsequent events, including second cancers and cardiovascular disease. These findings underscore the need to proceed cautiously with therapeutic modifications because a reduced treatment intensity or duration may compromise disease control and promote late treatment complications.

COMPLICATIONS

Acute Side Effects

Acute side effects seen during mantle irradiation include temporary loss or change in taste, low posterior scalp epilation, xerostomia, skin erythema (particularly on the neck and

shoulders), and occasional nausea and vomiting necessitating antiemetics. Acute effects of para-aortic irradiation are uncommon, but nausea and vomiting can occur. Late effects of para-aortic irradiation are also uncommon. Small bowel obstruction is rare because of the infrequency of surgical staging. For the few patients who have had abdominal surgery and irradiation, small bowel obstruction necessitating surgical intervention is related to the total dosage given: 1% for dosages less than 35 Gy and 3% for dosages greater than 35 Gy (167).

Long-Term Side Effects

Long-term adverse sequelae of greatest concern that are specific to irradiation in children include impairment of muscle and bone development (9,188–190) and injury to the lungs

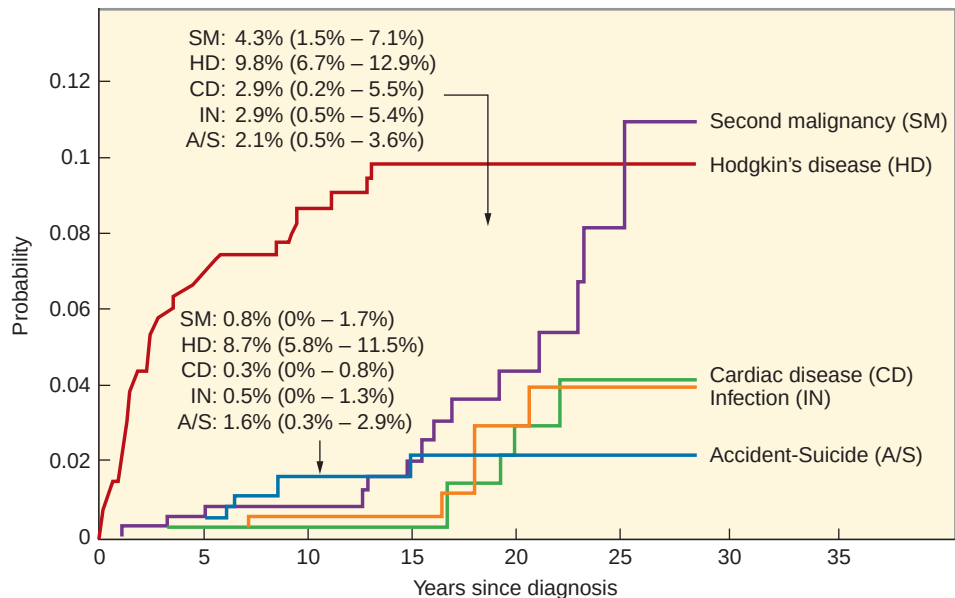


Figure 7.14 Cumulative incidence functions for cause-specific deaths among St. Jude children's research hospital cohort with Hodgkin's disease from second malignancy, Hodgkin's disease, cardiac disease, infection, and accident or suicide. Ten- and 20-year estimates are shown, with 95% confidence intervals in parentheses. (From Hudson MM, Poquette CA, Lee J, et al. Increased mortality after successful treatment for Hodgkin's disease. *J Clin Oncol*. 1998;16(11):3592–3600, with permission.)

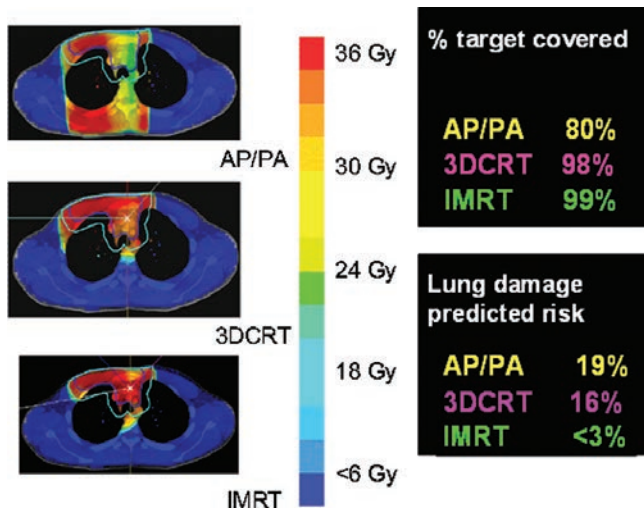


Figure 7.15 Color wash depictions of conventional, 3D-CRT, and IMRT treatment plans delivered to mediastinal disease. Target coverage improved with increasing conformality while the predicted lung damage risk decreases.

(191–194), heart (164,187,195–197), thyroid gland (198, 199), and reproductive organs (126,200–207). Survivors who underwent surgical staging with splenectomy also have a lifelong risk of overwhelming sepsis from encapsulated bacterial organisms (208,209). Cardiovascular dysfunction and secondary carcinogenesis may result in early mortality in long-term survivors (132,164,196). Pulmonary fibrosis can compromise the quality of life in survivors. Long-term complications are discussed extensively in Chapter 20 and are briefly outlined here. Fortunately, these effects are less common with the use of modern treatment programs (99,101).

Chronic pneumonitis and pulmonary fibrosis should be rare in the current era of treatment for primary HL (Fig. 7.15). Predisposing therapies include thoracic radiation and ABVD chemotherapy (113,163,191–194). The bleomycin in ABVD can cause both acute pulmonary compromise and late pulmonary fibrosis and can be augmented by the fibrosis that can be associated with pulmonary radiation. A “radiation recall” phenomenon can be seen when RT is administered after doxorubicin. Asymptomatic pulmonary dysfunction that improves over time is observed after contemporary combined-modality treatment (188,194).

Cardiovascular disease is a major concern in survivors of PHL. Cardiac dysfunction is most commonly observed after anthracycline therapy, particularly doxorubicin (195,196,197,210). Young children may be at a greater risk for anthracycline injury than adults because of an adverse effect on cardiac myocyte growth. This is suggested by studies of childhood leukemia survivors who demonstrate a high frequency of abnormalities of afterload and contractility (211). Mediastinal irradiation and other chemotherapeutic agents (e.g., cyclophosphamide) may predispose patients with PHL to anthracycline-related myocardiopathy (196–197). The risk at delayed time points (more than 20 years) has not been established. An increased risk for inpatient care for cardiovascular disease was identified in HL patients diagnosed with HL at age 40 years or younger. A family history of congestive heart failure and coronary artery disease has also been shown to increase risk for these conditions in HL survivors (212).

Radiation also injures the pericardium and myocardium in a dose-related fashion (195,197,210). High-dose (35- to 44-Gy) mantle irradiation produces cardiac injury in 13% of children and adults, most commonly manifest as constrictive pericarditis or accelerated coronary atherogenesis. Stanford investigators reported that the actuarial risk of developing cardiac disease necessitating pericardectomy was 4% at 17 years in a series of long-term survivors of childhood HL (197). Most patients with severe pericardial complications were irradiated before the introduction of subcarinal shielding and received little or no cardiac blocking. Premature coronary artery disease and acute myocardial infarction may also increase mortality risk in patients treated with mediastinal radiation in dosages of more than 30 Gy before 20 years of age (196). Screening echocardiogram, exercise stress test, and resting and 24-hour ECG identified numerous clinically significant cardiac abnormalities in HL patients who had mediastinal irradiation at a median age of 16.5 years (range, 6.4–25 years). Significant valvular defects were detected in 42%, autonomic dysfunction in 57%, persistent tachycardia in 31%, and reduced hemodynamic response to exercise in 27% of patients (213). With the introduction of techniques that reduce the radiation dosage to the heart, the rates of radiation-associated cardiac injury have declined dramatically. Likewise, myocardial infarctions have not been systematically reported in children treated with combined-modality regimens using lower radiation dosages and volumes and protective cardiac shielding. Again, the impact of subclinical cardiac injury after low-dose RT may not become apparent until larger cohorts of survivors treated with these regimens begin to age.

Thyroid sequelae are common after RT for PHL. Hypothyroidism, hyperthyroidism, thyroid nodules, and thyroid cancer have been observed in long-term survivors (198,199). Of these, hypothyroidism, particularly compensated hypothyroidism, defined as thyroid-stimulating hormone (TSH) elevation in the presence of a normal thyroxine (T4) level, is the most common thyroid abnormality. Risk factors for hypothyroidism include younger age at treatment and higher cumulative radiation dosage. As many as 78% of patients treated with radiation dosages greater than 26 Gy demonstrate thyroid dysfunction, as indicated by elevated TSH levels (194,199). Because persistent TSH elevation most often signals impending gland failure and may be a carcinogenic stimulus to the gland, thyroid hormone replacement therapy should be instituted. Gland suppression with thyroid hormone replacement is also recommended for patients who develop thyroid nodules after radiation. Replacement therapy should suppress gland function, as indicated by a TSH of 0.5–1.5 mIU/mL. Periodic withdrawal of hormonal therapy in asymptomatic patients permits assessment of gland recovery, which has been observed in some patients serially monitored after RT. Persistent and enlarging nodules should be monitored with ultrasound and periodic biopsies for malignant degeneration because thyroid carcinoma is a common second malignancy after HL (198). The risk of gonadal injury after HL is related to the type and intensity of treatment. In boys, high-dose pelvic radiation may produce a transient oligospermia or azoospermia, but spermatogenesis typically recovers (206,214). Six to eight cycles of MOPP (or similar hybrid chemotherapy-containing alkylators) produces irreversible sterility in 80–90% of male patients; fertility may be preserved if treatment is limited to three or fewer cycles (204). Recovery

of gonadal function 10–15 years after MOPP chemotherapy has been rarely reported. COPP/ABV was also associated with male infertility in a majority of young men in a study conducted by Hobbie and colleagues (215). Anthracycline-based regimens such as ABVD (or similar hybrid) usually are associated with full recovery of spermatogenesis after a temporary period of azoospermia (201,216). In contrast, testicular Leydig cell function is more resistant to the effects of antineoplastic treatment, so growth and puberty are adversely affected only in boys treated with very high cumulative dosages of alkylating agent chemotherapy. Risk-adapted therapies reducing or eliminating gonadotoxic alkylating agent chemotherapy offer young men with newly diagnosed HL excellent prospects to maintain fertility (202).

Young women have a higher chance of maintaining regular menses after treatment for HL than older women. The risk of ovarian failure after pelvic radiation is high but can be reduced by midline ovarian transposition (oophoropexy) (200). Although most young women maintain or resume menses after MOPP (or similar hybrid) chemotherapy, they are predisposed to early menopause, particularly if they also received abdominal-pelvic radiation (126,203,207). In a report of female HL survivors by the Late Effects Study Group, 42% of women treated with alkylating agent chemotherapy and subdiaphragmatic radiation had experienced menopause by the age of 31 years, compared with 5% of control subjects (203). In a study of female HL patients treated at the Norwegian Radium Hospital, premature ovarian failure was identified in 37.4% of patients. The risk was significantly higher if patients received chemotherapy in addition to radiation. The risk was increased further if the chemotherapy regimen included an alkylating agent. Women younger than 30 years developed premature ovarian failure later in life but had the same cumulative risk as women older than 30 years (217). Reports by other groups have not indicated an excessive risk of premature menopause in young women treated with supradiaphragmatic RT alone (207).

The overall cumulative risk of developing a subsequent malignancy after treatment for PHL ranges from 7% to 8% at 15 years from diagnosis and rises to 16–28% by 20 years (133,137,218). Tumor histologies comprise two main types: acute myeloid leukemia (including a pancytopenic myelodysplastic syndrome) and solid tumors. Secondary leukemias exhibit a brief latency with a peak frequency in the first 5–10 years after treatment. The risk decreases to less than 2% after 10 years from diagnosis. Clinical and treatment factors correlated with secondary leukemogenesis include older age at treatment, history of splenectomy, presentation with advanced disease, treatment with high cumulative dosages of alkylating agents, and history of relapse (133,137,219,220–225). In contrast to secondary hematopoietic malignancies, the risk of developing a second solid tumor increases with the passage of time from diagnosis, with a latency usually exceeding 8 years from diagnosis. A variety of solid tumors have been observed, most commonly involving the breast, thyroid, bone, and soft tissues (39,133,137,218,219,226,227–229, 227–231). Female breast cancer is a particular concern but is likely to be less common with current radiation doses and techniques, since it is associated with RT fields that include breast tissue (especially mantle fields), and higher radiation doses. It is noteworthy that females may also be at higher risk for nonbreast second-

ary malignancies, primarily thyroid cancer, and this is unexplained (230). Recent investigation into genetic polymorphisms suggests that certain individuals may be predisposed to the development of secondary malignancies. Further study into the genomic variability of this population may help to define an individual's susceptibility to develop a second cancer (232). Secondary malignancies in PHL are discussed in detail in Chapter 20.

FUTURE INVESTIGATIONS

Devising new strategies to treat children with HL is problematic because of the overall success of current treatment regimens. However, grouping patients into different risk categories allows investigators to construct protocols intended to diminish therapy-induced toxicity for patients with favorable prognoses, improve treatment effectiveness for patients with unfavorable prognoses, and aim for both goals in patients who are intermediate in their prognosis. Unfortunately, the ability to conduct clinical trials in which the differences in survival between treatment arms are likely to be small is compromised by the large patient numbers necessary to detect such differences. If a reduction in treatment toxicity is the intended goal of a new regimen, then many years of follow-up are necessary to prove effectiveness. Some generalizations regarding ongoing efforts in clinical trials for PHL are as follows:

- Patients with early-stage disease (I, IIA without bulk disease, and perhaps IIB disease with sweats as the only systemic symptom) have an excellent prognosis. Therefore, can the intensity and duration of chemotherapy be decreased, and can agents be used that are associated with less severe side effects? Concomitantly, can the volume and perhaps dosage of RT be reduced? Can the amount of chemotherapy be based on the response to the initial cycles? Will chemoprotectants and radioprotectants prove useful?
- Patients with disease of an intermediate stage or with characteristics indicating that their prognosis is intermediate (II with bulky disease, IIB with fevers or weight loss, IIIA) are appropriate for studies that intend to increase efficacy without increasing toxicity. Generally, this entails modification of existing chemoradiotherapy programs.
- Patients with advanced-stage disease (IIIB, IV) need more effective treatment regimens. These might include increasing dosage intensity or the rate of drug delivery and combining agents into new regimens. The use of hematopoietic growth factors may assist in drug delivery. Defining the role of RT in such trials will continue to be an important objective.

Of interest, ongoing trials are evaluating the paradigm of early response using functional imaging as a prognostic factor for therapy reduction or intensification.

Finally, immunotherapeutic approaches are under development and investigation, such as the use of antiferritin antibody jointed with yttrium-90 (233), EBV-specific cytotoxic T lymphocytes (234), and monoclonal antibody immunotherapy targeting cell surface antigens (e.g., CD20, CD30) (235,236). If effective, these novel approaches will provide an alternative to cytotoxic treatment approaches with potentially fewer adverse long-term treatment effects.

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Non-Hodgkin Lymphoma

Mary S. Huang, Nancy J. Tarbell, and Howard J. Weinstein

Malignant lymphoma was described by Hodgkin in 1832 (1) and was distinguished from leukemia by Virchow in 1845 (2). Progress in treating children with non-Hodgkin lymphoma (NHL) mirrors the recognition of the systemic spread of the disease and underlying biology. Response to therapy and overall prognosis depend on the underlying histologic subtype, primary site, and the extent of disease (3,4). Historically, local therapy resulted in an overall survival of 10–30% (4). New multiagent protocols result in overall survivals of 70–95% (5–8).

Childhood NHL is distinguished from adult NHL by differing frequencies of histopathologic types and by the greater frequency of extranodal presentations (9,10). The pediatric NHLs are mostly (more than 95%) high grade and include the following four major subtypes: B- and T-lymphoblastic lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, and anaplastic large-cell lymphoma (ALCL) (Fig. 8.1). Many of these high-grade lymphomas disseminate noncontiguously, evolve into a leukemic phase, and involve the central nervous system (CNS) (10). The more common low-grade lymphomas seen in adults, such as follicular and marginal zone, are rare in children (9).

EPIDEMIOLOGY AND ETIOLOGY

The lymphomas are the third most common malignancy in children younger than 15 years of age. They are rare under the age of 3 years, peaking in incidence from age 7 to 11 years. There is approximately a 3:1 male:female ratio (3,4,6). Lymphomas account for approximately 10% of all childhood cancers: 60% are NHL and 40% are Hodgkin disease (11). There is geographic variation in the incidence of the NHLs. For example, in equatorial Africa, the Burkitt lymphoma accounts for almost 50% of all childhood cancers. In this setting, endemic Burkitt lymphoma is invariably positive for Epstein-Barr virus (EBV), in contrast to about 10% of cases of sporadic Burkitt lymphoma. However, both endemic and sporadic cases of Burkitt lymphoma have the same chromosomal translocations involving one of the loci encoding immunoglobulin heavy or light chains and the c-myc oncogene. The exact role of EBV in the pathogenesis of Burkitt lymphoma and other malignancies is unknown. NHL occurs in association with congenital immunodeficiency syndromes such as X-linked lymphoproliferative syndrome, ataxia telangiectasia, Wiskott-Aldrich syndrome, and common variable immune deficiency disease, presumably caused by host defects in immunoregulation or gene rearrangement (12,13). Immunosuppressive therapy and acquired immunologic disorders including HIV also increase the risk of developing NHL (13). These are predominantly



Figure 8.1 Denis Parsons Burkitt (1911–1993) was the son of an engineer. A Protestant raised in Northern Ireland, he lost an eye in a fight as a schoolboy. He graduated as a physician in 1935 and trained in surgery but had difficulty in obtaining surgical positions because of his visual loss. Eventually, he was posted as an Army physician in Africa and subsequently worked as a missionary physician. He characterized a previously undescribed aggressive head and neck cancer of childhood. Michael Epstein attended one of Burkitt's lectures in England, suspected a viral origin, and requested a tissue sample. Epstein and Yvonne M. Barr isolated the virus (Epstein-Barr virus). Burkitt also described the crucial influence of dietary fiber on health and disease.

diffuse large B cell or Burkitt subtypes. Screening for HIV and other immunodeficiencies should be considered for all children with NHL, especially for those with B-cell lymphomas.

CLINICAL PRESENTATION

Several subtypes of NHL in children are associated with distinct clinical manifestations and sites of disease (Table 8.1). Symptoms leading to diagnosis usually are of short duration. Approximately 25% of children with NHL have an anterior mediastinal mass (usually T lymphoblastic or diffuse large B cell) and present with wheezing, stridor, and cough

Table 8.1
Clinical and Biologic Features of NHL in Children

WHO Classification	Percentage of Cases	Common Primary Site	Immunophenotype	Chromosomal Changes	Genes Affected
Burkitt lymphoma	40	Abdomen or H/N	sIgM with light chain restriction CD10, CD19, CD20	t(8;14), t(2;8), or t(8;22)	Ig heavy- or light-chain genes and <i>MYC</i>
Diffuse large B-cell lymphoma (includes mediastinal)	20	Mediastinum, H/N, bone	sIgM > G (75%) CD79a, CD19, CD20, CD22	3q27, 8q24 and t(14;18) in adults	<i>BCL-2</i> (adult, <i>BCL-6</i>)
B-lymphoblastic lymphoma	5	Bone, skin, H/N	TdT, CD10, CD19, CD79a	Hyperdiploid >50 (ALL)	<i>TEL/AML1</i> (mostly in ALL)
T-lymphoblastic lymphoma	25	Mediastinum	TdT, CD2, CD3, CD4, CD5, CD7, and CD8, CD13 or CD33	14q11.2, 7q35, 7p14–15	<i>TALI</i> , TCR receptors, <i>HOX 11</i> , <i>RBTN1</i>
Anaplastic large-cell lymphoma	10	Skin, soft tissue, bone, mediastinum	CD30, EMA	t(2;5) or variant translocation	<i>NPM-ALK</i>

ALL, acute lymphoblastic leukemia; EMA, epithelial membrane antigen; H/N, head and neck; Ig, immunoglobulin; TCR, T-cell receptor; WHO, World Health Organization.

Adapted from Jaffe ES, Harris NL, Stein H, et al. Classification of lymphoid neoplasms: the microscope as a tool for disease discovery. *Blood* 2008;112:4384–4399.

progressing to dyspnea. The majority of these patients are adolescents, and their presentation may pose a medical emergency (14). Patients with large anterior mediastinal masses are at risk of cardiac or respiratory arrest during general anesthesia or deep sedation. A careful workup including a chest computed tomography (CT) scan with airway measurements is essential (15) before attempting any procedures. The least invasive procedure (e.g., biopsy of a peripheral lymph node) should be carried out. If these procedures are not successful in providing a diagnosis, then a CT-guided needle biopsy of the mediastinal mass should be considered (16). In some clinical situations (e.g., orthopnea or significant airway narrowing), preoperative or preprocedure steroids should be considered for up to 48 hours. The use of steroids has largely replaced localized irradiation in this setting. Primary gastrointestinal involvement occurs in about 30% (usually Burkitt histology), commonly presenting as an abdominal mass with ascites, an “acute abdomen” from an intussusception, or rarely a malnutrition syndrome with colitis symptoms (6,17). The majority of children with Burkitt lymphoma presenting with an ileal–cecal intussusception have limited gastrointestinal involvement that is amenable to complete surgical resection (Murphy stage 2 or group A). In 20–30% of children, the head and neck, including the Waldeyer ring or cervical lymph nodes, is the site of origin. The remainder of patients have miscellaneous primary sites, including bone, breast, skin, epidural space, or noncervical lymph nodes (6). Involvement of the bone marrow at diagnosis occurs in 10–30% of patients with Burkitt and lymphoblastic lymphomas. Overt CNS involvement at diagnosis is not common but is mostly seen in children with advanced-stage Burkitt and lymphoblastic lymphomas. Children who develop Burkitt lymphoma in endemic areas of the world often have a mass in the head or neck region (especially jaw) in contrast to the

abdominal presentation typical of nonendemic Burkitt lymphoma.

EVALUATION

A biopsy of a lymph node or mass or examination of pleural or ascitic fluid is necessary to establish the diagnosis. Although histology continues to be the primary determinant of therapy, morphology with immunohistochemistry is supplemented by cytogenetic, and molecular genetic studies. The workup includes complete blood cell count with differential, routine chemistries with electrolytes, calcium, phosphorus, magnesium, uric acid, liver and renal function tests, lactate dehydrogenase (LDH), chest radiograph, bone marrow aspirate and biopsy (18), and a lumbar puncture with cytocentrifugation. Abdominal, thoracic, and head and neck CT scans should be obtained and a magnetic resonance imaging (MRI) scan may provide additional information depending on the presenting site (19). Gallium and, more recently, positron emission tomography (PET) scans are now part of the initial staging for some patients with NHL and are particularly helpful in assessing response to induction therapy for diffuse large B-cell lymphoma and ALCL (20,21). Laparotomy is not indicated for staging and is performed only for abdominal presentations necessitating surgical intervention (e.g., ileal–cecal intussusception). There is no data to support surgical debulking of NHL in children.

STAGING AND CLASSIFICATION

Originally, the Ann Arbor staging system for the Hodgkin disease was used for NHL (see Table 7.1) (22). The usefulness of this system in pediatric NHL is limited, and an alternative staging system proposed by Murphy et al. (6) has become

widely accepted (Table 8.2). This system recognizes typical patterns of disease presentation and has greater prognostic utility than the Ann Arbor system. In Burkitt lymphoma and large B-cell lymphomas, another staging system developed by Patte et al. (23) is also used (Table 8.3). It classifies patients according to tumor burden and surgical resection.

The current most widely accepted histologic classification system is the World Health Organization (WHO) classification that was updated most recently in 2008 (24,25). This system has been validated as highly reproducible in international studies and has evolved to incorporate histology as well as immunohistochemistry, gene expression profiling, cytogenetic, molecular and clinical features.

As previously discussed, over 95% of the pediatric NHLs are high grade and fall into four major histologic subtypes (lymphoblastic lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma, and ALCL). T- and B-cell lymphoblastic lymphomas comprise about 30% of NHL in childhood; T cell is the more common type. Mature B-cell lymphoma includes Burkitt lymphoma (35–40% of cases) as well as diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBL). Together, the latter two comprise approximately 20% of NHL in childhood. In the current WHO classification, PMBL is considered distinct from other DLBCLs based upon its unique clinical, histologic, and molecular features. Other mature B-cell lymphomas, including pediatric marginal zone lymphoma, pediatric follicular lymphoma, and MALT lymphoma, are also recognized as distinct entities that rarely occur in childhood. Within the category of mature T-cell lymphoma, ALCL accounts for approximately 10% of NHL in childhood.

B-cell lymphoblastic lymphoma consists of cells with round or convoluted nuclei, fine chromatin, inconspicuous nuclei, and scant, faintly basophilic cytoplasm. In B-cell lymphoblastic lymphoma, the tumor cells are characteristically express TdT, CD10, CD19, and CD79a, which is identical to the most common immunophenotype of B-acute lymphoblastic leukemia (ALL) in

Table 8.3
Clinical Staging of B-Cell Lymphomas

Stage	Extent of Tumor
A	Resected stage I and abdominal stage II
B	Multiple extra-abdominal sites; nonresected stage I, II, III, and IV (CNS negative, BM > 25%)
C	Intra-abdominal tumor stage IV (CNS positive), BM > 25% (Burkitt leukemia)

From Patte P, Auperin A, Gerrard M, et al. Results of the randomized international

FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: It is possible to reduce treatment for the early responding patients. *Blood*. 2007;109:2773–2780.

CNS, central nervous system; BM, bone marrow.

childhood (24). The T-cell lymphoblastic lymphomas are also TdT positive, but express a combination of T-cell antigens (CD2, CD3, CD4, CD5, and CD8) similar to that of T-cell ALL. T-cell lymphoblastic lymphomas share many clinical and biologic features with T-cell ALL (26,27). When the bone marrow is involved with lymphoblasts (>25%), the distinction between lymphoma and leukemia becomes difficult. Subtle distinct biologic differences between the blasts in T-lymphoblastic leukemia and lymphoma are being recognized with newer molecular assays (28).

Burkitt lymphoma tumor cells are monomorphic, medium-sized cells with round nuclei, multiple nucleoli, and basophilic cytoplasm. A “starry-sky” pattern is the result of benign macrophages that have ingested apoptotic tumor cells. Cells are typically sIgM, CD19, CD22, CD79a, and CD10 (24). Most, but not all cases have a cytogenetic abnormality involving the MYC gene at band 8q24.

Table 8.2
Murphy and St. Jude Children’s Research Hospital Staging System for Childhood NHL^a

Stage I	A single tumor (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen
Stage II	A single tumor (extranodal) with regional node involvement Two or more nodal areas on the same side of the diaphragm Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm A primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only ^b
Stage III	Two single tumors (extranodal) on opposite sides of the diaphragm Two or more nodal areas above and below the diaphragm All the primary intrathoracic tumors (mediastinal, pleural, thymic) All extensive primary intra-abdominal disease ^b All paraspinal or epidural tumors, regardless of other tumor sites
Stage IV	Any of the preceding stages with initial CNS or bone marrow involvement ^c

^aSee Refs. 6 and 10.

^bA distinction is made between apparently localized gastrointestinal tract lymphoma and more extensive intra-abdominal disease. Stage II disease typically is limited to a segment of the gut with or without the associated mesenteric nodes only, and the primary tumor can be completely removed grossly by segmental excision. Stage III disease typically exhibits spread to para-aortic and retroperitoneal areas by implants and plaques in mesentery or peritoneum or by direct infiltration of structures adjacent to the primary tumor. Ascites may be present, and complete resection of all gross tumor is not possible.

^cIf marrow involvement is present initially, the number of abnormal cells must be 25% or less in an otherwise normal marrow aspirate with normal peripheral blood picture.

Diffuse large B-cell lymphoma consists of tumor cells that are larger than lymphocytes with vesicular nuclei, basophilic cytoplasm, and a moderate-to-high proliferation fraction (25). The nuclear size is equal to or greater than that of a normal macrophage. DLBCL can be subdivided into several subclasses based on either immunophenotyping or DNA microarrays (24). These large B-cell lymphomas typically express CD19, CD20, and CD22, and 50–75% express cytoplasmic or surface immunoglobulin. PMBLs in addition to presenting in the mediastinum are typically associated with compartmentalizing alveolar fibrosis and, in contrast to other DLBCLs, typically do not express immunoglobulin. Alterations of oncogenes involved in adult DLBCL such as BCL6 and BCL2 are very rare in children with DLBCL, whereas rearrangement of the MYC oncogene is more common in pediatric compared to adult DLBCL (29,30).

ALCL consists of lymphoid cells that are usually large with abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei. The cells are CD30, and the majority of pediatric cases are also positive for the anaplastic lymphoma kinase (ALK) protein and have the chromosomal translocation t(2;5)(p23;q35) involving the nucleophosmin (NPM) and ALK genes (24).

PROGNOSTIC FACTORS

The most prominent prognostic determinant in childhood NHL is the clinical stage. Tumor burden, as measured in part by serum LDH, has been predictive of outcome in some series, especially for Burkitt lymphoma (6,23,31,32). In general, patients with localized Murphy stage I and II lymphomas have a better prognosis than those with more extensive stage III and IV. However, stratified therapy has resulted in excellent outcomes for both low- and high-stage disease. Site of involvement has also been prognostic. For example, presentation of PMBLs has been recognized as having significantly higher risk for relapse than other DLBCLs (23,55). In the past, bone marrow involvement was associated with a poor prognosis, but with intensive chemotherapy it is no longer an adverse prognostic factor (23,31,32). Before the use of preventive CNS therapy, CNS relapse developed in 30–40% of children with stage III and IV Burkitt and lymphoblastic lymphomas. CNS relapses were also noted, albeit in a much lower percentage, in children who had head and neck primary sites of other NHLs (6,33,34). Overt CNS involvement at diagnosis is rare and is associated with a poorer prognosis. In this situation, cranial irradiation plus intrathecal (IT) chemotherapy is necessary for children with lymphoblastic but not Burkitt lymphomas (32,35).

SELECTION OF THERAPY

Chemotherapy

Because of the high likelihood of disseminated disease at presentation, all children with the high-grade subtypes of NHL, regardless of stage, receive systemic, combination chemotherapy. The four major histologic subtypes of childhood NHL respond to a wide range of drugs including steroids, anthracyclines, vinca alkaloids, topoisomerase 2 inhibitors, and alkylating agents, but different combinations and schedules are optimal for particular histologies. Tables 8.4 and 8.5 list some of the commonly used regimens and treatment outcomes.

For limited stage lymphoblastic lymphoma, treatment with the use of ALL therapy is effective, with approximately 85–90% disease-free survival (26,35). The use of more intensive ALL chemotherapy regimens has also resulted in excellent outcomes for most children with advanced-stage disease (disease-free survival of 80–85%) (7,35,34). Similar to the case with ALL patients, there is evidence that poor initial response to treatment, most notably steroids, appears to confer a worse prognosis with event-free survival (EFS) only in the 50% range (35). The least toxic and most effective method of CNS prophylaxis for these patients remains unclear. Both cranial irradiation and IT methotrexate have been very effective but are associated with neurocognitive late effects. Data from recent studies indicate that intensive IT methotrexate with or without systemic high-dose methotrexate is adequate therapy to prevent CNS relapse (34,50).

For the purposes of treatment, high-grade mature B-cell lymphomas have been treated similarly. Burkitt lymphoma, in contrast to DLBCL, is much more likely to involve the bone marrow and CNS and much more likely to be complicated with a tumor lysis syndrome.

Although histologically and clinically distinct, both Burkitt lymphoma and DLBCL respond well to treatments as outlined below. For low-stage Burkitt lymphoma as well as DLBCL, short-duration therapy with cyclophosphamide, doxorubicin, vincristine (Oncovin), and prednisone (CHOP) or cyclophosphamide, vincristine (Oncovin), prednisolone and doxorubicin (Adriamycin) (COPAD) results in excellent relapse-free survivals of 90–98% and 85–90% (5,31,35–38), respectively. For higher stage and higher risk groups, the lymphoma malignant B type (LMB)-96 protocol, a multiagent intensive chemotherapy regimen for B-cell lymphoma, has resulted in greater than 90% 4-year EFS. LMB-96 includes 3–5 months of intensive cycles of cyclophosphamide, vincristine, prednisone, high-dose methotrexate, doxorubicin, cytosine arabinoside (AraC), and etoposide (23,32).

Table 8.4

Low-Stage/Low-Risk Patients

WHO Classification	Regimen	EFS (%)	References
Lymphoblastic lymphoma, T and B	BFM-95; BFM- like	85–90	35
Burkitt	CHOP or COPAD (LMB96)	90–98	5,33
Diffuse large B cell	CHOP or COPAD (LMB96)	90–98	5,33,36
Anaplastic large cell	CHOP	85–90	5,36

Table 8.5
Advanced-Stage/High-Risk Patients

WHO Classification	Regimen	EFS (%)	References
Lymphoblastic lymphoma, T and B	BFM-95 50 ^a	75–80	35
Burkitt	LMB96	80–95	23,32
Diffuse large B cell	LMB96	80–95	23,32
Primary mediastinal large B cell	LMB96	60–70	38,55
Anaplastic large cell	APO APO ALCL 99	70	39,41

^aPatients deemed high risk by poor prednisone response (Ref. 35).

As noted previously, within the high-grade mature B-cell lymphoma group, PMBL stands out clinically, with significantly inferior EFS, in the less than 70% range, using LMB therapy. With the adriamycin, prednisone, vincristine (oncovin), 6-mercaptopurine, and methotrexate (APO) protocol, which does not include an alkylating agent but features intensive doxorubicin, durable EFS of approximately 70% has also been seen (39). This regimen has never been directly compared to an LMB approach. Developing new treatment strategies for this small subset of patients will be a focus of future interest.

Rare low-grade mature B-cell lymphomas, pediatric follicular lymphoma, pediatric marginal zone lymphoma, and MALT lymphoma, occur in childhood. For the former two presenting with low-stage disease, many patients have done well with resection and observation only. For ocular MALT lymphoma, treatment has consisted of resection followed by radiation therapy without adjuvant chemotherapy (40). Efforts to collect clinical information and pathologic specimens to further characterize these rare pediatric lymphomas and determine best approaches are in progress.

For early-stage ALCL, CHOP is effective therapy (36). The APO regimen has also been effective for higher stage ALCL in children (disease-free survival 70–75%) (39). Other regimens for ALCL have been modeled after B-cell protocols and report similar results (41).

In recent years, outcomes for pediatric patients with NHL have improved dramatically. Optimal combinations of agents, intensity, and duration of therapy have evolved for disease groups. In the future we anticipate further stratification of treatment regimens and the addition of disease-specific agents, such as rituximab, in mature B-cell lymphomas (42,43) or agents targeting ALK in ALCL. Nelarabine appears to be specifically effective in T-cell lymphoblastic lymphoma, and recent promising data indicate that vinblastine may be particularly effective, even as a single agent, in ALCL (44,45). How best to incorporate these agents into existing regimens will be a focus of future efforts.

Radiotherapeutic Management

The role of radiotherapy in the management of all childhood NHL has decreased as systemic chemotherapeutic regimens have become more effective (5,6,46). As the overall survival improved for children with all stages and subtypes of NHL, studies designed to assess the need for regional radiation ther-

apy followed. This has evolved on a background of significant concerns for late effects of treatment, including neurocognitive effects of low-dose CNS radiation as well as the risk for second malignancy, cardiac and pulmonary toxicity in patients receiving radiation therapy to the mediastinum and neck combined with chemotherapy (47). Reports from the Pediatric Oncology Group (POG) demonstrated successful local and systemic control with chemotherapy alone for children with Murphy stages I and II NHL regardless of histology (5). The addition of localized radiation therapy (e.g., mediastinal RT) to chemotherapy was also not shown to benefit patients with advanced-stage lymphoblastic lymphoma (6). In the past 10 years, several groups have reported that primary lymphoma of bone in children can be treated successfully with chemotherapy alone (48,49).

As previously discussed, prophylactic CNS treatment is needed in the majority of children with NHL, thereby reducing the otherwise high risk of CNS relapse (33). The approach for all nonlymphoblastic histologies includes systemic and IT chemotherapy. It has become evident that there is no benefit to adding radiation therapy for CNS prophylaxis in Burkitt lymphoma (33,50). The current CNS preventive regimens for advanced-stage lymphoblastic lymphoma include either cranial irradiation and IT chemotherapy or IT chemotherapy and systemic chemotherapy only. The Berlin–Frankfurt–Munster (BFM) group safely reduced the dosage of cranial radiation therapy to 12 Gy for lymphoblastic lymphoma and eliminated it entirely from BFM-95 without increasing the CNS relapse rate (34). Cranial irradiation (12–18 Gy) is still warranted for the rare patient with lymphoblastic lymphoma with initial CNS disease or a CNS relapse. Patients with cranial nerve palsies at diagnosis, independent of cerebrospinal fluid findings, are treated in a similar fashion as children with initial CNS lymphoma.

The current indications for radiation therapy to involved sites of disease outside the CNS in pediatric NHL have become somewhat limited. Involved-field radiation is considered for patients who do not attain a complete remission after induction chemotherapy. This situation is relatively rare, but more common in PMBL. Given the increased rate of local failure compared to other pediatric NHLs, the role of involved-field radiation remains a topic of some debate.

As noted previously, rarely, low-grade mature B-cell lymphoma, such as pediatric follicular lymphoma, pediatric marginal zone lymphoma, and ocular MALT lymphoma, occur.

Limited data are available as to best therapy for these patients. Historically, ocular MALT in pediatrics has been approached as adult cases, with low-dose superficial radiation therapy (40). No role for radiation therapy in low-stage pediatric follicular lymphoma or pediatric marginal zone lymphoma has been established.

Involved-field radiation may also be considered for palliation of pain or mass effect, and consolidation to regions of local disease before or after bone marrow transplantation in patients with recurrent disease. Care should be taken to use modest fractionation schedules and to avoid exceeding normal tissue tolerance dosages because patients may be eligible for subsequent bone marrow transplantation necessitating total body irradiation (TBI) as a component of the preparative regimen.

Children with refractory or relapsed NHL can experience prolonged disease-free survival after treatment with high-dose chemotherapy or high-dose chemoradiotherapy followed by autologous or allogeneic bone marrow transplant (51–54). When TBI is a component of the preparatory regimen, fractionated courses to total dosages of 12–14 Gy are common (see Chapter 2). Disease recurrence rather than the morbidity of transplant is the predominant cause of failure in this setting. The strategy of irradiating the local sites of initial disease recurrence before or after transplant, whether or not TBI is used, should be considered (19,51). Dosages to these sites (usually at least 20 Gy) are constrained by normal tissue tolerances.

Historically, emergency radiation therapy for superior vena cava syndrome, acute airway compromise, or spinal cord compression has been used to provide rapid symptom relief. The response is particularly dramatic with lymphoblastic lymphoma and symptoms are usually improved within 48 hours of treatment. Usually 1.5–2 Gy per fraction for a total dosage of 6–7.5 Gy is adequate to relieve symptoms. Hyperfractionated regimens (1.2–1.5 Gy per fraction twice a day for a total dosage of 6–10 Gy) can also be used. Systemic steroids, particularly in the case of mediastinal mass, are more commonly used and generally are equally effective. On rare occasions emergency radiation therapy or treatment with steroids is appropriate in the absence of a histologic diagnosis. Despite the rapid response with either, this can be done without significantly compromising tissue diagnosis if sampling can occur within 48 hours of treatment (16).

RESULTS OF THERAPY

Before 1975, when therapy was directed to the identifiable gross tumor, few children survived. The small number of patients who did survive had favorable presentations, including limited resectable abdominal disease or involvement of a single nodal region or extranodal site. With current intensive multiagent regimens, survival is generally excellent for all patients, including

those with disseminated disease and adverse prognostic factors such as bone marrow involvement, CNS involvement, and high serum LDH. Most relapses occur within 12 months of diagnosis for Burkitt lymphomas and within the first 2–4 years for the other histologic subtypes. Late relapse has been reported with ALCL and B-lymphoblastic lymphoma.

Children with stage I to II disease have 2-year disease-free survival rates of 85–98% (5,6,31,35–37). Children with stage III disease have an 85–90% 2-year disease-free survival. Those with stage IV disease and marrow involvement have an 85–90% disease-free survival, and those with CNS disease (Burkitt lymphoma) have an 80% EFS. Patients with PMBL have had significantly worse EFS at 60–70% (38,55).

Patients undergoing transplantation early in their disease course (i.e., after first relapse or second complete remission) have 2-year disease-free survival approaching 50%, whereas those with refractory disease fare less well (5–20%) (51,53).

With improvements in survival in many groups of patients, recent efforts have focused on maintaining excellent EFS with reduced late toxicity. Incorporating more specific targeted therapies for patients with less favorable subgroups, notably PMBL, may be helpful as a focus of future development.

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Ewing Sarcoma

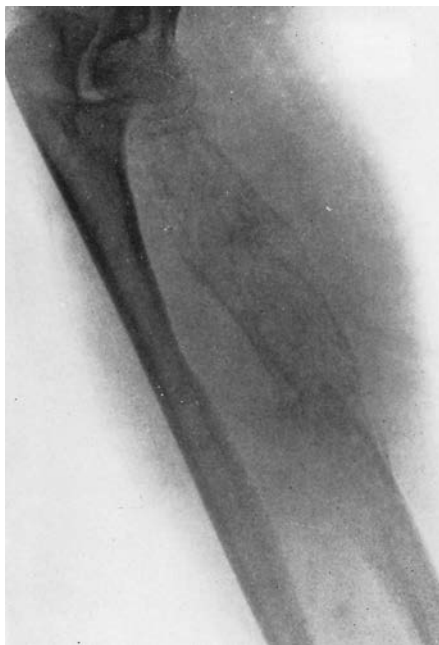
Karen J. Marcus, Torunn Yock, and Nancy J. Tarbell

James Ewing (1866–1943) first described the bone tumor that bears his name in 1921 (1). He observed that the malignancy was most common in teenagers, occurred in the metaphyseal and diaphyseal region of long bones or in the flat bones, was associated with pain and often fever, had a histologic appearance of highly vascular sheets of small round cells, and was quite sensitive to radiation (Fig. 9.1) (2).

Ewing was a leading authority on cancer. He became professor and chair of pathology at Cornell Medical School in New York City and went on to serve as director of the Memorial Hospital, playing a crucial role in the growth of

what is now known as the Memorial Sloan–Kettering Cancer Center (2).

Ewing sarcoma is the second most common childhood primary bone tumor. The tumor is slightly less common than osteosarcoma and represents 3% of pediatric cancers. Approximately 200 cases occur annually in the United States. Although it presents in the pubertal age range in 40% of patients, the age at diagnosis is more variable than that of osteosarcoma: 30% of cases occur in children younger than 10 years and 5% occur in young adults older than 20 years. Boys are affected more often than girls, at a ratio of 1.5–2:1. Age at



A



B

Figure 9.1 **A:** In the fourth edition of his textbook *Neoplastic Diseases: A Textbook on Tumors* (1940), James Ewing of the Memorial Hospital, New York, described a “diffuse endothelioma of radius, diffuse absorption without destruction of shaft, spontaneous fracture, wide invasion of muscle, duration 1 year.” Ewing wrote that “the first indication is for treatment by radiation in full doses, and over considerable periods. This recommendation is based on the reported cure of certain cases ... by radiation alone, and on the clinical disappearance of the disease by variable periods in many more cases. The response to radiation also confirms the diagnosis. The danger of metastases occurring while this treatment is in progress is probably negligible, since the tumor tissue generally undergoes rapid liquefaction and necrosis.” **B:** Ewing illustrated the excellent response of the tumor to radiotherapy.

diagnosis parallels the earlier onset of puberty in girls, with a median time of onset 3 to 4 years younger than in boys. Ewing sarcoma is rare in children of Asian or African descent (3).

PATHOLOGY

Ewing sarcoma consists of monomorphic sheets of small, round malignant cells with hyperchromatic nuclei and little cytoplasm. There is a dearth of associated stroma. Cells usually are periodic acid–Schiff (PAS) positive, indicating the presence of glycogen granules. Glycogen in the tumor cells and the demonstration of the *MIC2* gene product on the tumor cell membrane help identify Ewing sarcoma (4,5). The tumor cells are also uniformly vimentin positive and often cytokeratin positive, indicating origin from epithelial and neuronal elements (6).

Sarcomas are subdivided into two classes; first class is composed of tumors displaying complex karyotypic abnormalities with no distinct pattern, and the second class includes tumors associated with particular chromosomal translocations that result in specific fusion genes. The Ewing sarcoma family is in the second class of sarcomas. Ewing sarcoma and primitive neuroectodermal tumor (PNET) have been linked to the specific chromosomal abnormalities involving a reciprocal translocation between chromosomes 11 and 22: t(11;22) (q24;q12). This genetic rearrangement is detectable in 86% to 90% of tumors. Approximately 5% to 10% of Ewing sarcomas do not contain t(11;22) but instead have a translocation between chromosomes 21 and 22: t(21;22) (q21;q12). However, this alternate rearrangement has molecular consequences similar to those of t(11;22) (7).

The 11;22 translocation juxtaposes the *EWS* gene with the *FLI* gene, a member of the *ETS* transcription factor family. The 21;22 translocation juxtaposes the *EWS* gene to another *ETS* family member, *ERG*. There are structural similarities between these two translocations, suggesting that they bind to similar DNA target sites. The *EWS–FLI* fusion was the first sarcoma gene to be cloned (8). *EWS–FLI* can produce malignant transformation of some but not all cell lines. The *EWS/FLI* gene appears to act as a transcription factor. Its mechanism of action appears to be a modulation of transcription of target genes. Ewing sarcoma and PNET translocation seems to fall in a developing class of tumor-associated chromosomal translocations that form chimeric transcription factors (7). The formation of aberrant transcription factors is associated with many human malignancies. We may conclude that the probable mechanism of carcinogenesis in Ewing sarcoma is a translocation that produces an aberrant transcription factor. These factors can cause deregulation of pathways, resulting in tumorigenesis. Using retroviral systems to biologically screen cDNA from cells transformed by *EWS/FLI*, platelet-derived growth factor-C (PDGF-C) has been identified as the target of *EWS/ETS* transcriptional deregulation (9). Therefore, Ewing sarcoma cytogenetics may help us to understand oncogenic mechanisms.

The *EWS* gene is a member of the *ETS* family of transcription factors defined by the *ETS* domain. The *FLI* gene appears to be involved in early hematopoietic, vascular, and perhaps neuroectodermal development (10). Evidence suggests that *EWS–FLI* fusion protein is the key oncogenic lesion in Ewing sarcoma. *EWS–FLI* acts as the dominant oncogene (11). The transcription factor resulting from the translocation replaces the *EWS* RNA-binding domain by the *FLI–ETS* domain with the resulting aberrant transcriptional

effects. A number of genes have been identified as direct or indirect regulatory targets of the aberrant protein produced by the *EWS–FLI* translocation (9,12). A major hurdle in the attempts to generate model systems of the Ewing family of tumors is the toxicity of the fusion gene. The identity of the cells from which Ewing tumors originate has remained elusive. The observation of the t(11;22) translocation leading to the *EWS–FLI* expression suggests the existence of a primary cell transformed by *EWS–FLI*. Evidence from a genetically defined *EWS–FLI* model system suggests a mesenchymal origin of these tumors (13). Recent publications have shown that the t(11;22) breakpoint location and therefore the exact amino acid composition of the resultant *EWS–FLI* fusion oncoproteins might have prognostic relevance (14–16). Therefore, the importance of the availability of specimens for genetic analysis cannot be overemphasized (16).

CLINICAL PRESENTATION

Pain is the most common presenting symptom, noted in approximately 90% of cases. Local swelling or mass effect related to the bone tumor is apparent in a majority of children. A distinct soft tissue mass can be appreciated clinically in one third of cases. Significant limitation of movement has been described in 25% of presentations. Neurologic symptoms or signs occur in 15% of children, either as spinal cord compression or peripheral nerve compression. The latter is most often apparent with lesions of the pelvis or about the knee. Fever is present in 10% of cases and has been related to tumor size and metastatic disease at diagnosis.

The diagnostic evaluation of the patient with Ewing sarcoma is shown in Table 9.1. Laboratory findings may include high leukocyte count, a nonspecific finding indicative of tumor bulk or extensive disease. A high leukocyte count has been related to increased risk of tumor recurrence (16,17). Pretreatment serum lactate dehydrogenase (LDH) is of prognostic significance, and the degree of LDH elevation has been related to tumor volume (17). Positron emission tomography using fluorine-18 fluorodeoxyglucose is being studied for detection of osseous metastases in bone tumors and appears to be a sensitive and specific modality in Ewing sarcoma and PNET.

Table 9.1

Clinical Evaluation of the Patient with Ewing Sarcoma

Pathology tests
Biopsy with routine histology
Electron microscopy
Immunohistochemistry
Cytogenetics
Radiographic tests
Computed tomography and magnetic resonance imaging of the local tumor extent
Chest computed tomography
Bone scan
PET scan
Bone marrow aspirate and biopsy
Laboratory tests
Routine chemistries, including lactate dehydrogenase

PET, positron emission tomography.

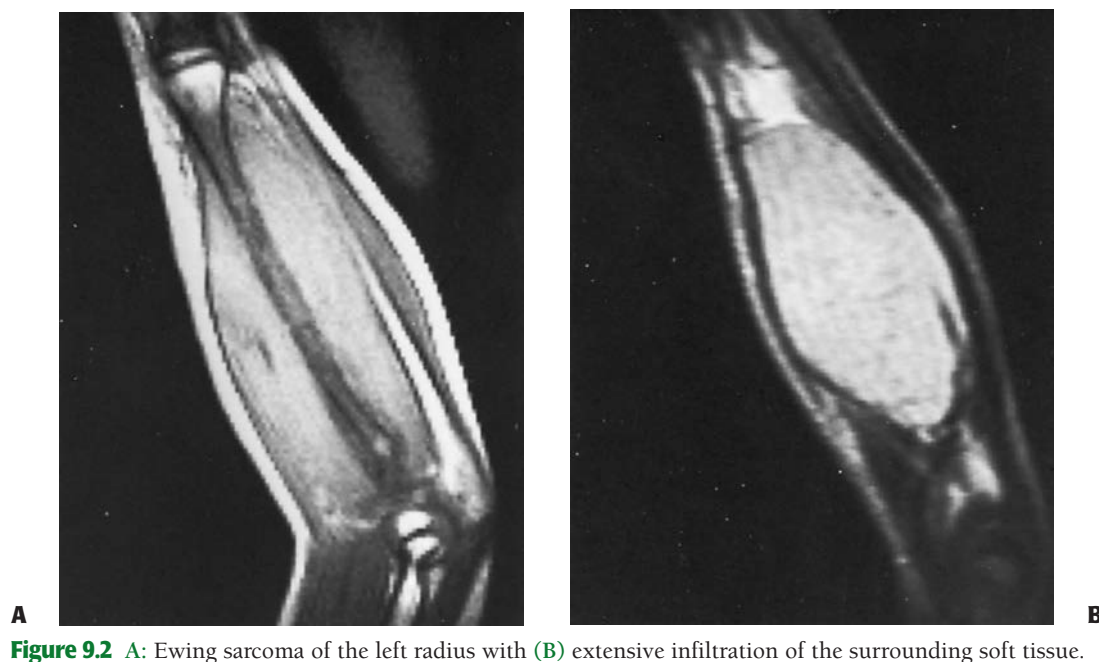


Figure 9.2 A: Ewing sarcoma of the left radius with (B) extensive infiltration of the surrounding soft tissue.

The diagnostic features of Ewing sarcoma are radiographically defined as a permeative, destructive lesion of bone. In long bones, the tumor most often presents along the metaphyseal region or within the diaphysis (i.e., at the mid-shaft level). The periosteum often is displaced by the underlying tumor, resulting in the clinical sign of Codman triangle, representing a bone expansile lesion. Although bone expansion is common, new bone formation beyond the periosteal margin is rare. An associated soft tissue mass is typical, occurring in more than 50% of long bone neoplasms (18,19). Both computed tomography (CT) and magnetic resonance imaging (MRI) appear necessary for most sites and are comple-

mentary. Using both studies has added substantially to the determination of disease extent, identifying extraosseous involvement and the degree of marrow infiltration linearly (Fig. 9.2). CT has been valuable in outlining the bone and soft tissue extent of central Ewing sarcoma. Better definition of tumor extent by CT scans is credited with improvement in control of pelvic Ewing sarcoma (20). MRI has added to this definition of tumor (Fig. 9.3) (21). Radionuclide bone scan may also be of value, although it may exaggerate the linear tumor extent. MRI may show edema. Whether direct microscopic extension of tumor is associated with the edema is unknown at present.

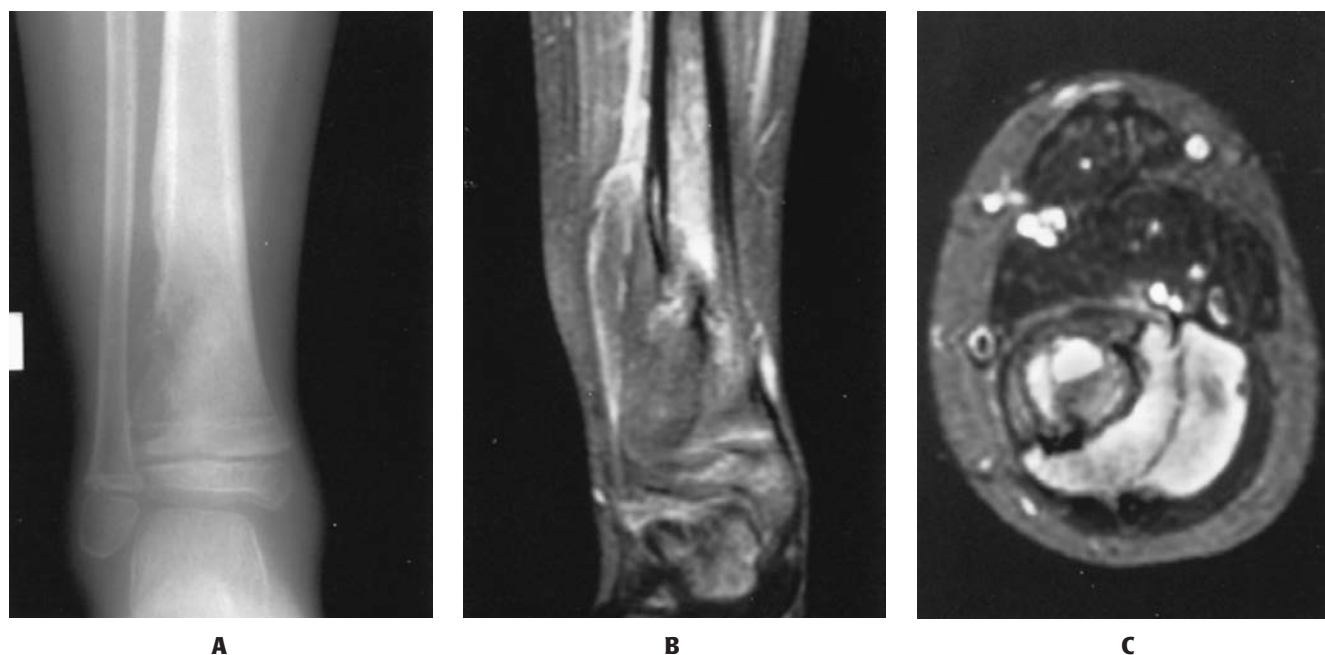


Figure 9.3 A: Ewing sarcoma of the tibia seen on a plain radiograph shows cortical disruption, “onion skinning,” and a suggestion of soft tissue involvement. B,C: Coronal and axial magnetic resonance imaging show extensive soft tissue infiltration.

Table 9.2
Prognostic Factors in Ewing Sarcoma

Negative
Metastases at diagnosis
Large tumor volume (>200 mL)
Pelvic/central location of primary
Age over 17 years
Positive
Good response to chemotherapy

Approximately 53% of Ewing sarcomas have a primary site in an extremity, and 47% have central primaries. Ewing sarcoma presents in the proximal extremities in 20% to 30% and distal extremities in 30% to 40% of cases (22–24). Metastases are present at diagnosis in approximately 20% to 25% of patients.

Primary lesions of the rib are associated with direct pleural extension and significant extraosseous soft tissue mass in a majority of cases (25,26). The original description of thoracopulmonary malignant tumors by Askin et al. in 1979 characterized small round cell tumors in this location as a separate clinicopathologic entity, often called Askin tumor (27). He described a female predominance and a short median survival (8 months). These tumors tend to have a large soft tissue component that can displace most of one lung with or without much rib involvement. This patient group has special management issues (28,29).

The frequency of overt metastasis is estimated at 25% to 30% for pelvic primaries and less than 10% for tumors of the extremities or ribs. The sites of metastatic disease at diagnosis parallel the distribution noted with treatment failure, most often involving the lungs (40%) or bones (40%), with less common disease involving the bone marrow, lymph nodes, soft tissue, visceral sites, or, rarely, the central nervous system (30). No formal staging system has been recognized for Ewing sarcoma. The disease factors most recognized as prognostically significant include the bone of origin or primary site, older age, tumor size, presence or degree of soft tissue extension, and identification of hematogenous metastasis at diagnosis (Table 9.2). Smaller tumors (less than 200 mL in volume) and distal extremity tumors tend to be favorable (24,31). At present, the most important prognostic factor at diagnosis appears to be the presence of metastasis (32,33). Reports suggest that the response to initial chemotherapy is significant as well (34). The prognostic importance of the *EWS-FLII* fusion in Ewing sarcoma warrants additional study (14,15).

SELECTION OF TREATMENT

Local Control

The relative roles of surgery and radiation therapy for local treatment of Ewing sarcoma have long been debated. In 1953, Wang and Schulz (35) reported 5-year survival in 6 of 36 children treated with wide-field irradiation, as compared to 1 of the 14 treated by primary surgical resection. Using 50 Gy to the entire bone, Phillips and Sheline documented survival in 5 of 21 cases in 1969 (36). After these reports, Ewing sarcoma was generally treated with radiation therapy except for small tumors in expendable bones. Reviews have indicated an overall rate of local tumor control of 75% to almost 95% after primary radiation therapy (3,22,37–41).

Historically, the use of radiation therapy has been the local treatment of choice. However, the role of surgery has increased because of several developments. These important developments include the recognition that the local failure rate of radiotherapy for Ewing sarcoma ranges from 9% to 25%. In addition, the development of innovative surgical techniques allowing preservation of limb and structural bone function has promoted surgery as an alternative to radiation. The routine use of cytoreductive chemotherapy, as discussed later in this chapter, often produces a significant decrease in the soft tissue component, rendering tumors more readily resectable. In addition, the concern over second malignancies from radiation therapy has prompted the reevaluation of the role of surgery as well (42).

However, the data concerning local control with radiation therapy alone are difficult to interpret. Difficulties in assessing response to radiation therapy are evident in the slow rate of resolution of CT, MRI, and radionuclide bone scan findings after irradiation. The significance of residual soft tissue abnormalities and persistent areas of increased uptake on technetium scans is uncertain (22,23,34,43). In patients who have hematologic metastasis, the implication of residual recurrent tumor at the primary site confirmed by biopsy or autopsy is uncertain because of the possibility of reseeding from the primary tumor (20,44).

Several other fundamental factors make it difficult to interpret the data comparing surgery and radiotherapy for local treatment. The local recurrence rate after radiation is strongly correlated with the primary tumor site. Local failure of extremity lesions is on the order of 5% to 10%, compared with a local failure rate for pelvic lesions of 15% to 70%. Local recurrence after radiation therapy of pelvic lesions is expected to improve with improved tumor imaging and the widespread use of computerized radiotherapy treatment planning. Therefore, old data may be of more limited use in contemporary management. It should be noted that tumor size affects local control. Local control for tumors more than 8 cm in diameter is on the order of 80%, compared with 90% for those less than 8 cm in diameter. The fact that larger tumors are more likely to be treated with radiation instead of surgery influences the clinical results of these modalities.

Some patients are treated with a combination of surgery and radiation therapy. Several factors make it difficult to interpret this data. These include the important effect of quality of radiotherapy on local control. In many “surgical” series, the comparison is not surgery with radiotherapy but rather radiotherapy compared with radiotherapy and surgery. This is analogous to the treatment of many other solid tumors with radiation therapy with resection.

Many surgical series include patients who are at lower risk. They include people who have undergone ray resection of the hands and feet, removal of the wing of the ileum, lower sacrum (lower than the S3 bone), ribs, clavicle, or body of the scapula. One must also consider the relative functional deficits that will be experienced during high-dose irradiation, surgery alone, and surgery with irradiation. In this context, when selecting local treatment for childhood Ewing sarcoma one must consider the rehabilitation capacity and the psychological adjustment of the patient with these local treatments (25,45,46).

Fundamentally, when attempting to compare surgery with radiation therapy in the management of Ewing sarcoma, there is the problem of case selection. Studies are not strictly comparable, so surgery and radiation can be seen not as competitive

but as complementary. However one additional matter must be considered in comparing radiation therapy with surgery: the risk of second malignant neoplasms. As we will describe later in this chapter, radiation and alkylating agents combine to increase the risk of second malignant neoplasms after the treatment of Ewing sarcoma. Studies indicate that the relative risk of sarcomas in the treatment field is related to the radiotherapy dosage and the extent of exposure to alkylating agents.

The relative functional deficits that will be experienced during high-dose irradiation, surgery alone, and surgery with irradiation must also be considered. In this context, when one is selecting local treatment for childhood Ewing sarcoma, the patient's rehabilitation capacity and psychological adjustment should be considered (4,40,47).

Surgery

The role of surgical resection in combined-modality treatment was addressed by the Memorial Sloan-Kettering Cancer Center (23,48). With overall disease-free survival approaching 80% at 3.5 years, Rosen et al. (49) described local treatment failure in 34 (21%) patients after radiation therapy and aggressive multiagent chemotherapy, compared with 0 of 33 patients who underwent surgical resection in addition to chemotherapy. In an influential review of the Mayo Clinic experience with Ewing sarcoma, Wilkins et al. (50) related a significant impact of surgical resection on overall survival: 74% at 5 years, compared with 27% in patients treated without surgery. Other reports have also described improvement in local control with the addition of surgery (22,25,40,45,51–53). However, the studies reflected *selected* surgical intervention. For example, in a review by Wilkins et al. (50) of 27 children with microscopically complete resection in a total series of 65 cases, the analysis included 11 patients treated with radiotherapy and no adjuvant chemotherapy. These 11 patients were included in the analysis of the “nonoperated group” and were compared with the patients receiving surgery plus chemotherapy, clearly biasing the results to favor the surgical group. In a more balanced comparison, Brown et al. (22) described improvement in local control with surgery in extremity lesions. There were local recurrences in 0 of 5 resected cases, compared with 3 of 15 patients treated with primary radiation therapy. Brown et al.'s analysis pointed out the selected use of surgery in 35 of 67 patients, clearly selecting cases with distal and smaller lesions for surgery.

Treatment results after surgical resection when combined with chemotherapy have been excellent, even considering the selection factors inherent in surgical subsets. In cases with complete or good partial response to preoperative chemotherapy, Hayes et al. (54) described disease-free survival in 11 of 11 cases with negative operative margins and no added irradiation. Most other series addressing the impact of surgery have incorporated postoperative radiation therapy, often at reduced dosage levels (25,45,47,49,50,53,55). The addition of surgery for “dispensable bones” (e.g., fibula, rib, smaller lesions of the hands or feet) often is considered a significant addition to therapy with little attendant functional deficit, although excellent results have also been reported with irradiation (44). Options for surgical management have also been considered primarily in the very young population, in whom radiation late effects would be more significant (55–58).

Appropriate comparison of surgical results for Ewing sarcoma entails attention to the adequacy of radiation therapy in

the control arm (23,43). The German Cooperative Ewing's Sarcoma Study (CESS) reported a significant difference in local control and survival favoring the cases operated on in the CESS-81 trial (20,40,55). On review, the high rate of local failure in the radiation therapy group was attributed to a substantial number of cases with inadequate irradiation volume. In fact, a report by Sauer et al. (55), on the same cohort, showed equivalent results of surgery or radiation therapy in small lesions. In addition, the CESS initiated a quality assurance program in 1984. The results of the subsequent study (CESS-86) demonstrate a marked improvement in local control with irradiation compared to the previous trial. From 1986 to 1991, 177 patients with localized Ewing sarcoma were treated with chemotherapy plus radical surgery or surgery plus radiation (45 Gy) or irradiation alone (60 Gy total), with a central treatment planning review for quality assurance. Results are now comparable to those of the surgery group (3-year relapse-free survival 67% after irradiation, 65% after surgery, and 62% after resection plus irradiation) (37,41,43,51,59,60). If the functional results are similar, the potential for second malignancies in patients treated with irradiation for Ewing sarcoma would favor surgery as the treatment of choice for small extremity lesions, dispensable bones, or very young children. High-risk lesions may benefit from combined surgery and radiation (37,61).

Chemotherapy

Early studies established the role of chemotherapy in primary management of Ewing sarcoma (17,50,62). Multiagent regimens incorporating vincristine, actinomycin D, cyclophosphamide, and Adriamycin (VACA) resulted in overall survival rates of 50% to 75% for patients without metastasis at diagnosis (17,22,39,54,63). The Intergroup Ewing's Sarcoma Study (IESS) I (1973–1978) demonstrated the importance of combining alkylating agents and anthracyclines. The IESS-II (1978–1982) showed that early and intensive chemotherapy combined with local treatment of the primary tumor was beneficial (17,38,64,65).

The 5-year relapse-free survival and overall survival improved from IESS-I to IESS-II. The local control rate improved as well, with a local failure rate of 15% on IESS-I and 9% on IESS-II.

CESS-81 was conducted from 1981 to 1985 (40,59,66,67). Patients received VACA for two cycles followed by local therapy and two additional cycles of the four-drug chemotherapy program. The result of this study of local therapy, which was not randomized, showed a 5-year relapse-free survival of 54% for the patients treated with surgery only, 68% for those treated with surgery and postoperative irradiation, and 43% for those treated with radiotherapy alone. The local failure rate was strikingly different: 6% for surgery alone, 17% for surgery and postoperative irradiation, and 50% for radiotherapy alone. The high local failure rate in the radiotherapy-alone arm was clearly secondary to major radiotherapy volume deviations. Midway through the trial, central review of radiotherapy was instituted resulting in a decline in local failure.

The response of the primary tumor to chemotherapy as an important prognostic factor has been demonstrated in patients undergoing surgery after initial chemotherapy (68). Picci et al. (58) studied 118 patients between 1983 and 1993 and graded the surgical specimens from grade I to III, with

grade I having gross visible tumor, grade II microscopic tumor, and grade III specimens with total necrosis. The 5-year disease-free survival ranged from 34% for grade I to 95% in the grade III group (58). Others have confirmed that tumor necrosis after induction chemotherapy carries a favorable prognosis (32,68).

The proportion of patients with distant metastasis is another measure of chemotherapeutic responsiveness. Marcus et al. (21) analyzed the impact of tumor size on survival; the dominant pattern of failure for large tumors remained distant metastasis despite aggressive chemotherapy. Jurgens et al. (40) described distant metastasis in 29% of the CESS-81 cases; isolated distant metastasis occurred in 10%. The updated results of IECS-II demonstrated a 63% survival at 5 years, with 25% of patients developing distant metastases only (65).

The substitution of ifosfamide for cyclophosphamide was tested in the CESS-86, which included 177 patients from 1986 to 1991 (20,40,59,66,67,69,70). Patients whose primary tumors were judged to be smaller than 100 cm³ received induction VACA. Those with larger tumors received vincristine, actinomycin, ifosfamide, and adriamycin (VAIA). Local therapy, at the discretion of the treating physician, was given at week 10. This was followed by four courses of VACA for the smaller tumors and four courses of VAIA for the larger tumors. When a curative resection was conducted, no additional radiation was given if there were no significant risk factors for local recurrence, such as positive margins. However, if the operative bed was at risk for local persistence of tumor, patients were randomized to once or twice per day postoperative irradiation. For patients in whom a curative resection was possible but there was only small residual disease after induction chemotherapy, surgery was not performed and patients were randomized to once- or twice-a-day radiation. When a tumor resection was not undertaken and there was substantial tumor, patients were randomized to receive either 45 Gy of conventional irradiation once per day to a larger field with a 15-Gy cone-down boost to a total of 60 Gy or 44.8 Gy of twice-daily radiation to a larger field followed by a 16-Gy boost with twice-daily irradiation.

In CESS-86, 22% of the patients were treated locally with surgery, 53% with surgery and radiation, and 25% with radiation alone. Although the patients treated with surgery alone had a low rate of local failure, they had a higher rate of distant metastases. Local treatment did not influence survival. In addition, there appeared to be no difference between once- and twice-daily irradiation. Tumor volume greater than 200 mL and poor histologic response to chemotherapy had a negative effect on outcome by both univariate and multivariate analysis (69).

The impact of local therapy modality for the 1,058 patients enrolled in the CESS and the European Intergroup Cooperative Ewing's Sarcoma Study (EICESS) trials was reported. After induction chemotherapy patients with resectable tumors had excellent local control, with a local relapse rate of 7.5%. Comparable local control was achieved in patients given preoperative radiotherapy in the EICESS-92 trial to patients for whom there was a high likelihood of close resection margins or in whom further tumor reduction was expected to allow function-preserving surgery. For patients treated with definitive radiotherapy, local relapse was 26%, significantly higher than for those able to undergo resection; however, this cohort represented a negatively selected group of patients with unfavorable tumor sites.

The synergistic effectiveness of etoposide in combination with alkylators was studied in the Children's Cancer Group (CCG) Study 7881 and Pediatric Oncology Group (POG) Study 8850 (70). This trial evaluated the use of VACA with and without ifosfamide and etoposide to treat newly diagnosed Ewing sarcoma or PNETs. This phase III randomized trial was open from 1983 to 1994. Patients were randomly assigned to receive 49 weeks of standard chemotherapy with VACA or the experimental treatment, which alternated VACA with the ifosfamide-etoposide combination. The trial demonstrated, in terms of both increased survival and overall survival, the superiority of six-drug chemotherapy to four-drug chemotherapy for localized disease (Table 9.3). There was an improvement in local control for patients with localized pelvic Ewing sarcoma who received the ifosfamide-etoposide combination (71). This improvement was irrespective of the local control modality used. However, no benefit was attributable to six-drug chemotherapy for patients with metastatic disease.

Intensification of chemotherapy to improve the outcome of patients with Ewing sarcoma and PNET was tested in two trials. These two sequential prospective randomized trials tested the hypothesis that intensification of chemotherapy can improve the outcome over standard-dose chemotherapy in patients with nonmetastatic tumor. The first such trial was open from 1995 to 1998, and the second from 2001 to 2005. Both

Table 9.3

**National Cancer Institute Protocol INT-0091
(Children's Cancer Group Study 7881 and
Pediatric Oncology Group Study 8850)**

Characteristic	Distribution
Primary site	Pelvic (23%) Femur (18%) Rib (13%) Tibia (10%) Humerus (7%) Others (29%)
Local therapy	Surgery (38%) Radiotherapy (39%) Surgery and radiotherapy (23%)
Five-year event-free survival for patients with local disease	4 drugs (54%) vs. 6 drugs (69%), $p < 0.0005$
Five-year overall survival for patients with local disease	4 drugs (61%) vs. 6 drugs (72%), $p < 0.0007$
Event-free survival for patients with metastatic disease	22%, no difference between the two arms

Biopsy patients were randomized to receive either vincristine, adriamycin, cyclophosphamide, and actinomycin D or these four drugs plus ifosfamide and etoposide. The therapy lasted ~51 weeks. Local therapy was administered at weeks 9 to 15.

Data from Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *N Engl J Med*. 2003;348:694-701.

trials used interval compression as the method of dosage intensification and were limited to patients with newly diagnosed localized disease. The analyses of these studies included event-free and overall survival, toxicity, and the relationship between the intensification achieved and outcome. The first trial failed to show an improvement with dose intensification (72). However, the second trial, which accrued 564 eligible patients randomized to either every-three-week or every-two-week chemotherapy cycles, demonstrated superior event-free and overall-survival for the every-two-week regimen (Richard Womer, personal communication). The differences for both event-free and overall-survival were statistically significant. Local control from these two studies is being analyzed to understand the impact of chemotherapy on local control.

In the management of metastatic disease at presentation, little progress appears to have been made during serial studies. For example, in IESS-I patients with metastatic disease were treated with VACA for a 5-year survival of 30%. In IESS-II drugs were VACA plus 5-fluorouracil, and the 5-year survival was 28%. In the aforementioned CCG-POG trial recently completed, the 2-year survival was 22%.

Radiotherapeutic Management

The role of radiation therapy in primary management of Ewing sarcoma is generally evaluated in each patient with a team including surgeons, medical oncologists, and radiation oncologists. As previously discussed, there is controversy concerning the relative advantages of irradiation and surgery with preoperative or postoperative irradiation (21,43, 51,60,73).

Volume

Local control of tumor with irradiation improved after the general acceptance of a target volume encompassing the entire medullary cavity to moderately high dosage levels (30,74). Suit (75) summarized the experience of the 1950s and 1960s in recommending irradiation to the entire involved bone with a higher-dose boost to the primary tumor site. He noted few instances of marginal or distant intramedullary recurrence with such treatment. However, subsequent studies have reported irradiation results based largely on treatment techniques that have not included the opposite epiphysis, noting no marginal recurrences despite high variable rates of local tumor control (21,51,76).

The importance of adequate treatment volume and radiation quality cannot be overemphasized. The results of the CESS-81 study indicated an excessive rate of local recurrence attributed to poor quality control for radiation therapy. Protocol modification to include central planning for radiation therapy diminished the frequency of local failure (55,76).

Brown et al. (22) analyzed the sites of local recurrence, describing consistent failure in the primary tumor volume for patients with lesions of the extremities and pelvis. Marginal failures occurred infrequently, limited to patients with rib primaries. In a study reducing treatment volume and dosage, Hayes et al. (54) found a high rate of local recurrence (25% isolated, 35% overall). However, treatment failures were localized within the primary target volume in 13 of 14 instances using a limited, postchemotherapy tumor extent to define the soft tissue component of the irradiation fields.

Data addressed the efficacy of diminished treatment volumes (31,77). Local or tailored fields encompassing the primary

tumor with a 3- to 5-cm margin rather than the whole bone have been studied (Fig. 9.4). Marcus (31) reported excellent local control using tailored fields, noting the ability to spare a component of the long bones in tumors less than 8 cm in diameter, whereas full-bone irradiation is often needed to achieve a 4-cm margin around larger tumors. Despite the higher overall rates of local failure in the St. Jude Children's Research Hospital study, Hayes et al. (54) also noted local control in 12 of 14 patients with lesions less than 9 cm in diameter using smaller target volumes.

An important study in the determination of the proper field size for the irradiation of localized Ewing sarcoma was POG-8346. Between 1983 and 1988, 184 children were studied. Of this group, 179 were truly eligible for the study; 79% had localized disease, and 21% had metastases. Induction treatment was cyclophosphamide and adriamycin followed by local treatment with either surgery or radiation therapy. This was followed by actinomycin D and vincristine. Patients treated to the local site with radiation therapy were randomized to receive whole bone irradiation to 39.6 Gy with a 16.2-Gy boost or involved-field irradiation to 55.8 Gy. For the 104 patients with localized disease who were irradiated, the 5-year event-free survival was 42%, with no difference in event-free survival between those randomized to receive large or small fields. The local control rate was only 45% for those not treated according to the protocol-specified volume (78).

The current recommendations for treatment volume mandate the use of MRI whenever possible to identify the tumor extent. The entire bony abnormality and soft tissue mass are included, identified at diagnosis before either surgery or chemotherapy as the gross tumor volume (GTV), with a 1.5- to 2-cm margin added to cover potential occult tumor. An additional margin, generally determined by the institution, is then added. This results in the planning target volume (PTV) to account for daily setup, patient movement, and an additional margin for dosimetric considerations. The exception to this method is the case of a large soft tissue mass that protrudes into a body cavity at diagnosis and is responding to chemotherapy and allowing normal tissues to move back to their normal position. In this circumstance, the initial GTV excludes the prechemotherapy volume if that volume previously extended into the body cavity. The volume of infiltrative soft tissue disease is not modified. The entire original bony abnormality is always treated.

In postoperative irradiation, the appropriate target volume has not been adequately defined. Based on the data supporting local volume for primary radiation therapy, one would recommend treatment to the preoperative tumor bed with adequate margins, later reducing the treatment fields to documented sites of tumor residual in incompletely resected lesions. In all cases with residual tumor in the operative specimen, encompassing the surgical incision appears to be important.

Dosage

Early reports established the efficacy of radiation dosages of 50 to 60 Gy at 180 to 200 cGy per fraction, describing better local control than is achieved with a total dosage of less than 45 Gy (6,79). Dosage recommendations have included 40 to 45 Gy to the entire medullary cavity, with a boost to the primary site to cumulative levels of 55 to 60 Gy (75).

The IESS-I results indicated no dose-response relationship between 40 and 68 Gy (48). Using 50 Gy in 25 fractions,

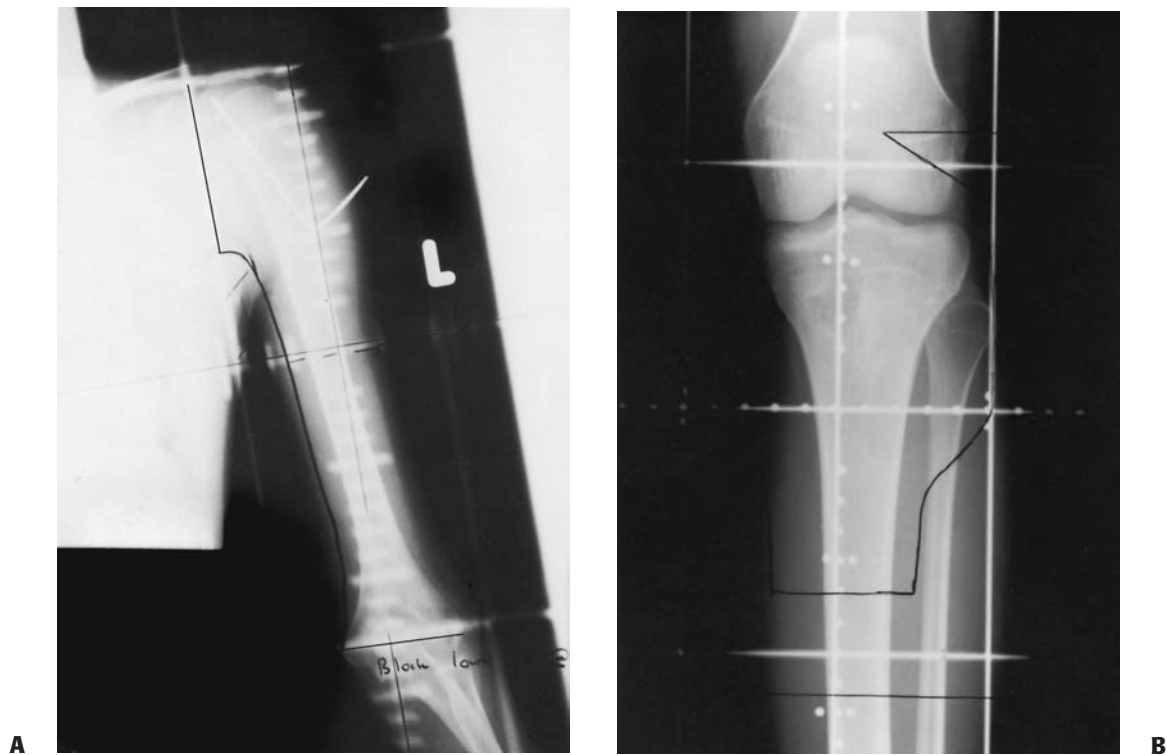


Figure 9.4 Changes in treatment volume for Ewing sarcoma. **A:** Field encompassing the entire length of the medullary cavity for a tumor involving the proximal left humerus. **B:** Tailored field encompassing only the proximal aspect of the leg for a limited tumor of the left tibia; there is a 5-cm distal margin beyond known bone involvement as demonstrated by all imaging procedures. In recent years, national protocols have called for a 2- to 3-cm margin.

the National Cancer Institute reported clinically apparent local recurrence in 20% of cases (39). Whether the lower frequency of local recurrence in the IESS and selected single-institution series using 60 Gy reflects a dose-response relationship is uncertain based on available data (43,48).

Alterations in total dosage and the time-dose relationship were found in University of Florida research using hyperfractionated irradiation (31,80,81). Patients were treated with 120 cGy twice daily to 36 Gy for initial target volumes encompassing the primary tumor in 4-cm margins. Subsequent reduced fields were used to cumulative levels of 50.4 Gy (with total resolution of the soft tissue component by preirradiation chemotherapy) and 55.2 Gy (with no response to chemotherapy). For patients with a lesion less than 8 cm in diameter, local recurrence was documented in only 1 of 11 children (82). In a review of the University of Florida series of patients treated between 1969 and 1987, those with tumors 8 cm or smaller treated with twice-daily irradiation had a local control rate of 88%, compared with 92% for once-daily radiation. However, for those with tumors larger than 8 cm, the local control rate for twice-daily radiation was 88%, compared with 58% for once-daily irradiation. Evaluation of this data must be tempered by the previously cited randomized trial of CESS, which did not show a benefit to multiple-daily-fraction irradiation (40,59). With larger lesions, some have used more aggressive systemic therapy and total body irradiation (TBI; 400 cGy twice daily) with reported improved local and overall disease control (21).

The current dosage recommendations are 55.8 Gy for gross residual disease and 50.4 Gy for microscopic disease.

Lesions of the vertebral body are treated with 45 Gy. Standard, once-per-day fractionation is generally used. No dosage modifications are recommended for smaller tumors, although normal tissues should be protected whenever possible. The shielding of critical structures must also be weighed against the possibility of underdosing known tumor-bearing tissue.

Chemotherapy influences local control. Aforementioned studies suggested a local control benefit from the addition of adriamycin, and more recent reports address the prognostic implications of the histologic response of the primary tumor to chemotherapy. The recent randomized trial CCG-7881 and POG-8850 showed a local control benefit of VACA with ifosfamide and etoposide compared with VACA alone (Table 9.4) (70). It is likely that along with improved imaging (MRI and functional MRI) for tumor identification, improvements in chemotherapy will increase local control of the primary tumor.

Technique

Radiation delivery techniques have dramatically improved over the years. Currently the standard of care around the country is three-dimensional (3D) CT and MRI-aided radiation planning. The improved imaging and its incorporation into the planning process for radiation treatments have allowed increased sparing of normal tissues and better dose localization into the tumor. The imaging studies of CT, MRI, and PET scanning can be used and often registered to the planning CT scan to better delineate the gross target volume and clinical target volumes. Currently, 3D conformal radiotherapy

Table 9.4**Influence of Chemotherapy on Local Control of Ewing Sarcoma in CCG-7881 and POG-8850**

Characteristics	VACA (%)	VACA-IE (%)	P Value
Five-year cumulative incidence of local failure	15	9	<0.01
Systemic failure	21	20	0.92
Local and systemic failure	5	2	0.1
Any local failure	20	11	

IE, ifosfamide and etoposide; VACA, vincristine, actinomycin D, cyclophosphamide, and adriamycin.

Data from Grier HE, Krailo MD, Tarell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *N Engl J Med*. 2003;348:694–701.

(3DCRT) and intensity-modulated radiotherapy (IMRT) are widely available and considered the standard of care for these tumors when they require radiation therapy. However, another major advance with tremendous promise is proton radiation, which will be used more commonly as more facilities open over the next decade.

Sophisticated radiation therapy techniques will achieve maximal local tumor control while minimizing treatment-related complications. For extremity lesions, sparing a strip of linear soft tissue is fundamental. Avoiding circumferential irradiation decreases the likelihood of significant late fibrosis and edema (43,83). To achieve adequate coverage, treatment plans incorporating oblique opposed fields or angled pairs with compensating wedges may be necessary. Conventional opposed anterior-posterior or lateral field configurations may be ideal if adequate soft tissue can be spared. Immobilizing casts or molds are important for daily reproducibility and accuracy during treatment (see Chapter 22).

Large extremity lesions often necessitate irradiation of the adjacent joint. With the same attention to normal tissue sparing, the major late problem associated with joint irradiation appears to be greater growth alterations if both epiphyses of the joint are included, particularly at the knee (41,83).

Lesions of the distal extremities, including the ankle, feet, and hands, present individualized problems regarding treatment planning. The use of tissue compensation, immobilizing devices, and detailed attention to dosimetry are critical to achieving excellent tumor control and functional integrity (23,79). The use of a water bath to achieve dosage homogeneity has been suggested. Alternatively, a single-photon beam incident on the contralateral surface of the hand or foot may be combined with an ipsilateral electron field.

For pelvic lesions, techniques to avoid full-dose irradiation of the bladder often are possible with oblique or multi-field configurations. Carefully including the soft tissue extent, often more impressive on CT or MRI studies, will ensure maximal tumor control. For vertebral Ewing sarcoma, uniform irradiation of the adjacent vertebrae will minimize late effects. The use of weighted opposed anterior-posterior fields or a wedged-pair technique generally ensures adequate coverage of the vertebrae, of necessity including the spinal canal.

Rib lesions (Askin tumor) are generally large tumors, often with extension to the pleural surfaces. This site warrants special consideration because it is often associated with a large soft tissue component (67). The surgeon must not attempt to remove the tumor initially before chemotherapy. After biopsy, chemotherapy should be given for large lesions

because it induces tumor shrinkage (29,84). In thoracic rib and soft tissue primaries, the postchemotherapy volume appears adequate to define the irradiation volume. If resection is done first, margins may be positive and may necessitate a much larger volume of irradiation. The radiation volume often is limited by organ toxicity such as the heart in left-sided lesions. Resection after chemotherapy may be adequate if operative margins are clearly negative after nearly complete response to chemotherapy. If the resection margins are positive or the tumor is incompletely resected, local irradiation is indicated to increase the likelihood of local tumor control (22,26,28,54,84). Inclusion of the pleural cavity in patients with cytologically positive effusions has been recommended because the pattern of failure as described by Askin et al. (27) included the pleura in a significant number of cases. There is also a risk of pleural relapse in patients with Askin tumor and no initial pleural effusion. Some clinicians attempt to treat the pleural surface but spare the lung by using external beam electrons. An alternative technique is intrapleural radioisotope application. A small amount of dye is placed in the pleural cavity with saline and the patient is rotated. Free flow is confirmed by fluoroscopy. As an alternative, a tracer amount of radioactivity may be used to confirm free flow in the pleural space with a gamma camera. After free flow is confirmed, a therapeutic dose of ^{32}P is instilled to irradiate the pleural surface. The patient is turned periodically to distribute the isotope (84). The treatment of the entire pleural surface in the absence of a positive pleural effusion is controversial.

There is a limited experience with brachytherapy for Ewing sarcoma. Potter et al. (85) described six patients treated with chemotherapy, external beam irradiation, and intraoperative high-dose rate brachytherapy for close surgical resection margins. All six children are alive and well.

Improvements in imaging modalities, particularly the routine use of MRI scans to assess tumor extent, provide more accurate target definition. Technologic advances in radiation therapy treatment delivery will also allow greater sparing of normal tissue without compromising tumor treatment. Such technologic advances may include the use of intensity-modulated radiation therapy and the use of protons.

Proton radiation is similar in quality as photon radiation, which means that it causes ionizing events in cells and causes DNA damage that is believed to be the lethal event in tumor cells. However, it has the advantage over photon radiotherapy (IMRT or 3DCRT) in that it better localizes the dose to the tumor with better sparing of the normal surrounding tissues. Dose to nontarget normal tissues is decreased by a factor of

2 or more in many cases. Protons deliver maximum dose at a finite range, in contrast to photons that have infinite range with dose decreasing exponentially with depth. When treating a tumor at some depth in tissue, protons enter the tissue with a decreased entrance dose compared with photons, and then deposit a higher dose in the tumor. Protons have no exit dose beyond the tumor being targeted (86). Photons entail both an entrance dose and an exit dose to normal tissues in the process of targeting a tumor. The result is similar dose distribution to the tumor itself but decreased dose to normal tissue (87,88). This technique therefore should result in reduced acute and long-term side effects including a reduction in second malignancy risk. Protocols are open at some proton centers in the United States and these centers use protons instead of photons to treat the patients with the endpoints of morbidity and side effects (Fig. 9.5A,B).

Radiation Therapy for Metastatic Disease

The efficacy of low-dose irradiation in controlling pulmonary micrometastases is documented in the IESS-I study. The frequency of pulmonary relapse was lower and survival rates were higher with prophylactic pulmonary irradiation in comparison to triple-drug chemotherapy alone (17,48,57,89).

For patients with metastatic Ewing sarcoma of the lung, local irradiation to the lungs and primary site are valuable in overall disease control (30,66). An interesting review addressed the role of lung irradiation for Ewing sarcoma with pulmonary metastases at diagnoses (66). Of patients accessioned to CESS studies from 1981 to 1992, 42 presented with pulmonary metastases. One died of progressive disease before irradiation. The other patients either had a complete radiographic remission after chemotherapy ($n = 25$) or chemotherapy with resection of the lung metastases ($n = 4$). Twenty-two patients received bilateral lung irradiation at doses of 12 to 21 Gy. Six had no additional treatment after chemotherapy or surgery, and one underwent bone marrow transplantation. Of the 10 patients in complete remission, 9 had received lung irradiation and 1 had undergone complete resection of lung metastases. Overall, one of six patients was in complete remission without lung irradiation, compared with 4 of 10 who received 12 to 16 Gy and

5 out of 6 who received 18 to 21 Gy. These data suggest the value of lung irradiation for a patient with pulmonary metastases at diagnosis of Ewing sarcoma, and they appear consistent with the suggestion from IESS-I that pulmonary irradiation may sterilize micrometastatic disease in the well-oxygenated lungs. A currently open prospective randomized international trial is comparing bilateral whole lung irradiation to high-dose chemotherapy-based regimen using busulfan and melphalan in patients with pulmonary metastases. The results of this important multi-institutional trial will help to determine the best management for patients with pulmonary metastases.

The treatment strategy for patients presenting with bone metastases is under investigation. Treatment of the primary site using a tailored field is recommended. Although irradiation of bony metastatic sites is generally recommended, this treatment remains unproven and one must be cautioned to limit the irradiation to less than 50% of total bone marrow volume.

Total Body Irradiation and Stem Cell Transplantation

TBI has been used in advanced Ewing sarcoma since the late 1960s (44). Improvement in survival using TBI led the Princess Margaret Hospital group to studies incorporating sequential hemibody irradiation with an attenuated three-drug chemotherapy regimen (90). The use of low-dose, fractionated TBI (15 cGy twice weekly to cumulative levels of 150 cGy) at the National Cancer Institute (NCI) has been followed by studies using “intensification TBI” (400 cGy twice daily), both at NCI and the University of Florida (21,39). These initial reports have yielded different results, with a positive impact in the University of Florida series and little or no impact in the NCI series. The NCI series has been updated, and the long-term results continue to demonstrate no benefit to this approach (91).

Burdach et al. (92) reported using TBI (12 Gy, 1.5 Gy twice daily) and simultaneous high-dose melphalan, followed by etoposide and stem cell rescue. Their results (17 patients) are encouraging, with 7 of 17 patients disease free, $45\% \pm 12\%$ at 6 years, compared with $2\% \pm 2\%$ for the historic control group.

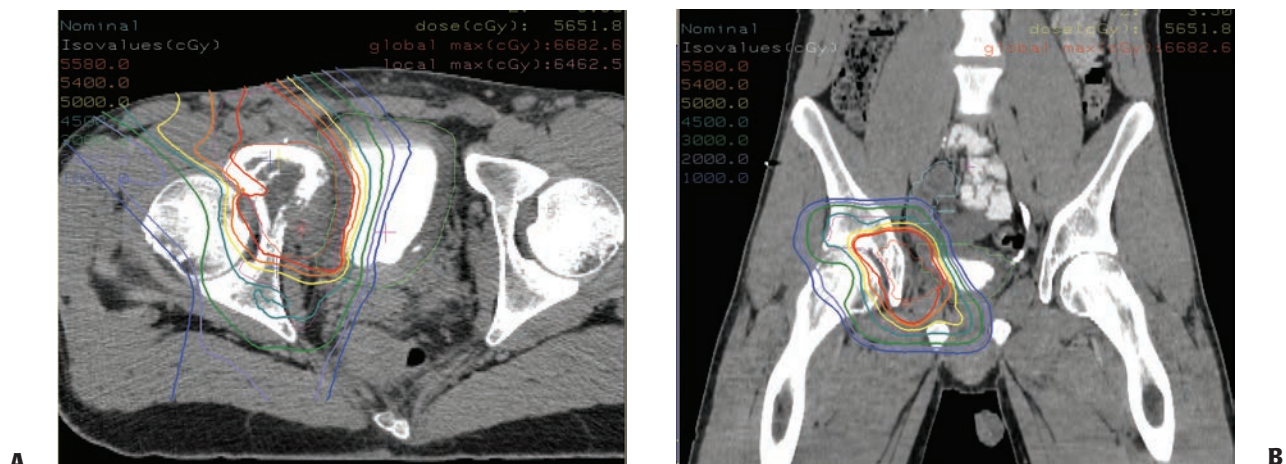


Figure 9.5 A,B: Example of a teenage boy with a pelvic Ewing sarcoma planned with proton radiotherapy. Note sparing of even low dose to most of the bladder, rectum, small bowel and contralateral hip.

Reports using a non-TBI regimen appeared to yield similar results (19,89). Overall, reports of improvements in overall survival for patients with advanced local or metastatic disease have been mixed (93,94).

CURE RATES AND SIDE EFFECTS OF TREATMENT

Current experience with Ewing sarcoma indicates 5-year disease-free survival in 50% to 75% of patients with localized disease at diagnosis (17,25,53,65). There have been late relapses, and the 10-year survival is decidedly worse than the 5-year survival. A limited number of single-institution reports indicate higher disease-free survival (21,40,49). Survival clearly parallels initial disease extent (38). Disease-free survival greater than 75% has been documented for limited-volume Ewing sarcoma involving the distal extremities. Survival rates of only 25% to 35% are achieved with large central lesions (22,38,40,53).

Overall functional results after treatment of Ewing sarcoma have correlated closely with the degree of attention to detailed local management. Selection of primary surgery for lesions permitting function-preserving resection with negative or microscopically positive margins may decrease late effects of high-dose irradiation, particularly in prepubertal youngsters (25,52,53).

With appropriate radiation therapy, patients treated for Ewing sarcoma of the extremities had excellent functional results in more than 60% of cases. The NCI late effects review noted minor alterations in leg length or minimal symptoms of soft tissue change in another 20% of cases (81). Significant treatment-related morbidity occurred in 20% of the NCI cases and was related primarily to larger primary lesions or post-treatment fracture of the femur. Significantly higher morbidities have been reported in series combining systemic chemotherapy with dosages greater than 60 Gy (22,53,83). In a limited number of patients treated with 70 Gy to the primary site, severe functional deterioration was reported in 26% of patients (49).

The risk of fracture after treatment has also been related to total dosage. Fracture appears to correlate more directly with the extent of cortical disruption at the time of biopsy, in addition to tumor size and younger age at presentation (17,20,52,56).

Limited changes have been reported after primary irradiation of tumors of the upper extremities. Some degree of hip dysfunction and potential growth disturbances are documented in long-term follow-up of patients with pelvic Ewing sarcoma. Combined cyclophosphamide-irradiation cystopathy has also been noted in such cases (22,41). One of the primary concerns regarding irradiation is the impact on bone growth. Morphologic changes of the irradiated epiphysis have been reviewed in the NCI series (83). Quantitatively, reduction and subsequent growth relates to the sites of epiphyseal irradiation and the age at treatment. Overall functional results are less favorable in very young children (41,83) (see Chapter 19).

The high incidence of secondary tumors in Ewing sarcoma was originally suggested in the combined reporting of the Late Effect Study Group (LESG), assessing the frequency of secondary bone sarcomas in 9170 children

Table 9.5
Second Malignancies in Patients Treated in the German Cooperative Ewing Sarcoma Studies CESS-81 and CESS-86

Type of local treatment in a total population of 674 patients followed for a median of 7 years	Cumulative risk of any second malignancy after 15 years (%)
All patients	4.6
Local treatment with surgery alone	0.9
Local treatment with surgery and postoperative irradiation to 36 Gy	6.1
Local treatment with definitive irradiation to 46 Gy	6.7

Data from Dunst J, Ahrens S, Paulussen M, et al. Second malignancies after the treatment for Ewing's sarcoma: a report of the CESS-studies. *Int J Radiat Oncol Biol Phys*. 1998;42:379–384.

surviving more than 2 years after treatment for cancer. The rate of carcinogenesis in patients with Ewing sarcoma was second only to that in patients with retinoblastoma in this study. There was a sharp dose–response relationship after dosages to the bone of more than 60 Gy. With the current standard in Ewing sarcoma of 45 to 55 Gy, this risk of second tumors appears to be less than in the original reports. In contrast to the 22% actuarial risk of second tumors reported by LESG (94), more recent data demonstrate a cumulative incidence of 9.2% for any second malignancy and 6.5% for secondary sarcoma (46). Here again, a dose–response relationship was demonstrated, with no secondary sarcomas seen with a dosage of less than 48 Gy. The risk of secondary leukemia may be greater with high-dose regimens as well (95).

In an overall review of second malignancies after treatment for Ewing sarcoma in CESS-81 and CESS-86, the addition of radiotherapy to surgery or treatment with radiotherapy alone was associated with a higher cumulative risk of second malignancies (Table 9.5) (96). The Childhood Cancer Survivor Study, a retrospective study of 13,581 children diagnosed with cancer before age 21 and surviving at least 5 years, reported a 5% cumulative incidence of secondary malignancies at 25 years for the entire cohort (42). The incidence continued to increase over the follow-up period. Survivors of Ewing sarcoma were at higher risk of developing second malignant tumors than others in the cohort. Other factors in addition to radiotherapy were found to play a role in the development of a second malignant tumor. The use of anthracycline increased the risk of soft tissue sarcoma, and the use of alkylators increased the risk of secondary bone tumors. Although children treated for Ewing sarcoma and PNET must be followed up over the long term, the success in treatment should not be overshadowed by these adverse sequelae.

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Osteosarcoma, Chordoma, and Chondrosarcoma

Shiao Y. Woo and Edward C. Halperin

Osteosarcoma is the most common primary malignant bone tumor in children. The tumor derives from bone-forming mesenchyme (1–9) (Fig. 10-1A,B). The majority of cases occur in the second decade of life, and there is a male predominance. The incidence is one to three new cases per million per year (Fig. 10-2) (10).

Inactivation of the retinoblastoma (Rb) gene may be important for osteosarcoma formation. Rb is a tumor suppressor gene that is discussed in detail in Chapter 5. A common karyotype change in osteosarcoma is deletion of the short arm of chromosome 17, where the *p53* gene is localized; *p53* is a nuclear phosphoprotein with properties of a tumor suppressor

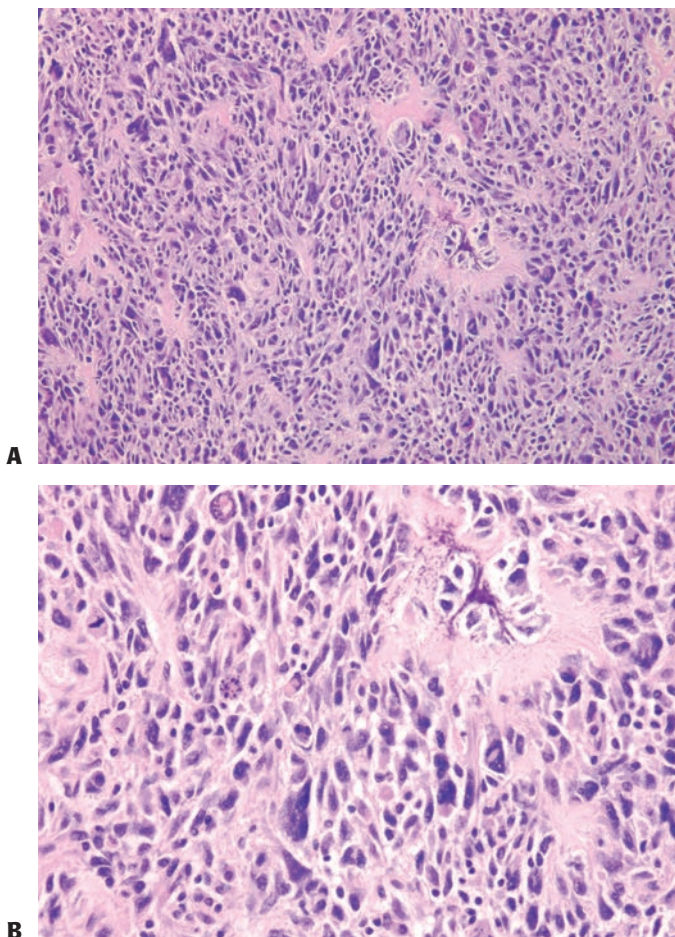


Figure 10.1 A,B: Histopathology of osteosarcoma: low power (A) and high power (B).

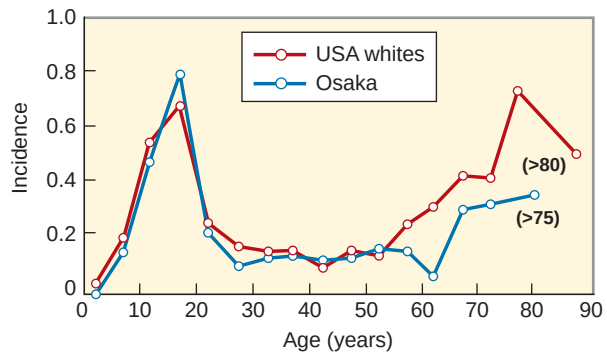


Figure 10.2 Osteosarcoma incidence per 100,000 population per year by age. The peak for older people is associated with Paget disease. (Reproduced from Ishikawa Y, Tsukuma, H, Miller RW, et al. Low rates of Paget's disease of bone and osteosarcoma in elderly Japanese. *Lancet*. 1996;347:1559, with permission.)

gene (11). Genetic studies on human, canine, and murine osteosarcomas have revealed mutation of *c-kit* (12) and *TP53* (13) genes, over-expression of urokinase plasminogen activator/uPA receptor (14), CRM1 (15), Ezrin (16), alpha V integrin and vascular endothelial growth factor (17), runt-related transcription factor Runx2 (18) and *URG4* gene (associated with cell proliferation) (19), increased phosphorylation of *cJun*, *JNK* and *ERK1/2* (20), and expression of cyclooxygenase (COX-2) (21) and somatostatin receptors (22). Some of these genetic alterations may have oncogenic or prognostic significance and may also be potential therapeutic targets. High-resolution array comparative genomic hybridization in combination with interphase fluorescence in situ hybridization has been shown to detect chromosomal instability and genomic imbalance that have been correlated to response to chemotherapy (24).

Second malignant neoplasms can occur in patients with osteosarcoma treated with surgery alone or with surgery and chemotherapy, perhaps as a result of these genetic abnormalities (24–26). Osteosarcoma may develop in long-term survivors of heritable Rb. These secondary osteosarcomas may arise in or outside the irradiated field and in children treated without radiotherapy (see Chapters 5 and 20).

SIGNS, SYMPTOMS, EVALUATION, AND STAGING

Osteosarcoma usually occurs in the metaphyses of the long bones, especially around the knee joint. The bones most commonly involved are the femur (approximately 40% of cases),

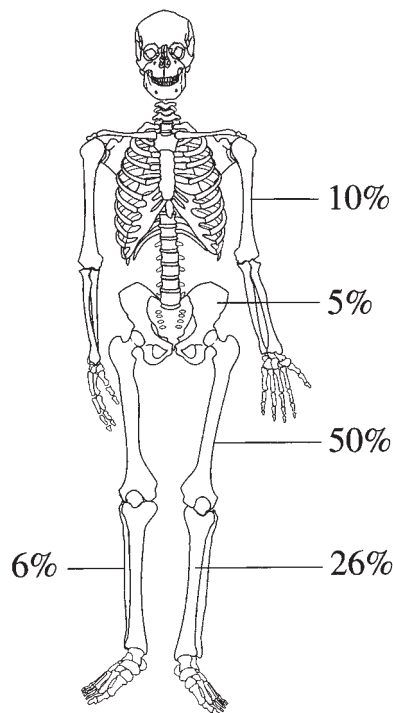


Figure 10.3 Skeletal distribution of primary osteosarcomas in patients treated on the Neoadjuvant Cooperative Osteosarcoma Study Group protocols of the Cooperative German–Austrian–Swiss Osteosarcoma Study Group. (Modified from Bielack S, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1702 patients treated on Neoadjuvant Cooperative Osteosarcoma Study Group protocols. *J Clin Oncol.* 2002;20:776–790, with permission.)

tibia (15%), and humerus (15%) (Fig. 10-3) (1,3,4,10,27). The usual clinical presentation is swelling or pain. A few patients present with a pathologic fracture.

The tumor has a typical appearance on conventional radiographs. There are poorly defined margins, interrupted periosteal new bone, and soft tissue invasion. Where the bony cortex is penetrated at the edge of a tumor, there may be a periosteal elevation and vertical spicule formation (Codman's triangle) (3,4,27). Computed tomography (CT) and magnetic resonance imaging (MRI) help delineate the intramedullary extent of tumor as it tracks along the marrow cavity and the soft tissue extent of tumor (4,28) (Fig. 10-4). The bone scan has nearly 100% sensitivity for the presence of malignant bone tumor, although the specificity is less. On the bone scan one may observe osteoblastic activity in the shaft of the long bone proximal to the primary tumor. This may represent reactive change and not indicate the presence of malignancy (4). Thallium scintigraphy also aids in tumor localization. A surgeon may order an angiogram to determine tumor vascularity, detect vascular displacement, determine the relationship between vessels and the tumor, and identify vascular anomalies. The most common sites of distant metastases are the lungs and bones (3,6,27–31). To evaluate pulmonary metastases, a plain chest radiograph is used to identify chest nodules or cannonball lesions. A CT of the chest can be used to assess the presence or absence of small nodules (31).

If we are to improve the treatment of osteosarcoma, it will be important to adapt therapy to the individual patient's



Figure 10.4 An 18-year-old right-handed high school senior presented to medical attention when his tennis game and weight-lifting activities were inhibited by pain in his left shoulder. Diagnostic images showed a mixed sclerotic and lytic mass in the proximal left humerus. Incisional biopsy made the diagnosis of osteosarcoma. The patient was treated with induction chemotherapy in the hope of producing a substantial tumor response eventually leading to limb-sparing surgery. Unfortunately, within 2 years of the initial diagnosis widespread pulmonary metastases developed, refractory to chemotherapy, which led to the patient's death.

prognostic factors (32). The conventional means of doing this is a staging system. The presence or absence of metastases and the use of histologic subtyping do help predict prognosis (Table 10.1). A variety of factors have been investigated as potential prognostic factors. As will be discussed later in this chapter, histologic response to neoadjuvant chemotherapy is useful in predicting outcome. However, information of this type is available only after chemotherapy and surgery. Clinical features with predictive value in determining outcome include the duration of presenting symptoms (shorter is worse), tumor size (larger is worse), location of the primary tumor (head, spine, rib, and pelvic sites are worse), and weight loss of >10 lb. Tumor size seems strongly predictive of outcome and may be calculated as either absolute tumor length (>10 cm), relative tumor length given as the proportion of tumor length to the overall length of the involved bone (more than one third of the involved bone), or absolute tumor volume (>70 or 150 cm³) (35,36).

There is no widely used staging system for osteosarcoma. Some clinicians simply separate patients into two groups: those with localized disease and those with metastatic disease. The system developed by Enneking and adopted by the Musculoskeletal Tumor Society is used by some orthopedic oncologists. However, there are few low-grade osteosarcomas, so in this system most tumors are stage II or III (Table 10.2). One study from the European Osteosarcoma Intergroup suggested that patients with chondroblastic tumors had a slightly superior survival to those with other histologies, but this difference did not reach statistical significance and awaits confirmation in other research (34).

The Cooperative German–Austrian–Swiss Osteosarcoma Study Group (COSS) has provided an extensive evaluation of prognostic factors in high-grade osteosarcoma of the extremities or trunk. In an evaluation of 1702 patients treated on

Table 10.1
A System for Osteosarcoma Subclassification by Histology and Origin

Centrally Located Tumor

Primary tumors

Conventional: About 75% of patients fall in this category. This group may be additionally subdivided based on the predominant matrix pattern into the following three subgroups:

Osteoblast, 14.4 (54%)

Chondroblastic, 9.6 (70%)

Fibroblastic (spindle cell stroma with a herringbone pattern similar to that seen in fibrosarcoma), 10.7 (57%)

Telangiectatic (characterized by a purely lytic radiographic appearance and a macroscopic and microscopic resemblance to aneurysmal bone cyst), 14.5

Small cell

Malignant fibrous histiocytoma subtype

Low-grade intraosseous (a rare low-grade fibro-osseous lesion often confused with fibrous dysplasia)

Multicentric

Gnathic

Secondary tumors

Associated with Paget disease, 64.2

Radiation-induced

Associated with other benign pre-existing condition (i.e., fibrous dysplasia)

Juxtacortical tumor, 1.0

Parosteal (often arises from the posterior distal femur in older patients. Generally it is a low-grade spindle cell tumor with well-formed, parallel trabecular bone. Some patients may dedifferentiate into a higher grade lesion)

Periosteal (typically involves femur or tibia)

High-grade surface

The death rates per 100 patient-years, correlated with histologic group and calculated by Taylor et al. (33), are shown in bold type, and the 5-year survival rates from the European Osteosarcoma Intergroup (34) are in parenthesis. The death rates for the three subtypes of conventional osteosarcoma are similar. There is some controversy in the literature concerning the prognostic importance of the telangiectatic variant. Most authorities now believe that with aggressive therapy, there is no prognostic difference attached to this diagnosis variant. It is generally agreed that the prognosis for patients with juxtacortical tumors is better and that the prognosis for tumor associated with Paget disease, an entity seen in adults, is decidedly worse. From Refs. 1,4,7,9,33,35, and 43, with permission.

neoadjuvant osteosarcoma protocols, the investigators found that the long-term survival of patients with limb primaries was superior to that of those with axial primaries, patients who presented without metastases had higher survival rates than those who presented with metastases, patients with extremity sarcomas occupying less than one third of the bone had higher survival rates than those with sarcomas occupying more than one third, and distal extremity tumors had a

superior outcome to proximal tumors. The response to chemotherapy (i.e., the amount of tumor necrosis at the time of resection in a setting of neoadjuvant chemotherapy) also was a highly important predictor of outcome along with the extent of surgical resection (Table 10.3) (37–39).

SELECTION OF THERAPY

Surgery

The major modalities of therapy are surgery, radiation therapy and chemotherapy.

Local Disease

The biopsy site should be selected to allow access to the infiltrating edge of the tumor. In general, either minimal or no cortical bone should be removed in order to reduce the risk of pathologic fracture (42–46).

The classic definitive operative procedure is an amputation above the region of the affected bone or a disarticulation at the joint above the lesion. Traditional teaching is that if one resects the bone beyond the site defined by all radiographs as the most proximal extent of disease and if the margins are pathologically negative, the chance of stump recurrence is negligible (44,45). In recent years surgical treatment for local osteosarcoma has changed. New limb salvage procedures have been performed with gratifying results (47).

Table 10.2
The Enneking Staging System for Osteosarcoma

Stage I	Low Grade
	IA. Confined to bone of origin
	IB. Extension beyond bone of origin
Stage II	High Grade
	IIA. Confined to bone of origin
	IIB. Extension beyond bone of origin
Stage III	Metastatic Disease
	IIIA. Confined to bone of origin
	IIIB. Extension beyond bone of origin

Modified from Dameron JA, Pritchard DJ. Current combined treatment of high-grade osteosarcomas. *Oncology* 1995;9:327–350; and Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. *Clin Orthop*. 1980;153:106–120, with permission.

Table 10.3**Influence of the Histologic Response to Neoadjuvant Chemotherapy on Survival in Osteosarcoma**

Group (Reference)	Response	n	Survival	p
Istituto Ortopedico	≥90% necrosis	621	76% 5-year OS	0.0001
Rizzoli (38)	<90% necrosis	437	48% 5-year OS	
Pediatric Oncology	≥90% necrosis	26	73% 5-year EFS	
Group 8651 (41)	<90% necrosis	16	44% 5-year EFS	

EFS, event-free survival; OS, overall survival.

Limb-sparing operations may be selected if there is no evidence of neurologic or vascular compromise by the local tumor, if the surgeon believes that he or she can obtain an adequate margin around the primary osteosarcoma, and if there is a plan for reconstruction that will provide better function than amputation. Relative contraindications to limb sparing include the presence of a pathologic fracture, a poor response to neoadjuvant chemotherapy, or skeletal immaturity that will lead to significant limb growth discrepancies (48).

What is an adequate surgical margin for local management of osteosarcoma? A radical margin entails removal of the entire bone of origin with accompanying soft tissue involvement, as is achieved by a hip disarticulation for a distal femoral tumor. A wide margin is defined as excision of the tumor with a cuff of surrounding normal tissue, and a marginal margin entails excision of the tumor and its surrounding reactive pseudocapsule. Local control is improved by the adequacy of the surgical margin and the response to neoadjuvant chemotherapy (Table 10.3). It is generally accepted that limb-sparing surgery has a slightly greater risk of local tumor recurrence than does amputation. Amputation has a slightly greater risk of local recurrence than does disarticulation (Table 10.4). A good chemotherapeutic response may allow the surgeon to have a tighter margin on the primary tumor and exclude more normal tissue from the resection. However, to know before surgery whether a marginal excision is reasonable, one must have an idea of what tumor response was achieved by chemotherapy. Unfortunately, no single imaging study can reliably provide this information, although plain radiographs, CT, bone scan, MRI, and FDG-PET scan can be used to make a reasonable prediction (48,50).

Table 10.4**Local Recurrence Rates for Osteosarcoma as a Function of the Extent of Surgery**

Site (Reference)	Type of Operation	Local Recurrence rate (%)
Distal femur (37)	Limb sparing	11
	Above-the-knee amputation	8
	Hip disarticulation	0
Pelvis (49)	Radical or wide	48
	Marginal	70
	Intralesional ^a	92

^aSome patients were irradiated.

The reconstruction technique elected after limb-sparing procedures depends on the location of the osteosarcoma, whether there is joint involvement, the extent of bone and soft tissue resection, the patient's age, the functional demands of the patient and the family, and the prospects for rehabilitation. When the excision is intra-articular (within or involving a joint), reconstruction options include custom segmental total joint replacement, whole segment osteoarticular allograft (i.e., from a cadaveric donor), allograft–prosthetic composite reconstruction, arthrodesis (surgical fixation of a joint; artificial ankylosis) with autologous or allogeneic bone, or arthrodesis with a porous prosthesis allowing host bone ingrowth and bone graft. If a joint is not involved, one can reconstruct with autologous or allogeneic bone, a prosthesis, or a segmental prosthetic spacer. Rotation plasty is also an option in certain situations (2,51–53).

It is gratifying that, in modern pediatric oncology practice, the child with osteosarcoma may be offered limb-sparing options for local treatment beyond the traditional amputation or hip disarticulation. The previous discussion has cited indications and relative contraindications to limb-sparing surgery, the risk of local recurrence after various forms of surgery, options for reconstruction after tumor resection, and the need for adequate surgical margins. Although limb function after limb-sparing surgery is generally good in many patients, limb-sparing surgery is not for everyone faced with osteosarcoma. Case selection by a skilled orthopedic oncologist, invocation of sound oncologic principles, and adequate rehabilitative services postoperatively are all necessary to achieve the best possible function and cancer control.

Metastatic Disease

Surgery also plays a role in treating osteosarcoma metastatic to the lung. Some patients present with a primary tumor along with limited pulmonary involvement. Aggressive multiagent chemotherapy, surgical management of the primary tumor, and thoracotomy for resection of pulmonary metastases appear to have significantly increased survival in cases that seemed hopeless (Table 10.5) (54). The most common sites of metastases in the relapse of initially localized osteosarcoma are lung and bone (Fig. 10-5). When tumor relapses in the lung, surgical resection of pulmonary nodules may result in a prolonged disease-free interval and, together with aggressive chemotherapy, a small potential for cure (6,25,30,29,44,55,56). In some patients, repeated thoracotomies appear to have prolonged survival in the face of multiple episodes of pulmonary metastases (43). By diagnosing pulmonary recurrences earlier and with limited tumor bulk, thoracic CT may either

Table 10.5**Factors Predicting Event-Free Survival in Patients with Primary Metastatic Osteosarcoma in the German–Swiss–Austrian Cooperative Osteosarcoma Study Group Clinical Trials**

Factor	n	Five-Year Event-Free Survival ^a	p
Primary site			
Extremity	181	20%	<0.001
Trunk	21	5%	
Number of metastatic organ systems			
1	160	21%	<0.006
>1	42	10%	
Number of metastases			
1	38	55%	<0.001
2–5	69	19%	
>5	91	2%	
Isolated lung metastases			
Unilateral	46	45%	<0.001
Bilateral	70	4%	
1	24	58%	<0.001
2–5	41	23%	
>5	57	3%	

From Kager L, Zoubek A, Potechger U, et al. Cooperative German–Austrian–Swiss Osteosarcoma Study Group. Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. *J Clin Oncol* 2003;21(10):2011–2018, with permission.

open the possibility for a beneficial effect of surgery or simply create a lead-time bias (54).

Several variables must be considered when one uses metastasectomy for pulmonary metastases. These include the aggressiveness of the proposed operation, whether they are unilateral or bilateral, the interval between the development of the metastases and the treatment of the primary, the extent of vascular invasion, the presence or absence of hilar lymph node involvement, and whether additional salvage chemotherapy is available after surgery (48,49,57). The role of the bony metastasectomy is not well defined, undoubtedly because the occurrence of bony metastases in the setting of potentially salvageable osteosarcoma is far less common than that of pulmonary metastases (48).

Bielack et al. reviewed the outcomes of 249 consecutive patients with second and subsequent recurrences of osteosarcoma (58). With mainly chemotherapy and surgery, the 5-year overall and event-free survival rates were 32% and 18% for second, 26% and 0% for third, 28% and 13% for fourth, and 53% and 0% for fifth recurrences, respectively.

Radiation Therapy

Prebiopsy

Sweetnam (44) administered low-dose irradiation before the initial biopsy (approximately 10 Gy) to 29 patients in the hope of reducing the viability of cells that might be disseminated into the bloodstream by the biopsy. The 20% overall survival rate, no different from that of historic controls, discouraged additional investigation. Only 2 of 19 patients survived when treated with amputation without prior biopsy.

Primary and Preoperative Treatment

The Cade Technique

In the era before adjuvant chemotherapy, physicians were distressed by the practice of treating the primary lesion with

amputation or disarticulation, only to have the young patient die within 6 months of pulmonary metastases. Because the survival rate with surgical ablation alone was only 20%, many limbs were sacrificed in vain. Surgeons and radiotherapists reasoned that if high-dose local irradiation could obtain at least temporary control of the primary tumor, a time interval would be obtained that would allow the selection of cases suitable for a radical surgery. Patients who develop pulmonary metastasis in a 4–6 month waiting period after irradiation would be spared an unnecessary amputation. Those who did not develop pulmonary metastasis after the waiting period would undergo extirpation of the primary tumor. This philosophy was promulgated by English physician Sir Stanford Cade and is called the Cade technique. The 5-year survival rates of 15–20% were equivalent to those achieved in the preadjuvant therapy era with immediate surgical ablation. The delay in surgery appears to have cost no lives (10,56,59–67). There generally was a reduction in pain and swelling at the tumor site after the first 20 Gy. This response tended to continue for several weeks after completion of radiotherapy. In patients who underwent limb ablation after radiotherapy, a histologic analysis could be performed to assess the presence or absence of viable tumor. The majority of patients had a good or excellent local response (Table 10.6). There were some long-term survivors after aggressive treatment with radiation therapy alone (6,66).

Modern Series of Primary Photon Radiation Therapy

In modern radiotherapy practice, it is rare to be asked to use radiotherapy as the primary local treatment for osteosarcoma except for lesions in inaccessible sites. However, the data acquired with the Cade technique make it reasonable to consider the use of radiation in certain situations. Preoperative radiotherapy has been given in the context of a research

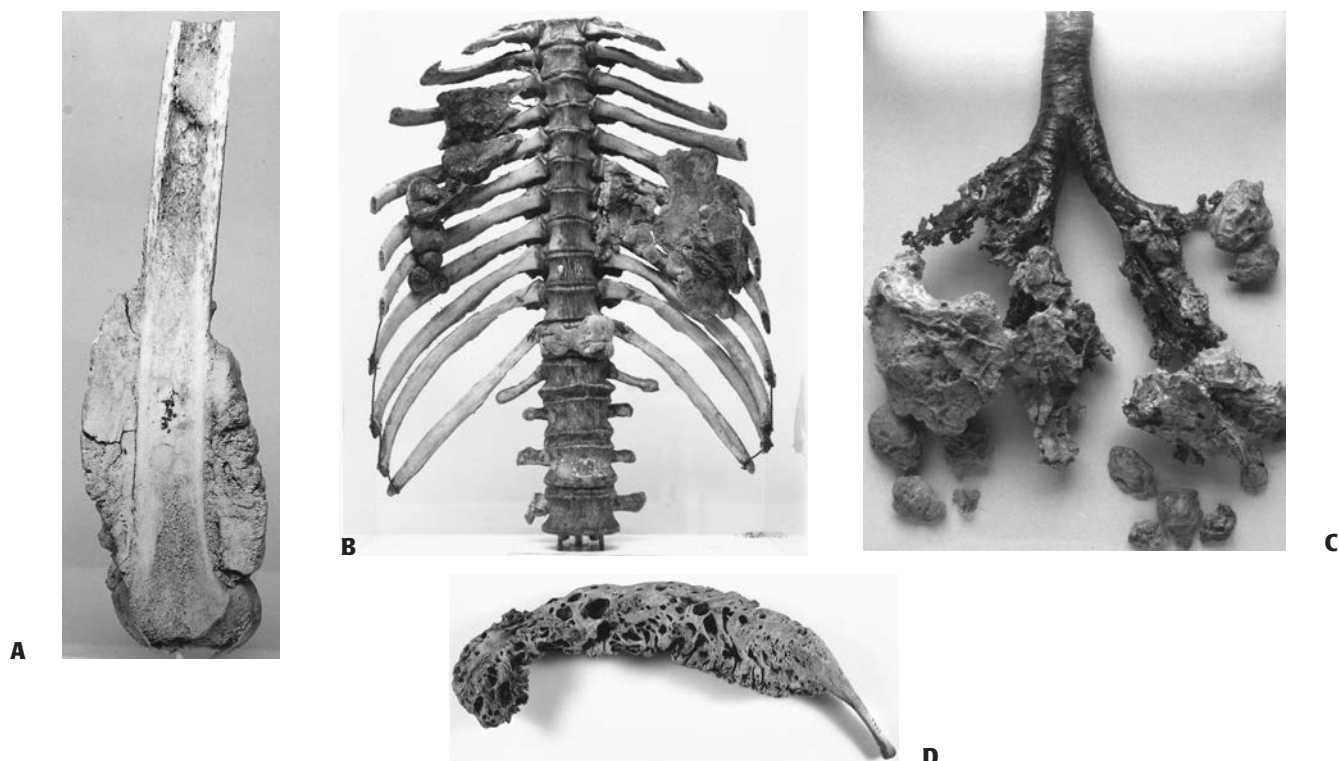


Figure 105 John Hunter (1728–1793) was an extraordinary surgeon, anatomist, teacher, and collector. His magnificent collection of scientific specimens was purchased by Parliament and placed in the custody of the Company of Surgeons, renamed the Royal College of Surgeons in 1800. These illustrations of osteosarcoma, taken from the Hunterian Museum, Lincoln's Inn Fields, London, appear by permission of the president and council of the Royal College of Surgeons of England. In November 1786, Hunter encountered a patient with “a hard swelling of the lower part of the thigh, as it were beginning from the knee ... the part began evidently to enlarge ... and was attended with more pain as it enlarged ... and the pain was now exhausting him much.” An amputation was done. Hunter described an “osteoid sarcoma” of the distal femur (A) and also noted the intramedullary spread of the tumor: “A short distance below the site of amputation there is a second hemispherical tumour in the medullary canal ... above the main growth, the disease having extended within the canal, in this case, for an unusual distance beyond the limits of the external swelling.” Four weeks after the amputation the patient “began to complain of a difficulty in breathing, but not attended with the least pain ... he began to lose his flesh and sink gradually, his breathing being more and more difficult ... he died; living only 7 weeks after the operation.” On autopsy, “bony tumors were found in the cellular membrane of the lungs, upon the pericardium, and some very large ones of the pleura, adhering to the ribs, and upon the anterior surface of the vertebrae of the back” (B,C). Hunter noted that “when the leg was amputated he had not the least symptom of any disease in the chest” but deduced that the lung metastases “had taken place a considerable time before the symptoms took place.” As for the osteoid appearance of the tumor, Hunter wrote that “one can figure to themselves a reason why the tumour which formed on the outer surface of the thigh-bone might become bony, because it might acquire that disposition from the bone it surrounded; but, from these tumours formed in the chest becoming bone, shows it was the nature of the tumours themselves.” The remaining figure (D) is “the osseous part of an osteosarcomatous tumour” from “the rib of a Horse” from Hunter’s collection. (Descriptions of this material are found in *Descriptive catalog of the pathological series in the Hunterian Museum of the Royal College of Surgeons of England*. Edinburgh and London: E. & S. Livingstone, 1972; Part I:133–138; Part II:75–77. Biographical material is from Allen E. Hunterian Museum [pamphlet], Royal College of Surgeons, 1974.)

protocol to reduce tumor viability before surgery, increase the probability of performing limb-sparing surgery instead of amputation, or reduce the risk of local recurrence (56,67). In patients with nonresectable primary tumors, such as difficult pelvic bone sites, vertebral column, frontal bones, or base of skull, and in patients who refuse definitive surgery, consideration should be given to precision high-dose irradiation. Modern photon techniques use three-dimensional computerized treatment planning and intensity-modulated radiation therapy. Neutron or proton beams can improve local control in certain circumstances and are discussed later in this chapter (71). There is also precedent for high-dose preoperative irradiation and rapid surgery, preoperative radiotherapy with local hyperthermic perfusion (72), intraoperative electron beam therapy (73), and radiotherapy with intra-arterial infusion of a radiosensitizer (74).

Data on photon irradiation as primary treatment for osteosarcoma, in lieu of surgery and in conjunction with aggressive chemotherapy, are available from Albrecht et al. from Berlin (59). They described seven patients with osteosarcoma who were treated from 1977 to 1992 according to contemporary COSS protocols (Table 10.7). Six patients refused the appropriate amputation or rotation plasty. One had a primary tumor described as inoperable. Each patient received 50–70 Gy of conventionally fractionated photon irradiation. The patient with the inoperable tumor died within 1 year of initiation of treatment. The remaining six patients are alive without evidence of recurrent disease 2–18 years after treatment (mean follow-up, 11 years). Three of the six survivors ultimately suffered a pathologic fracture 8–12 months after 50–70 Gy, and one of these subsequently had an amputation. This small clinical series suggests that photon radiotherapy in

Table 10.6**The Cade Technique: Management of Osteosarcoma with Primary Irradiation or Primary Irradiation and Selected Delayed Amputation (Excluding Parosteal Tumors)**

Authors Listed in Order of Increasing Dosage (References)	Dosage (Gy)	Clinical or Pathologic Local Response	Survival
Jenkin et al. (64,65)	50–60	Complete, 11% Partial, 63% None, 26%	2-year: 16%
van den Brenk et al. (81)	60–70, then 40–50 every 6 months	Severe limb deformity in long-term survivors	5-year: 12% (includes cases of chondrosarcoma and fibrosarcoma)
Lee et al. (56,66)	70–80	33% totally destroyed 33% doubtful viability 33% capable of growth and perhaps dissemination	5-year: 22%
Poppe et al. (10)	70–80	70% considerable radiation effect 19% moderate effect	5-year: 18%
Gaitan-Yanguas (63)	10–100	11% slight or no effect 44% no residual tumor	
Allen and Stevens (60)	79–100	56% residual tumor 60% reclassification 86% tumor sterilization	60% NED at 30–114 mo
Caceres and Zaharia (61)	80–120	16% remaining viable tumor 56% severe radiation damage 28% total tumor destruction 35% no tumor destruction	5-year: 18% (no difference from historical surgical controls, 22%)
Phillips and Sheline (67)	50–120	65% tumor in specimen	

NED, no evidence of disease.

conjunction with chemotherapy may be used to manage osteosarcoma if appropriate surgery is impossible or refused (59). Whether such patients are best treated with photons, neutrons, or protons is a matter for debate.

Some patients with unresectable osteosarcomas are treated with conventional external beam irradiation. The COSS described a series of patients with osteosarcoma of the spine who were treated with intralesional or marginal resections and also received photon irradiation, neutron beam treatment, or samarium. In the analysis of patients who underwent either incomplete surgery or no surgery, 7 received postoperative irradiation and 10 did not. The seven patients who received irradiation had a slightly higher long-term survival (50%) than those who did not (10%, $p = 0.059$) (84).

In 2003, COSS investigators described a group of patients with pelvic osteosarcomas treated between 1979 and 1998. Of 30 patients with intralesional surgery or no primary surgery, 11 received radiotherapy (65–68 Gy with photons, 2 were treated with neutrons, and 1 also received ^{153}Sm). The 5-year overall survival of the irradiated patients (16%) was superior to that of those not irradiated (0%, $p = 0.0033$) (85).

Machak et al. (86) reported a retrospective review of 31 patients with limb osteosarcoma who refused definitive surgery and were treated with cis-platinum, doxorubicin (IV or IA), or both. All patients received 40–68 Gy at 2.5–3 Gy per fraction, one fraction per day, or 1.25–1.5 Gy twice daily. With a median follow-up of 39 months, the predicted 5-year overall survival was 61%. Local progression-free survival was 56% (40% for 50 Gy or less, 77% for more than 50 Gy). There were five fractures, one skin necrosis, and one osteomyelitis. It is conceivable that use of neoadjuvant radiotherapy with chemotherapy increased the proportion of good responders of the time of surgery (87).

Hirano et al. (52) from Nagasaki University sandwiched 30 Gy (2–3 Gy per fraction) in the midst of preoperative chemotherapy in 15 patients with osteosarcoma. Histology of the resected specimens showed a tumoricidal effect in nine patients and a lesser effect in three.

Wagner et al. used a combination of short-course preoperative irradiation (19.8 Gy), surgical resection, intraoperative 90Y plaque brachytherapy to at-risk areas of the dura when applicable, and postoperative irradiation with sequential cone-downs to

Table 10.7

Significant Recent Cooperative Group Trials Addressing the Management of Localized Osteosarcoma

Study Name and Number of Eligible Patients	Primary Objective	Treatment Arms	Results	Comments (Reference)
Pediatric Oncology Group (POG)				
POG-8651 (n = 100)	To determine whether chemotherapy administered before and after definitive surgery is superior to surgery followed by adjuvant chemotherapy	Arm A: HDMTX + AP, then surgery, then HDMTX + BCD + ADR + AP Arm B: surgery, then HDMTX + AP + BCD	The 5-year survival is 76% for patients assigned to neoadjuvant chemotherapy and 79% for patients treated with the more traditional approach (p = 0.6)	There is no evidence of an advantage in event-free survival or survival for either treatment arm (41,78)
European Osteosarcoma Intergroup (EOI, a combination of the European Organization for Research and Treatment of Cancer and the Medical Research Council)				
EOI-80831 (n = 307 registered, 207 evaluable, 163 completed allotted chemotherapy)	This study began as a randomized phase II toxicity and response trial of two short, intensive chemotherapy programs	Surgery, randomization of chemotherapy of AP vs. AP + MTX	6-year survival: AP 65% + MTX 50% (p = 0.10) 6-year disease-free survival: AP 58% vs. AP + MTX 40% (p = 0.02)	The dosage intensity of AP was greater in the two-drug arm than the three-drug arm. This may have produced the superior outcome. Disease-free survival was better for patients planned for conservation surgery than amputation (76)
EOI-80861 (n = 407, 391 eligible)	To compare short, intensive chemotherapy with complex, longer-duration program based on the Rosen T10 program	Arm A: AP three cycles, then surgery, then three more cycles Arm B: ADR + V + HDMTX, then surgery, then BCD + ADR + V + HDMTX + AP	The median follow-up is 5.6 years. Survival in both groups is almost identical. 5-year progression-free survival is 44%	AP appears to be as effective as the more complicated program at a lower cost (75,77)
Scandinavian Sarcoma Group (SSG)				
SSG-VIII	To increase the number of good responders to neoadjuvant therapy with intensified	HDMTX + AP, then surgery; good responders get HDMTX + AP postoperatively, poor	The median follow-up is 6.9 years. The year event-free survival is 61%	Female sex, small tumor volume, and high serum MTX levels predict better
Children's Cancer Group (CCG)				
CCG-741 (n = 166)	To compare HDMTX with moderate-dose MTX in the context of a multiagent chemotherapy program	Surgery, ADR, then randomize to arm: Arm A, HDMTX + AV; Arm B, moderate-dose MTX + AV	38% disease-free survival at 48 mo. No difference between the two arms (p > 0.5)	Lower disease-free survival was associated with the presence of spontaneous tumor necrosis at presentation (78)

(continued)

Table 10.7

Significant Recent Cooperative Group Trials Addressing the Management of Localized Osteosarcoma (Continued)

Study Name and Number of Eligible Patients	Primary Objective	Treatment Arms	Results	Comments (Reference)
CCG-782 (<i>n</i> = 232)	To use histologic response of the primary tumor to neoadjuvant chemotherapy to determine postoperative chemotherapy	Biopsy, then HDMTX + AV + BCD, then surgery. All patients without local progression received BCD + AV + HDMTX. Then, if <95% necrosis, receive BCD + HDMTX + AV	5-year event-free survival was 53%. Patients with local disease progression in the induction phase had 48% 3-year event-free survival	A poor prognosis is associated with an evaluated alkaline phosphatase at diagnosis or a primary tumor in the proximal humerus or proximal femur (40,79,76)
Cooperative Osteosarcoma Study (COSS) Group of the German Society of Pediatric Oncology				
COSS-77 (<i>n</i> = 68)	Improved survival from adjuvant chemotherapy	Surgery, then HDMTX + AV	46% 14-year metastasis-free survival	Event-free survival was 48% for good responders and 48% for poor responders (80,81)
COSS-80 (<i>n</i> = 101)	Improved survival with neoadjuvant chemotherapy	Arm A: ADR + HDMTX + P, then surgery, then ADR + HDMTX + P Arm B: ADR + HDMTX + BCD ± β-IFN	5-year event-free survival: Arm A = 66%, Arm B = 64%	There was no difference in outcome between the two chemotherapy arms. There was no difference associated with the use of β-IFN (40,79–81)
COSS-86 (<i>n</i> = 153)	Stratified by risk group. High risk was large tumor, chondroid matrix, or poor bone scan response at week 5	Low risk: ADR + HDMTX + P, then surgery, then ADR + HDMTX + P High-risk Arm A: ADR + HDMTX + intra-arterial IP, then surgery, then ADR + HDMTX + IP High-risk Arm B: Same as Arm A except IP is intravenous	77% 5-year metastasis-free survival, 66% 10-year metastasis-free survival, 72% 10-year overall survival	Response rate is >76%, better than in previous COSS studies (82)
Children's Oncology Group (COG)				
CCG-7921, POG-9351 (<i>n</i> = 662)	To compare three-drug chemo with four-drug chemo. To determine if addition of MTP improves EFS and OS	Reg A: AP + MTX ± MTP Reg B: AP + MTX + I ± MTP	Similar EFS and OS between Reg A and B without MTP MTP-improved 6-year OS from 70% to 78% (<i>p</i> = 0.03)	Addition of ifosfamide was of no benefit. Addition of MTP improved survival

ADR, doxorubicin; AP, doxorubicin and *cis*-platinum; AV, doxorubicin and vincristine; BCD, bleomycin, cyclophosphamide, and actinomycin D; β-IFN, beta-interferon; EI, etoposide and ifosfamide; HDMTX, high-dose methotrexate; IP, ifosfamide and *cis*-platinum; MTX, methotrexate; P, *cis*-platinum; V, vincristine; MTP, muramyl tripeptide.

50.4–58.2 Gy (total 70.2–77.4 Gy) to treat bone tumors mainly involving the spine and pelvis (68). For patients with osteosarcoma, the 5-year local control, disease-free survival and overall survival were, respectively, 75%, 50%, and 67%.

Dincbas et al. showed that preoperative radiation therapy (usually 35 Gy in 10 fractions) and preoperative chemotherapy (three courses) allowed successful limb-sparing surgery in 44 out of 46 patients (70). Tumor necrosis rate was >90% in 87% of patients, and 5-year local control rate was 97.5%. The overall 5-year survival rate was 44%.

Maxilla and Mandible

Some surgeons believe that a wide surgical excision of osteosarcoma of the maxilla or mandible is risky because of the functional consequences. Local recurrence and death after intralesional resection or resection with a positive margin are typical (88,89). Chambers and Mahoney (90) reported 33 patients treated with preoperative brachytherapy. Implantation was accomplished by drilling holes in the mandible and placing radium needles. The dosage was 100–160 cGy. Wide surgical excision of the involved hemimandible and adjacent soft tissue was performed 2–4 weeks after irradiation. Out of 11 children, 10 were long-term survivors with follow-up from 4 to 15 years. Suit (42,43) reported additional three cases (two of the mandible and one of the maxilla) locally controlled with a similar technique. Heroic brachytherapy is rarely necessary in modern practice. With radical surgical resection of the tumor, followed by reconstruction, local control of facial bone osteosarcoma is to be expected (91).

Lung

Historically, the propensity of osteosarcoma to metastasize to the lungs stimulated interest in the use of prophylactic lung irradiation (Table 10.8). The fundamental problem with thoracic irradiation is that pulmonary tolerance may be exceeded before necessary tumoricidal dosages are achieved (92). Abbattucci et al. (93), working from radiobiologic principles, showed that the exponential kill of clonogenic cells produced by fractionated radiotherapy, in principle, could eradicate subclinical metastases in a highly oxygenated lung. Visible tumor deposits, detectable on chest radiograph, measure 6–10 mm in diameter and contain 10^8 – 10^9 cells. If one assumes that the dosage needed to reduce the number of viable clonogenic cells in a tumor to 10% (D_{10}) is 4 Gy for osteosarcoma, then 20 Gy of fractionated irradiation should be able to prevent the growth of metastases containing 10^4 or 10^5 cells. However more recent experiments on canine osteosarcoma cell lines showed that the cells were relatively radio-resistant with a survival fraction at 2 Gy to be 0.62 and a mean alpha/beta ratio of 3.5 (94). Breur (95,96), analyzing 13 patients with microscopic pulmonary metastasis and extrapolating backward in time, showed that about 1 in 4 patients with subclinical metastasis has tumors containing about 10^5 cells. In principle, these small metastatic deposits would be curable by adjuvant pulmonary irradiation. This argument has been criticized by Baeza et al. (97).

The technique of prophylactic pulmonary irradiation involves parallel opposed anterior and posterior fields encompassing both the apices and posterior costophrenic angles of the lungs. Some physicians use a customized anterior cardiac shield, particularly if concurrent cardiotoxic

chemotherapy is used. The dosimetry conventions at many institutions do not make corrections for the increased transmission of radiation through healthy lung tissue. Uncorrected prescriptions, based on the inaccurate assumption that the lungs have the same density as normal tissue, underestimate the actual dosage given to the center of the lungs by about 14% (92).

The Role of Adjuvant Whole-Lung Irradiation in Osteosarcoma in Nonrandomized Studies

Lougheed et al. (98) thought that elective prophylactic lung irradiation of clinically normal lungs might delay the development of pulmonary metastases in osteosarcoma. They treated only one of the lungs, giving 15 Gy in combination with actinomycin D. Four of eight patients developed metastases in the untreated lung, but only one patient progressed in the irradiated lung.

Newton (99) reported that fewer patients developed pulmonary metastases in the early follow-up after elective pulmonary irradiation than nonirradiated patients. Only 4 of 13 irradiated patients progressed after prophylactic irradiation, although the effect was short lived. Caldwell (100) performed sequential elective bilateral whole-lung irradiation (WLI) in 38 patients with a variety of tumors, including 7 with osteosarcoma. Seventeen had no detectable metastases. Twenty-one, who had pulmonary nodules, received WLI followed by surgical resection or a local boost radiation field to a higher dosage. Three of the four patients with osteosarcoma had no detectable metastases at presentation and were alive and well with no active disease at 2–4 year follow-up.

Caceres et al. (101) treated seven evaluable patients with 20 Gy of prophylactic lung irradiation. Ten patients received adjuvant doxorubicin. After 13 months of follow-up, 3 of 7 irradiated patients were free of disease, compared with 6 of 10 on the chemotherapy arm.

Evaluating 62 patients with osteosarcoma in Toronto, Jenkin et al. (65) included 6 patients who received 15 Gy of prophylactic lung irradiation and actinomycin. All six developed diffuse pulmonary metastases in 2–6 months. The French Bone Tumor Study Group (102) published studies on a non-randomized series of 41 evaluable cases of extremity osteosarcoma treated with chemotherapy and 20 Gy of prophylactic lung irradiation. The 5-year disease-free survival was 58%, and the overall survival was 66%. This compared well with historic control, but there was marked lung toxicity including restrictive ventilatory effects, five life-threatening infections, and one death from *Pneumocystis carinii* pneumonia. A study by Gilchrist et al. (103) from the Mayo Clinic showed no benefit of prophylactic pulmonary irradiation in osteosarcoma.

Evidence from Randomized Studies

In 1976 Rab et al. (104) described a randomized trial of 53 patients from the Mayo Clinic. They were randomized to receive 15 Gy prophylactic lung irradiation (uncorrected) while receiving 100% oxygen with intravenous actinomycin D. The control group did not undergo prophylactic lung irradiation. The median survival time was 42 months in the irradiated arm and 25 months in the unirradiated arm. However, there was no significant difference in overall survival or disease-free survival. The European Organization for Research and Treatment

Table 10.8**Prophylactic Lung Irradiation in the Treatment of Osteogenic Sarcoma**

Authors (Reference)	Technique	Number of Patients	Survival	Comment
Breur et al. (29)	Local therapy of surgery, Cade technique, or radiotherapy, then randomized: 17.5 Gy WLI	44	5-year 55%	$p = 0.18$; metastasis-free
	Control	42	40%	
Burgers et al. (106)	Local therapy of surgery, Cade technique, or radiotherapy; then randomized: Chemotherapy 20 Gy WLI	65 25	5-year 30% 25%	No difference between the treatment arms.
Ellis et al. (107) Springfield et al. (35)	Local surgical therapy; 16 Gy WLI with partial heat block, doxorubicin	53 or 57	60% metastasis-free survival	Follow-up duration not clear
Jenkin et al. (64,65)	Cade technique; 15 Gy WLI $\pm$ actinomycin			All six developed lung metastases in 2–6 mo.
Lougheed et al. (98)	15 Gy irradiation to one lung only; actinomycin	8		Four patients developed metastases in the untreated lung, one in the treated lung.
Newton (99)	Radiation and delayed amputation for primary tumor; 19.5 Gy adjuvant WLI	14	43%	Minimum 52 mo follow-up; survival better than that of historical controls
Rab et al. (104)	Local therapy of surgery, Cade technique, or radiotherapy; then randomized: 15 Gy WLI + actinomycin	26	42%	WLI did not influence survival
	Control	27	38%	
Zaharia et al. (144)	Local therapy of surgery, nonrandomized: 20 Gy WLI 20 Gy WLI + doxorubicin	7 29	241 d median 843 d survival	$p < 0.33$.

WLI, whole-lung irradiation.

of Cancer (EORTC) conducted the two most important initial trials of WLI. The first study, Study O2, enrolled six patients. The use of local therapy plus 17.5 Gy of WLI achieved a superior but not statistically significant improvement in 5-year survival over local therapy alone. The subsequent trial permitted patients to undergo either definitive surgery, delayed technique, or radiotherapy. Among the 205 patients, 19% underwent amputation, and 29% underwent disarticulation. In the first arm of the study, adjuvant chemotherapy consisting of doxorubicin, vincristine, and methotrexate was given every 2 weeks for the first 12 weeks. This was followed by a consolidation phase in which these drugs were alternated with cy-

clophosphamide every 4 weeks for 6 months. The total adjuvant chemotherapy period was 41 weeks. The second treatment arm was identical to that of Study O2 with no chemotherapy but with WLI to a total dosage of 20 Gy after air correction. In the third treatment arm, the chemotherapy of Arm 1 was used, followed after 12 weeks by WLI. The 5-year overall survival for this study was 43%, with no significant difference between the three treatment arms. The disease-free survival at 5 years was 24%. An unpublished analysis cited by Burgers (105) asserts that “the localization of pulmonary metastases was mainly behind the dome of the diaphragm behind the heart and mediastinum in those patients who were irradiated. These areas had received a smaller dose, as the irradiation passes

partly through non-aerated tissue.” No other assertions similar to this appear in the literature. Subgroup analysis showed that the 5-year disease-free survival in patients younger than 17 years was 50% in the irradiated patients and 31% in the unirradiated patients ($p = 0.074$) (29).

As chemotherapy became more popular for osteosarcoma, the EORTC and the International Society for Pediatric Oncology (SIOP) jointly launched the O3 trial in 1978. Two-hundred forty patients younger than 30 years were randomized to receive treatment with adjuvant chemotherapy, prophylactic lung irradiation to 20 Gy, or chemotherapy with prophylactic irradiation. The type of adjuvant treatment did not significantly alter the overall survival, disease-free survival, or metastasis-free survival. The patterns of relapse were no different in the three groups. Acute toxicity was greater with chemotherapy and resulted in three deaths. The prophylactic lung irradiation was well tolerated, although more irradiated patients developed a late but asymptomatic deterioration in pulmonary function (105,106).

Between 1979 and 1984, approximately 57 patients with osteogenic sarcoma were enrolled in a University of Florida protocol in which patients had definitive surgical treatment of the primary tumors. Within 7 days of the surgery, all patients received WLI to a total dosage of 16 Gy in 10 fractions with parallel opposed anterior and posterior fields with 8-MV photons. An anterior heart block was used. After WLI, patients received five courses of doxorubicin. Detailed results of the efficacy of this program have not been published. In reports published 4 and 8 years after the study was closed to patient accrual, the crude survival was approximately 67% and the crude metastasis-free survival was about 56% (107).

In the “Standards, Options and Recommendations” (SOR) project conducted by the Federation of French Cancer Centers, a thorough review of the literature from January 1992 to October 2003 was performed. One conclusion was that whole-lung prophylactic irradiation is not indicated in nonmetastatic osteosarcoma (108).

Cases of breast cancer developing in long-term survivors after elective WLI for osteosarcoma have been reported (109,110). There may also be a higher risk of breast cancer in women who have had osteosarcoma but never underwent WLI (111). In light of the association of osteosarcoma with abnormalities of tumor suppressor genes, concern is warranted about radiation-induced malignancy.

WLI for Advanced Osteosarcoma

Thoracotomy offers a chance of cure for some patients with pulmonary metastatic disease. Patients more likely to be cured by thoracotomy include those with fewer than four lesions completely removed at the first thoracotomy, unilateral disease, and a prior disease-free interval of at least 18 months (30,112–114).

When WLI is used for overt pulmonary metastases one would expect little effect. Individual lung lesions may respond to high-dose “rifle shot” fields (45,65). Weichselbaum et al. (112) reported an aggressive program for treating metastatic osteosarcoma with chemotherapy, WLI, and boost irradiation to individual metastases. Three of 10 patients were alive without evidence of disease. Equivalent or better results have been achieved with chemotherapy, thoracotomy, and no WLI (54).

Giritsky et al. (80) failed to show a benefit of prethoracotomy or postthoracotomy irradiation. However, the Study O3 suggested that successful metastasectomy was possible more often after previous prophylactic lung irradiation than after adjuvant chemotherapy (105).

Extracorporeal Irradiation

Among the more innovative uses of radiotherapy in osteosarcoma treatment has been extracorporeal irradiation. Limb conservation has been changed from being an exception to standard practice in the primary management of osteosarcoma of the extremities. Bony defects created by limb-sparing procedures may be treated with custom-made prostheses with mobile joints, osteoarticular allografts, allograft-prosthesis composites, or intracalary segments filled with autografts. The complication rates from some of these procedures can be high.

Reimplantation of a bone autograph after tumor-ablative extracorporeal irradiation has several theoretical advantages. A major advantage is the precise anatomic fit of the reimplanted bone segment. This may increase the probability of joint mobility. In skeletally immature patients, limb-sparing surgery must be performed carefully to avoid later limb length discrepancy. Extracorporeal irradiation can avoid the growth discrepancy commonly seen in prosthetic replacements by avoiding resection of the normal growth plate and appositional bone growth from surrounding healthy bones. The reimplantation of irradiated bone avoids some of the other problems associated with allografts such as dependence on a bone bank, graft rejection, and the risk of viral transmission. It is also theoretically possible that dead tumor cells in the irradiated bone may stimulate a desirable immunologic response (115,116).

Hong et al. (116) from New South Wales, Australia, have described four patients with osteosarcoma who received a single dose of 50 Gy delivered to bone extracorporeally using a linear accelerator or blood product irradiator. The bone was wrapped in a sterile wrapping, taken for irradiation, and then returned to the operating room. After reimplantation, it appears that the reimplanted bone serves as the framework for appositional bone growth from surrounding healthy bones. There is no evidence of local tumor recurrence at a median follow-up of 19.5 months. For the most part, the functional outcome appears to have been good. Yamamoto et al. (115) described the use of extracorporeal irradiation to treat a distal radius osteosarcoma. This patient received 60 Gy in a single fraction. Araki et al. (117) used 50 Gy to treat 20 patients with primary bone tumors, including osteosarcoma and malignant fibrous histiocytoma. At a median follow-up of 45 months, there was no evidence of local recurrence or symptoms of graft failure such as severe pain or severe fracture.

Chemotherapy

For many years it was accepted that the long-term survival of patients with osteosarcoma treated with radical surgical ablation alone was approximately 20%. A 1978 M. D. Anderson Cancer Center trial used cyclophosphamide, vincristine, melphalan, and doxorubicin and achieved a 2-year survival rate of 50% (87). Subsequent pediatric trials from M. D. Anderson used the T7 protocol of preoperative intra-arterial cisplatin, surgery, and postoperative programs of doxorubicin, methotrexate, cis-platinum, and cyclophosphamide in various

combinations. Patients undergoing limb salvage had a 58% 110-month disease-free survival. Patients undergoing amputation had a 54% disease-free survival (difference not significant). Optimum survival (80%) was found in patients with more than 90% tumor necrosis, induced by the preoperative chemotherapy, at the time of amputation. Survival was also correlated with smaller primary tumor volumes (118). Patients with a poor histologic response had a 33% disease-free survival rate (40,79).

In a separate report from the M. D. Anderson group covering the years 1979–1982, reporting 37 patients of the age of 16 years or older with extremity lesions, preoperative doxorubicin and intra-arterial cis-platinum were followed postoperatively by the same drugs. Patients who suffered cis-platinum toxicity received dacarbazine as a substitute.

Based on these results, the T7 protocol was modified by the use of cis-platinum, doxorubicin, bleomycin, cyclophosphamide, and dactinomycin in the postoperative period. This was called the T10 protocol (79). Sixty additional patients, treated from 1983 to 1988, received intensified preoperative intra-arterial cis-platinum. Postoperatively, complete responders received doxorubicin and cis-platinum (or dacarbazine), and partial or poor responders were changed to an alternating program of methotrexate, doxorubicin, or dacarbazine, and bleomycin, cyclophosphamide or actinomycin. Patients treated from 1979 to 1982 had a 54% 5-year disease-free survival. Those treated from 1983 to 1988 had a 69% 3-year disease-free survival (118).

In an attempt to confirm the preliminary good results of the T10 protocol, the Children's Cancer Group (CCG) undertook a single-arm trial of neoadjuvant chemotherapy that based the postoperative therapy on the histologic response of the preoperative chemotherapy. The protocol, CCG-782, accrued 268 patients with nonmetastatic osteosarcoma of the extremity between 1983 and 1986. Preoperative chemotherapy consisted of four courses of high-dose methotrexate and one course of bleomycin, cyclophosphamide, and dactinomycin. Good histologic responders (i.e., those with less than 5% residual viable tumor) were treated postoperatively with methotrexate, bleomycin, cyclophosphamide, dactinomycin, and doxorubicin. Poor histologic responders were treated with bleomycin, cyclophosphamide, dactinomycin, doxorubicin, and cis-platinum. The 8-year event-free survival was 53%. The overall survival rate was 60%. Good histologic responders had an 8-year postoperative event-free survival rate of 81% and a survival rate of 87%, whereas those with a poor histologic response had an 8-year postoperative event-free survival of 46% and a survival rate of 52% (82).

Pratt et al. (77) from St. Jude Children's Research Hospital, in studies open from 1973 to 1981, reported 76 patients who received doxorubicin, cyclophosphamide, and methotrexate at two different dosage levels after amputation. The actuarial 10-year survival was 46% and 56% for two chemotherapy protocols, compared with 18–25% for historic controls who received ineffective or no chemotherapy after amputation ($p < 0.001$).

Sequential chemotherapy trials were conducted at New York's Memorial Sloan-Kettering Cancer Center from 1976 to 1986. Patients received preoperative high-dose methotrexate with leucovorin rescue (some patients were randomized to additionally receive vincristine) and postoperative cyclophosphamide, bleomycin, doxorubicin, and actinomycin D. In recent years, patients who had a poor response to methotrexate

received doxorubicin and cis-platinum. The 10-year survival of 279 patients was 73%. As in the M. D. Anderson studies and other series, histologic response of the primary tumor to neoadjuvant chemotherapy was an important predictor of survival (41,75,76, 78,119–124).

The apparent successes of adjuvant chemotherapy trials were challenged by a research team at the Mayo Clinic. This group suggested that there might be a change in the natural history of osteosarcoma. Whereas the Mayo Clinic noted a 20% survival rate from ablative surgery in patients treated from 1963 to 1965, a comparable group treated from 1972 to 1974 without chemotherapy had a 50% overall survival rate (125). A randomized prospective trial reported by the Mayo Clinic Group showed that high-dose methotrexate as adjuvant therapy, in comparison to no chemotherapy, offered no benefit: Survival in both groups was 52% (120,126–128).

Two randomized prospective trials attempted to resolve the argument over the value of adjuvant chemotherapy. The University of California at Los Angeles (UCLA) trial randomized 59 patients with nonmetastatic osteosarcoma. All patients received preoperative doxorubicin. Thirty-two patients were randomized to receive adjuvant postoperative high-dose methotrexate, doxorubicin, bleomycin, cyclophosphamide, and actinomycin D. Twenty-seven patients received no adjuvant chemotherapy. Of the patients who received adjuvant chemotherapy, 55% remained disease free at a median of 2 years after excision of the primary tumor. Of the patients who received no adjuvant chemotherapy, only 20% remained free of disease ($p < 0.01$). Of 18 control patients treated before the trial, the overall disease-free survival was not significantly different from that of the 27 randomized control patients treated without chemotherapy from 1981 to 1984. Overall survival for randomized patients did not differ significantly between the two arms (130). When the larger group of patients who chose their therapy was combined with the randomized group, there was a significant overall survival benefit favoring chemotherapy at 6 years.

Link et al. (78,131–133) reported a randomized chemotherapy trial involving 36 patients. At 2 years, the actuarial relapse-free survival was 17% in the control group and 66% in the group receiving adjuvant cyclophosphamide, bleomycin, actinomycin, methotrexate with leucovorin rescue, doxorubicin, and cis-platinum ($p < 0.001$). A similar benefit to chemotherapy was observed among 77 patients who declined to undergo randomization but elected observation or chemotherapy.

The long-term results of the COSS-86 protocol included 171 eligible patients; 128 patients were stratified into the high-risk group. "Low risk" was defined as a tumor length of less than one third of the involved bone, less than 20% chondroid brown substance in the biopsy specimen, and more than 20% reduction of early- or late-phase activity in sequential bone scans. Other patients were considered to be at high risk. Doxorubicin, high-dose methotrexate, and cis-platinum were given to all patients. Patients who met one of the high-risk criteria received early systemic treatment intensification with ifosfamide added as a fourth agent. Postoperatively, the high-risk patients received cis-platinum intra-arterially or intravenously. In the total group of 171 patients, which included the high- and low-risk patients, overall event-free survival rates at 10 years were 72% and 66%, respectively. No benefit from intra-arterial cis-platinum was seen (134).

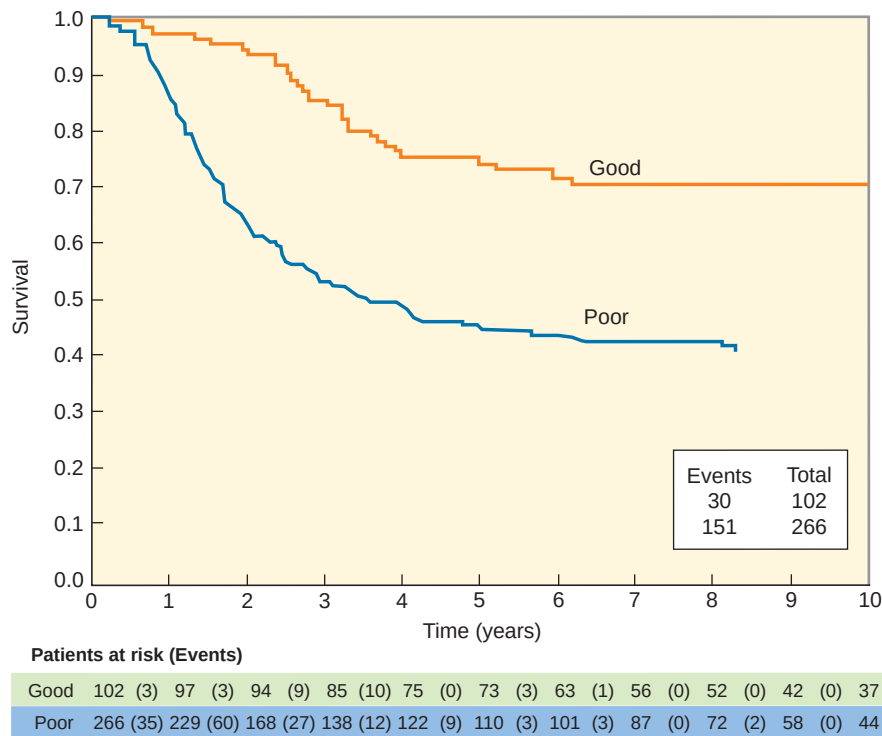


Figure 10.6 A Kaplan–Meier survival curve for patients in two consecutive trials of the European Osteosarcoma Intergroup shows improved survival for patients with at least 90% necrosis after preoperative chemotherapy ($p < 0.01$ with one degree of freedom). (From Hauben EI, Weeden S, Pringle J, et al. Does the histological subtype of high-grade central osteosarcoma influence the response to treatment with chemotherapy and does it affect overall survival? A study on 570 patients of two consecutive trials of the European Osteosarcoma Intergroup. *Eur J Cancer*. 2002;38(9): 1218–1225, with permission.)

A randomized trial of two chemotherapy regimens in operable osteosarcoma was conducted by the European Osteosarcoma Intergroup and reported in the *Lancet* in 1997 (135). Patients with operable, nonmetastatic osteosarcoma were randomly assigned to receive doxorubicin and cisplatin preoperatively or alternatively vincristine, methotrexate, and doxorubicin preoperatively and bleomycin, cyclophosphamide, dactinomycin, vincristine, methotrexate, doxorubicin, and cis-platinum postoperatively. Of the 407 randomized patients, 391 were eligible and were followed up for at least 4 years. The proportion showing more than 90% tumor necrosis in response to preoperative chemotherapy was about 29% in both regimens and was a strong predictor for survival. Overall survival was 65% at 3 years and 55% at 5 years in both groups. Thus, there was no difference between the two-drug and multidrug regimens. The two-drug regimen was shorter in duration and better tolerated (135).

A recently published trial by the Children's Oncology Group (COG) randomized patients to one of four arms: a three-drug regimen (cis-platinum, doxorubicin, methotrexate), a four-drug regimen (cis-platinum, doxorubicin, methotrexate, ifosfamide), the three-drug regimen plus muramyl tripeptide (MTP), and the four-drug regimen plus MTP (136). The addition of ifosfamide did not enhance event-free survival or overall survival. The addition of MTP significantly improved 6-year overall survival (from 70% to 78%) and resulted in a trend toward better event-free survival.

Currently the COG, COSS, EORTC/MRC, and SSG are conducting a Phase III trial to optimize treatment strategies for respectable osteosarcoma based on histological response to preoperative chemotherapy. The induction chemotherapy is with methotrexate, doxorubicin, and cis-platinum (MAP). Randomization occurs after surgery and assessment of histologic response. Patients with good histologic response

are randomized to receive either MAP or MAP + ifosfamide (MAPifn) and etoposide. Patients with poor histologic response are randomized to receive either MAP or MAP + pegylated interferon alfa-2b (MAPIE).

In Table 10-7, we summarize studies by several cooperative groups. The data indicate that surgery plus modern chemotherapy should achieve a 60–70% 5-year event-free survival (Figs. 10-6 and 10-7). It is not clear that neoadjuvant chemotherapy is superior to postoperative chemotherapy.

RADIOTHERAPEUTIC TECHNIQUE

Dosage

Osteosarcoma has a reputation of being radioresistant. However, this reputation is unjustified. Because radiotherapy was formerly used to treat bulky tumors, it is no surprise that local failures were common. The D_{50} values of human and rodent osteosarcoma cell lines are reported to be similar to those of most other mammalian tumors, perhaps with a higher D_q (67,137).

Canine osteosarcoma has been treated with a variety of dosage and fractionation schemes including 8 Gy three times at 0, 7, and 21 days and 8 Gy four times at 0, 7, 14, and 21 days. Radiotherapy is generally used to palliate the dog's pain and dysfunction. High response rates are achieved, albeit with short follow-up because most animals are euthanized for metastatic disease (137).

In a dose-response study of patients treated with the Cade technique, Gaitan-Yanguas (63) produced uniform tumor sterilization with dosages of 80–100 Gy and always found persistent tumor at 50 Gy or less. Phillips and Sheline (67) found viable tumor in 1 of 10 patients receiving less than 100 Gy and in 2 of 7 patients receiving at least 100 Gy.

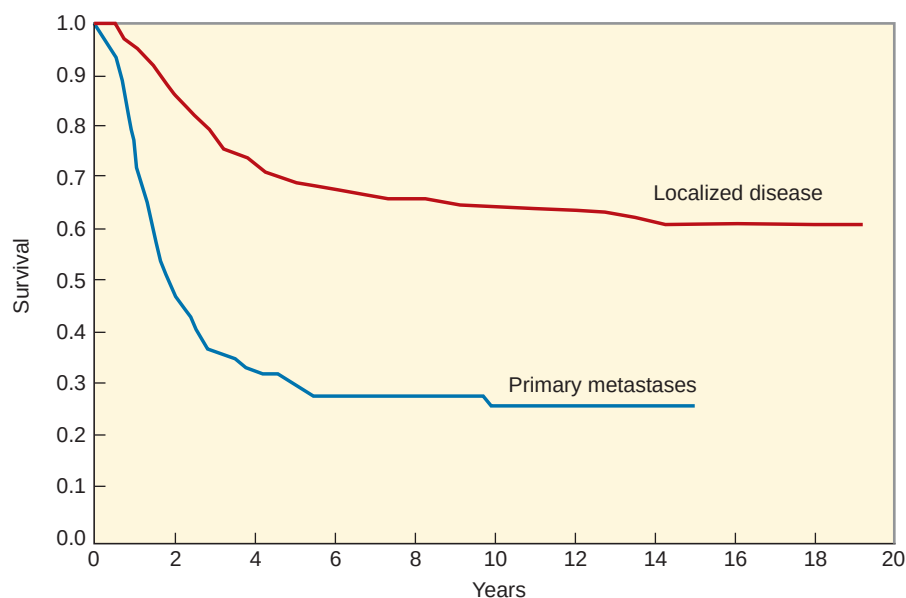


Figure 10.7 Overall survival for patients with localized disease, compared with those with metastases at diagnosis, in patients treated on Cooperative German–Austrian–Swiss Osteosarcoma Group protocols. (From Bielack S, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1702 patients treated on Neoadjuvant Cooperative Osteosarcoma Study Group protocols. *J Clin Oncol.* 2002;20:776–790, with permission.)

Lombardi et al. (138) administered 36 Gy at 6 Gy per fraction, with three fractions per week for 2 weeks to 21 osteosarcoma sites irradiated for palliation in 14 patients. There was a clinical response (disappearance of pain, decrease in tumor size, improvement in function) or radiologic response at 18 of the 21 sites. Of eight primary sites irradiated because of synchronous metastases, all showed a clinical or radiographic response. In five patients, radiotherapy was given where preoperative chemotherapy had not rendered the patient suitable for limb-sparing surgery. Surgery after radiotherapy revealed 95–100% tumor necrosis in all cases. Limb-sparing surgery was performed in three of five cases, but because of infectious complications related to soft tissue damage, all limbs were amputated eventually.

Caceres et al. (41) from Peru gave 60 Gy in 6 weeks to 15 patients in conjunction with chemotherapy. Postradiotherapy biopsy showed no evidence of active tumor in 12 of 15 (80%) patients. The whole specimen was studied, because of amputation or autopsy, in five patients. No viable tumor was found. Complications were common, including pathologic fracture, soft tissue fibrosis or necrosis, local infection, and moist desquamation. The degree of tumor necrosis seen by Caceres et al. is inconsistent with an earlier report from the same group of less impressive tumor destruction after 80–120 Gy at 10–12 Gy per fraction (Table 10.6) (61). If radiotherapy is to be used alone as definitive treatment for a small (less than 5 cm) osteosarcoma in an unresectable location such as the base of skull or vertebral body, or if a patient refuses surgery, the dosage should be as high as normal tissue tolerance allows, that is, 60–75 Gy at conventional fractionation with progressive shrinking-field technique (139,141).

When radiotherapy is used for prophylactic treatment of the lungs, the dosage is 13.5–19.5 Gy at 1.5 Gy per fraction. These dosages generally have been reported without lung correction factors being applied (29,104,142,144).

Volume

The treatment volume is determined by plain radiographs, bone scan, CT, and MRI. It is customary to define the tumor

volume based on the largest volume of these studies (the “worst-case volume”). A margin is then allowed.

Prophylactic WLI is directed to the entire substance of the lung. Particular attention must be paid to coverage of the apices of the lung and to the areas of the lung that curve over the surfaces of the diaphragms.

Technique

An immobilization device is generally needed. The field should be contoured specifically to the anatomic problem for the individual patient. In most cases, multiple fields are used. To maintain a functional limb after irradiation, a strip of skin should be spared, and one should avoid high-dose irradiation to the full width of the joint.

Some investigators have attempted to improve the local control rates of osteosarcoma by altering tumor and normal tissue oxygenation. Of historical interest, the tourniquet technique attempted to produce anoxia in both tumor and normal limb tissues to remove any advantage the tumor might gain from hypoxic areas. Using this technique, patients received fractionated irradiation up to total dosages of 75–160 Gy. In patients who were long-term survivors, the functional result was poor (122). One group reported local response rates of approximately 70% and reasonable limb function with tourniquet anoxia and high-dose-per-fraction treatment (i.e., three doses of 25 Gy). Radiation treatment under hyperbaric oxygen conditions was also investigated (81). A group of investigators from Stanford University reported a series of patients who had unresectable osteosarcomas or who refused amputation, treated with 42–48 Gy at 6 Gy per fraction, one fraction every 5 days, and pulsed 5'-bromodeoxyuridine infused as a radiosensitizer (71). Local control was achieved in seven of nine patients, four of whom were long-term survivors. Significant soft tissue injury occurred in five patients (74).

Neutron Therapy

Neutrons are a form of high linear energy transfer radiation. They offer several advantages over conventional photon or

electron radiotherapy. First, neutrons are better able to kill hypoxic cells than photons. The oxygen enhancement ratio for neutrons is on the order of 1.6, compared with 2.5–3.0 for photons. Second, repair of radiation-induced sublethal and potentially lethal damage is less readily accomplished after neutron irradiation than after conventional irradiation. Third, neutrons are toxic throughout the phases of the cell cycle (M, G1, S, G2), whereas photons are more toxic in late G2/M (145,146).

Kubota et al. (137) compared the biologic effects of 13-MeV neutrons with those of ^{137}Cs gamma rays in MG-63 human osteosarcoma cells in plateau phase growth and in multicellular spheroids. The relative biologic effectiveness varied slightly with the measurement technique but was in the range of 1.9–2.29. If one accepts the assertion that osteosarcomas are rapidly growing tumors with areas of necrosis and potentially hypoxic areas and that they are resistant to photon irradiation, then one might conclude that they would be more effectively irradiated by neutrons.

There is a small clinical experience with the use of neutrons for local control of osteosarcomas. Many of the patients treated had inoperable tumors or refused amputations (147). The results of neutron treatment are shown in Table 10.9. The 77 patients cited have an overall local control rate of 44 of 77 (58%). Clearly, there are risks from combining the results of 11 series to draw a conclusion. The local control rates of the individual series range from 0% to 100%, and these series include patients with tumors at a variety of locations. Dense fibrotic reactions can occur after neutron treatment, leading to severe complications and, in some patients, to amputation (152,153). For a patient with osteosarcoma who refuses definitive surgery or is medically or technically inoperable, it is reasonable to consider the use of neutrons. However, part of the informed consent for such treatment must include a discussion of the potential for serious late ill effects of such treatment.

Charged Particle Therapy

Osteosarcoma of the skull base and axial skeleton pose a particularly difficult problem for the pediatric radiation oncologist. These tumors are more difficult to extirpate at surgery. An initial gross and microscopic tumor resection is inhibited by the proximity of brainstem, spinal cord, cranial nerves, nerve roots, or vessels. However, these normal tissue structures also prevent the oncologist from using radiation as an alternative to surgery because tumoricidal dosages for osteosarcoma exceed the tolerance of critical neural tissue (156). Although three-dimensional or intensity-modulated treatment planning with multiple noncoplanar photon beams may be used in an attempt to achieve an acceptable dosage distribution, the penetrance and divergence of photons present significant limitations.

Protons and other charged particle beams (such as neon, helium, and carbon ions) have a finite dosage range with steep dosage fall-off beyond the Bragg peak. This property engenders a treatment beam that has little exit dosage beyond the deposition of energy in the target volume, making these beams distinctly different from photons. The advantage of protons resides solely in this physical difference because proton beams have no significant biologic advantage over megavoltage photons. Other charged particle beams have both the advantage

of rapid Bragg peak dosage fall-off and an increase in relative biologic effectiveness (137) (Fig. 10-8). Charged particles can be used to shape a dosage distribution around an osteosarcoma of the skull base or vertebral body with the possibility of maintaining the dosage to the adjacent brain or spinal cord within acceptable limits.

The Radiation Oncology Department at the Massachusetts General Hospital, in collaboration with the Harvard Cyclotron Laboratory, treated 15 patients with osteosarcoma with combined proton and photon irradiation (anatomic sites were base of skull, 7; cervical spine, 3; lumbar spine, 2; sacrum, 3). Dosages of 61.1–80 cobalt Gray equivalent were administered, and 14 of the 15 patients also received chemotherapy. At 5 years, the actuarial local control rate was 59% and the overall survival rate was 44% (156). In a series that includes skull base tumors of various histologies, Castro et al. (157) reported that 20% of disease-free survivors after charged particle therapy had grade III, IV, or V complications such as cranial nerve or vascular injuries. Investigators in Chiba, Japan, after conducting an initial Phase I/II trial with carbon ions (158), are treating patients with bone (including osteosarcoma) and soft tissue sarcomas to 52.8–73.3 GyE in 16 fractions with an overall 5-year local control rate of 81% (159).

Intraoperative Therapy

A combined specialty team at the Universidad de Navarra, Spain, treated 22 patients with osteosarcoma with preoperative chemotherapy, surgical excision, a 15–20 Gy intraoperative radiation therapy (IORT) electron beam boost to the tumor bed area, and postoperative chemotherapy (73). Five patients also received preoperative and postoperative external beam radiotherapy. There was only one local recurrence among the 22 patients, with a median follow-up of 18 months. Local recurrence after definitive surgery for osteosarcoma is uncommon, and it is not clear that the IORT was helpful.

An additional 32 patients with osteosarcoma were treated with IORT by Yamamuro and Kotoura (162). Before 1984, treatment consisted solely of exposing the primary tumor site and administering 50–60 Gy of IORT with 12–26 MeV electron beams. After 1984, patients received cisplatin and doxorubicin in combination with IORT. The clinical results from this small series, spread out over many years (1978–1990), must be interpreted with caution. Ten patients underwent limb amputation or prosthetic replacement 2–10 months after IORT. Eight patients had complete necrosis of the tumor cells throughout the specimen except for a “few scattered, markedly altered, presumably nonviable tumor cells in small clusters” (162). Two patients showed local regional tumor recurrence in nonirradiated areas, and one showed recurrence in the radiation field (a juxtacortical osteosarcoma). Joint function was reported as being satisfactory; five patients had some evidence of moderate to severe skin necrosis, but “among the patients who underwent neither limb amputation nor prosthetic replacement and survived longer than 1 year after IORT, about 58% sustained pathologic fracture through the lesions. All attempts of osteosynthesis failed to fuse the fracture site” (162).

Oya, Tsuboyama, and colleagues (163,165) from Kyoto University in Japan described 39 patients with osteosarcoma

Table 10.9 Literature Review of the Local Control Rates for Osteosarcomas After Neutron Therapy				
Year of Report	Reference	Reporting Institution	Number of Patients	Local Control
1980	155	Texas A&M Variable Energy Cyclotron	1	0/1
1981	160 ^a	Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands	3	0/3
1982	161	National Institute of Radiological Sciences, Chiba, Japan	41	33/41
1984	152	Fermilab, Batavia, Illinois	9	2/9
1986	153	Western General Hospital, Edinburgh	5	1/5 ^a
1989	146	University of Washington, Seattle	3	3/13 ^b
1994	164 ^a	Centre Hospitalier d'Orléans, France	4	4/4 ^c
1994	175	Beijing Medical University	5	1/5 ^c
2002	84	Cooperative Osteosarcoma Study Group	1	1/1
2003	85	Cooperative Osteosarcoma Study Group	2	0/2

MANTA, Mid-Atlantic Neutron Therapy facility.
^aA persistent mass and calcification were considered a local failure. For this reason, local control rates may be underestimated.
^bThese are 2-year actuarial data.
^cThese patients received combined local therapy with photons and neutrons.
Based on material found in the cited references and on Refs. 145–147.

of the extremities who were treated with definitive IORT. The tumor and a margin were treated with 45–80 Gy of electrons or x-rays in a single fraction while major vessels and nerves were retracted out of the treatment field. Nine local recurrences developed in these 39 patients. Eight were considered to be marginal recurrences or occurrences from unirradiated surrounding normal tissue. Complications included associ-

ated transient skin reaction attributable to radiation and two cases of mild peroneal palsy, possibly caused by irradiation. PostIORT fractures occurred in 13 patients. The problem seems to have been solved by the use of preventive nailing in more recent patients.
These series must be interpreted cautiously. It is possible that IORT, in combination with surgery and chemotherapy, may

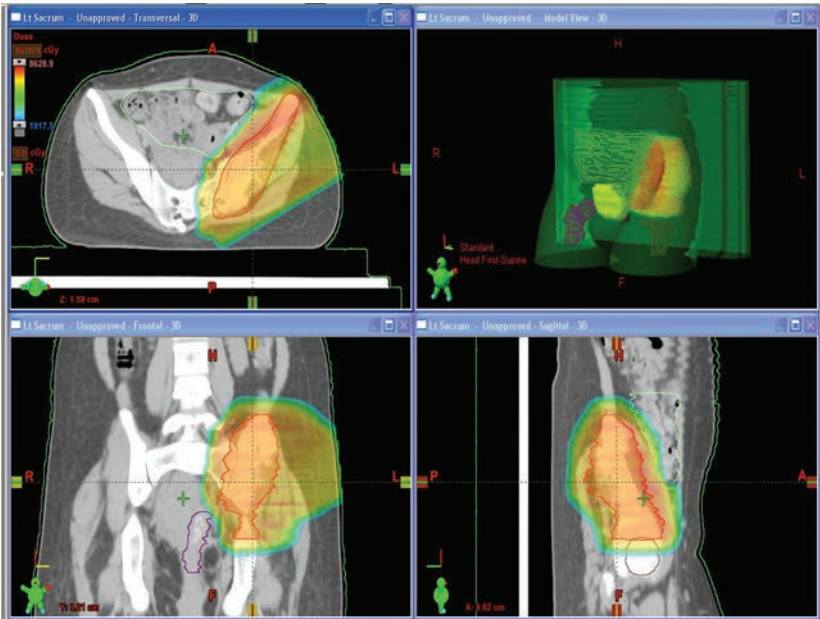


Figure 10.8 Proton radiation dose distributions for a large pelvic osteosarcoma. Note the sparing of most pelvic organs and the contralateral pelvic bones (bone marrow).

reduce the already low local recurrence rate for most cases of osteosarcoma. This is a testable hypothesis. The use of IORT as the definitive local control measure, as described by Yamamuro and Kotoura (162), must be considered investigational therapy with, apparently, a high risk of subsequent fracture.

Radioisotope Therapy

Bone-seeking radiopharmaceuticals are at an early stage of investigation in the treatment of osteoblastic osteosarcoma. The uptake of radiopharmaceuticals in adult skeletal metastatic lesions such as breast and prostate cancer results from an osteoblastic response in the normal bones surrounding the metastases. However, osteosarcoma often produces bone matrix within the target. A radioisotope that hones into bone and gives off radioactivity for a sufficiently long period of time may produce a therapeutic benefit.

Samarium-153 ethylene diamine tetramethylene phosphonate is a bone-seeking radiopharmaceutical. It is produced by neutron capture from ^{153}Sm to yield a radioisotope of high purity that has both a medium-energy beta emission for therapeutic purposes and gamma emission, which is useful for conventional gamma camera scintigraphic imaging. Compared with technetium-99m methylene diphosphonate preparations, which are used for routine bone imaging, ^{153}Sm has comparable or better bone:blood and bone:muscle ratios. Because of these favorable bone-seeking characteristics, ^{153}Sm has been used for palliative treatment of bone metastases (166).

In pilot studies of the use of ^{153}Sm to irradiate patients with osteosarcoma and bone metastases, all patients receiving high-dose samarium experienced severe pancytopenia and some needed transfusions. Stem cell infusion was needed. It appears that samarium treatment can reduce bone pain in some patients, albeit with significant toxicity. There also appears to be one long-term survivor, a patient with a large pelvic osteosarcoma and multiple primary pulmonary metastases who was treated with external beam radiotherapy to the pelvic lesion, multiagent chemotherapy, and samarium (166,167–170).

Fourteen patients with metastatic, unresectable, progressive, and/or recurrent osteosarcoma received high-dose ^{153}Sm (30 mCi/kg) and gemcitabine chemotherapy and peripheral stem cell rescue (172). Indicator lesions were improved on imaging in 8 of 14 patient, and alkaline phosphatase decreased in 6 of 8 patients. The investigators noted temporary lymphopenia but did not find significant nephrotoxicity or hemorrhagic cystitis. One patient with multiple lung metastases developed life-threatening pulmonary hemorrhage.

Palliation

It is reasonable to consider radiotherapy to palliate painful bony sites and treat spinal cord compression (Fig. 10-9) (64,65, 138,173). Unfortunately, the literature documenting the palliative efficacy of radiotherapy in osteosarcoma is sparse. The 1963 report by Lee and MacKenzie (66) of the Westminster Hospital, London, describes the results with the administration of 7000–8000 R with a 2-MeV Van de Graaff electrostatic generator. The authors note that “clinical response of the tumour was very variable. Sometimes there was apparent worsening: there might be sudden increase in the size of the tumor, with more pain. Such changes might be the result of hemorrhage, or fracture, or disintegration of bone. More often there was a gradual reduction of pain and

swelling, starting after some 2,000 R (sometimes much later) and continuing for several weeks after completion of treatment” (66). In 1975, deMoor (174) from Johannesburg described the use of radiation for palliation and noted that “pain relief or reduction in swelling was experienced generally, and often within the first 2–3 weeks of treatment.”

The series of Beck et al. (134) from the University of California at San Francisco included 44 patients with adequate information “to assess whether the treatment represented even a short-term subjective gain for the patient. In 19 patients (43%) there was definite palliation. Twenty-five patients (57%) had either no change or worsening of symptoms. Those who survived experienced relief only after surgery.” These authors used conventionally fractionated radiation with total dosages ranging from 5000 to 8000 cGy. In contrast, Lombardi et al. (138) administered 6 Gy three



Figure 10.9 When osteosarcoma metastasizes to bone, radiotherapy may be used for palliation. This 9-year-old boy presented with osteosarcoma of the left femur. Bone metastases were diagnosed a year and a half after the primary tumor was identified. When the child complained of pain in the spine, both magnetic resonance imaging and bone scan identified metastatic disease in conjunction with pulmonary metastasis. For spinal cord compression, palliative radiation therapy was administered.

times per week for a total of 36 Gy in six fractions over 2 weeks. In 14 patients with 21 evaluable sites, there was a clinical response in 18 (86%).

Machak et al. (86), describing 31 patients treated with curative intent with chemotherapy, reported “a clinical response and limb function restoration” in 24 of the 31 (77%) of patients but a good imaging and biochemical response in only 11. Of the 20 nonresponders, 15 (75%) improved after radiotherapy, supporting a palliative role for radiotherapy.

Mahajan et al. (176) recently reported a series of 39 patients with metastatic and/or recurrent osteosarcoma who were treated with radiation therapy (median dose 30 Gy in 10 fractions) and concurrent chemotherapy (most commonly ifosfomide or methotrexate). Subjective improvement occurred in 76% of painful sites. Sustained reduction of standard uptake values in positron emission tomography (PET)-CT scans or bone scans occurred in 72% of the patients. In this report the actuarial 4-year survival from the development of metastasis was 39%. Thus a substantial number of patients could have their painful bony sites palliated with a combination of short-course radiation and concurrent chemotherapy.

Chordoma and Chondrosarcoma

Chordoma is a rare tumor originating from the embryonal notochord and usually arises from the skull base, spine, and sacrum. Microscopically the tumor is pseudoencapsulated

and comprised of uniform cells that contain eccentric nuclei with dense chromatin as well as cytoplasmic vacuoles (physaliferous cells). The cells are usually immunopositive for cytokeratin, epithelial membrane antigen, S-100, and vimentin (Fig. 10-10). The histological subtypes include conventional, chondroid, and dedifferentiated. Children have a higher tendency than adults to present with atypical or dedifferentiated chordomas.

Chondrosarcoma originates from primitive mesenchymal cells or the embryonic rest of cartilaginous matrix of the cranium, and usually involves the long bones, pelvis, and, less commonly, head and neck including the base of skull (sometimes associated with Ollier syndrome). The histological subtypes include classic, mesenchymal, and dedifferentiated. Classic chondrosarcomas are divided into grade I, II, or III based on cellularity, nuclear size, mitotic rates, and the amount of chondroid matrix. Immunochemical stains are negative for cytokeratin and epithelial membrane antigen but positive for S-100 and vimentin. Constitutive activation of Hedgehog-mediated signaling has been implicated in the pathogenesis (177).

Treatment

The primary treatment for chordomas is surgery. Post-operative radiation therapy is generally necessary to reduce recurrence. In adults the results of proton therapy appear better than that of photon therapy, probably because of the

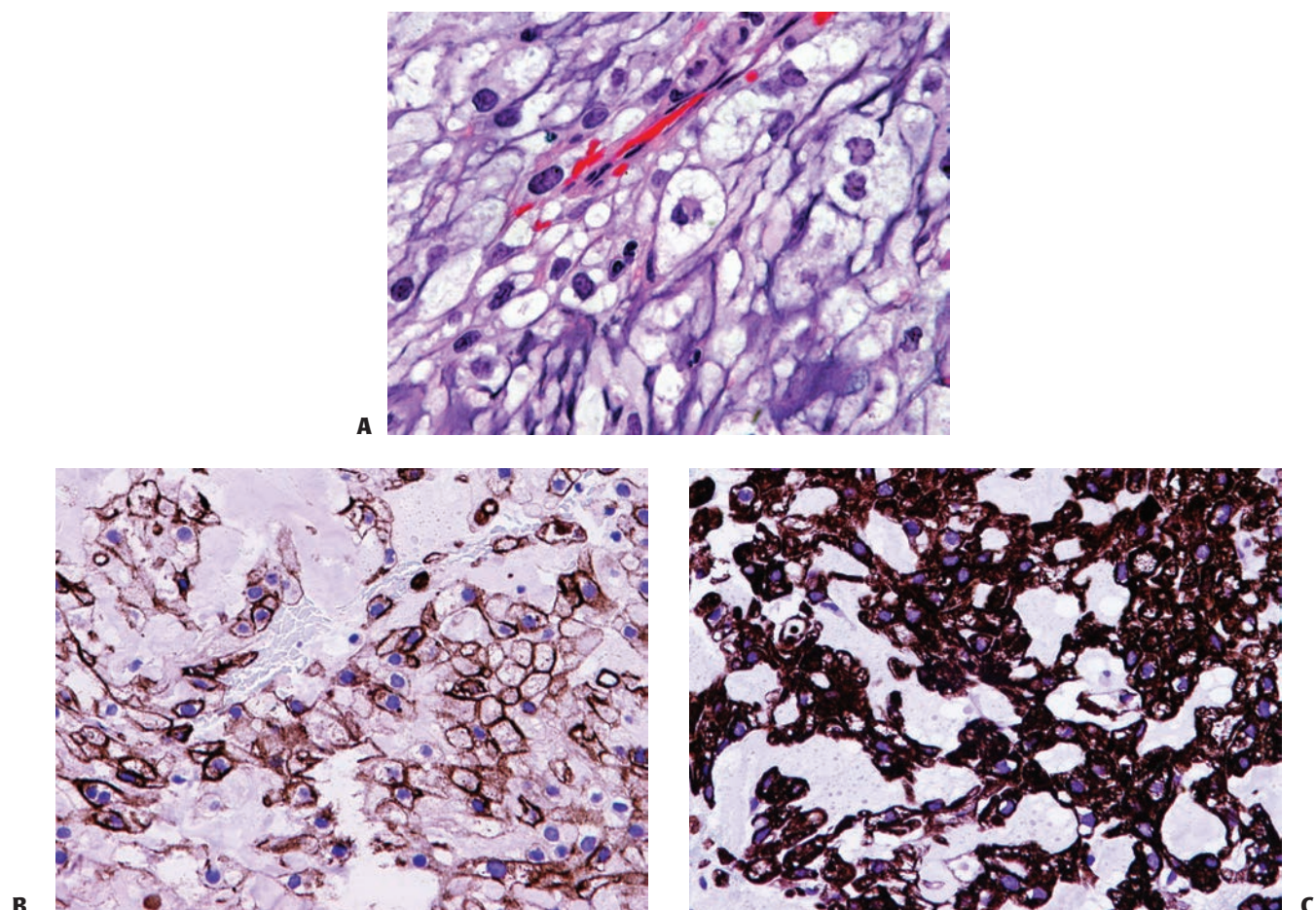


Figure 10.10 Histopathology of chordoma. Note the physaliferous cells (A) and the triad of positive immunohistochemical stains for keratins, EMA (B), and S-100 (C) proteins.

higher radiation dose delivered. In children, a small series reported 60% local control after passive-scattered proton therapy to doses ranging from 50.4 to 78.6 CGE (178). Another small series using scanning proton therapy to 74CGE reported no recurrence after a median follow-up time of 36 month (179). Late side effects including neurological deficits and pituitary insufficiency have been reported up to 30% of the patients. Recently a small series of children and young adults with skull base chordomas treated with carbon ion radiotherapy has been reported (180). With a median follow-up of 49 months, one out of seven patients with chordomas recurred. The value of chemotherapy is unclear.

Surgery is also the primary treatment for chondrosarcomas. Completely resected grade I chondrosarcomas do not need adjuvant treatment. Postoperative radiation therapy is usually offered to patient with higher grade or more malignant chondrosarcomas such as mesenchymal chondrosarcomas. For skull base chondrosarcomas treated with protons (scattered or scanning) the local control rates were 70–100% (178,179), and with carbon ion therapy the local control rate was reported as 100% (180). Mesenchymal chondrosarcoma is considered a malignant sarcoma in children. The Cooperative soft tissue sarcoma (CWS) and osteosarcoma (COSS) Study Groups of the German Society of pediatric Oncology and Hematology (GPOH) reported the result on 50 children and adolescents (median age 16.6 years) (181). All tumors were resected; 13 patients received chemotherapy and 6 patients received radiation therapy. The actuarial 10-year event-free and overall survival rates were respectively 53% and 67%. Seven of eight patients whose tumors were completely resected versus four of seven patients whose tumors were incompletely resected survived disease-free. One patient with local recurrence was salvaged after further surgery and radiation therapy.

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Rhabdomyosarcoma

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Rhabdomyosarcoma (RMS) is a highly malignant neoplasm that arises from embryonal mesenchyme with the potential for differentiating into striated muscle. Although the cells show differentiation along rhabdomyoblastic lines, RMS is not limited to cells with recognizable muscle cross-striations (1,2). Weber initially described RMS in 1854, but progress in our understanding of this complex neoplasm accelerated with Stout's landmark descriptive series in 1946 and the delineation by Horn and Enterline in 1958 of the four classic forms of RMS (3–5). RMS can arise almost anywhere in the body, is locally invasive, and rapidly disseminates early in its course. Near the beginning of the 20th century, the only cures were accomplished with radical surgery in the few fortunate children without metastases. Significant disfigurement and loss of function were common sequelae. High-dose radiation therapy (RT) increased the potential for local control but caused a different set of morbidities (6,7). As chemotherapy has become increasingly effective in eliminating micrometastatic disease and assisting in local control, the need for aggressive surgery and large-volume irradiation has diminished, although surgery and RT still play pivotal roles in the curative treatment of RMS (8). Overall survival rates have concomitantly increased from 15–25% to more than 70% (9–12).

RMS is a rare tumor with clinical and biologic heterogeneity. Consequently, multi-institutional trials were necessary to develop and refine treatment approaches. North American investigators of the Intergroup Rhabdomyosarcoma Study Group (IRSG) have played a paramount role in this progress, now in its sixth generation of protocols. The difficulty of this undertaking is clear in view of the myriad sites, stages, and histologies of RMS that are associated with different natural histories and prognoses (13). Beyond this, advances in imaging, changes in endpoints, and the need for mature data all increased the difficulty in conducting and comparing randomized, controlled clinical studies of patients with RMS. With this view, the IRSG was established through the collaboration of three multidisciplinary cancer treatment study groups (Cancer and Leukemia Group B, Children's Cancer Study Group, and the Pediatric Branch of the Southwest Oncology Group, which later became the Pediatric Oncology Group). Intergroup Rhabdomyosarcoma Study I (IRS-I) was open for patient entry from 1972 to 1978 (9). With an overall 5-year survival rate of 55% in IRS-I, IRS-II was designed to improve survival for the patient subgroups with poor outcomes and to refine treatment for the remaining

patients (10). IRS-II ran from 1978 to 1984, IRS-III from 1984 to 1991, IRS-IV from 1991 to 1997, and IRS-V from 1997 to 2005–2006. Although the previous generations of IRS studies were based on a surgically oriented clinical grouping system dependent on the tumor that remained after initial surgery, IRS-IV and IRS-V were based on a more biologically oriented staging system, discussed later in this chapter. These studies, each based on the results of its predecessor, have provided a database of over 4000 patients. The IRSG studies are now conducted through the Children's Oncology Group, the United States–based cooperative research network that formed from the merger of the Pediatric Oncology Group and the Children's Cancer Study Group. The current generation of studies opened in 2005–2006, upon the completion of IRS-V. Other multi-institutional group studies have also provided important data (14–17). Of particular note are the European-based International Society of Pediatric Oncology (SIOP) and the United Kingdom–based Children's Solid Tumor Group (CSTG) (15–17). Finally, many single-institution studies have also been quite informative regarding RMS (7,8,18,19). Progress in treating RMS is exemplified by the improvement in overall 5-year survival in the IRS studies: 55% in IRS-I, 63% in IRS-II, and 71% in IRS-III (Fig. 11.1) (9–11,20). Early results from IRS-IV show an overall 3-year survival rate of 86% for patients with nonmetastatic disease and 39% for patients with metastatic disease (12,21).

EPIDEMIOLOGY

RMS accounts for about 3.5% of all malignant disease in children younger than 15 years of age and 2% of cancer cases among adolescents and young adults 15–19 years old (22,23). RMS is the most common soft tissue sarcoma of childhood, representing about half of this otherwise very heterogeneous group of tumors. The annual incidence of RMS is 4.4 per million in white children and 1.3 per million in black children. There is a slight male predominance (1.4:1). Seventy percent of cases occur before the age of 10 years, with a peak incidence at 2–5 years of age (Fig. 11.2). Congenital anomalies have been identified in as many as one third of children with RMS, most commonly involving the gastrointestinal, genitourinary, cardiovascular, and central nervous systems (24).

Although the majority of cases of RMS occur sporadically, a small proportion is associated with genetic conditions, including the Li–Fraumeni syndrome (in which germ line mutations of p53 exist), neurofibromatosis type 1, Costello

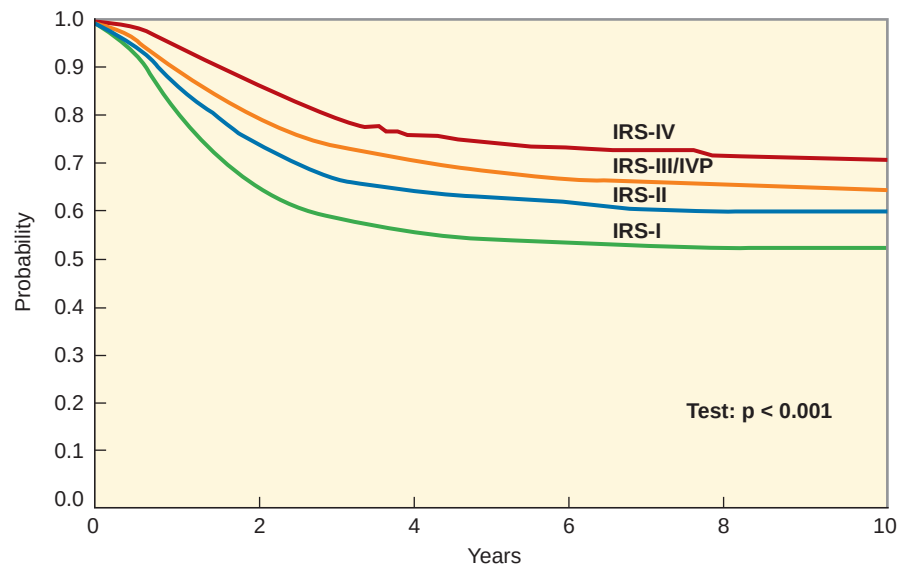


Figure 11.1 Improvement in 5-year survival of children with RMS treated on the IRS trials. (From Wexler L, Meyer WH, Helman LJ. Rhabdomyosarcoma and the undifferentiated sarcomas. In: Pizzo P, Poplack D, eds. *Principles and Practice of Pediatric Oncology*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006:988, with permission.)

syndrome, Noonan syndrome, and Beckwith–Wiedemann syndrome (25–28).

BIOLOGY

Although the origin and genetics of RMS remain unclear, clinical observations can provide direction for additional understanding of this tumor. If we can determine the tumor

characteristics that predict radiochemotherapy responsiveness or, conversely, tumor resistance to therapy and a propensity to disseminate, then we can select the patients in whom more or less toxic therapy should be used. Moreover, we may devise novel biologic maneuvers to treat such tumors that minimize normal tissue damage. Reducing the toxicity of therapy becomes increasingly important as the cure rate continues to improve. Areas in which progress has been made

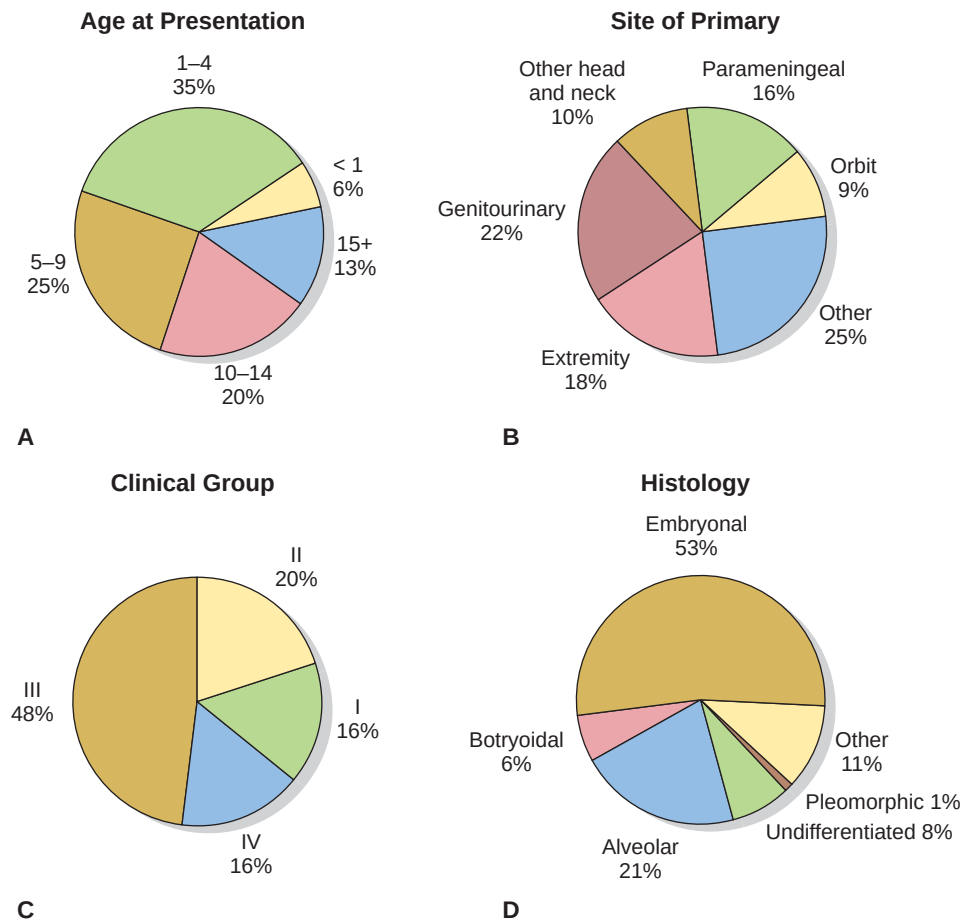


Figure 11.2 Clinical features of RMS from IRS-I, IRS-II, and IRS-III pooled data. **A:** Age at presentation; **B:** site of primary tumor; **C:** clinical group; **D:** histology. (Modified from Wexler L, Meyer WH, Helman LJ. Rhabdomyosarcoma and the undifferentiated sarcomas. In: Pizzo P, Poplack D, eds. *Principles and Practice Pediatric Oncology*. Philadelphia, PA: Lippincott-Raven; 2006:976, with permission.)

include the genetic control of myogenesis, tumor suppressor genes, and molecular diagnostics (29,30).

Cytogenetics

Alveolar RMS is usually characterized by one of two translocations, both of which involve the *FKHR* gene on chromosome 13 (29,30). The most common translocation, t(2;13) (p35;q14), fuses the *PAX3* gene, a transcription regulator, to the *FKHR* transcription factor. This translocation is present in about 60% of children with alveolar RMS. The less common translocation, t(1;13)(p36;q14), fuses the *PAX7* transcription regulator to *FKHR* and is involved in about 20% of cases. This latter translocation seems to occur in younger patients and to be associated with a higher event-free survival rate than the *PAX3* gene rearrangement. Approximately 20% of alveolar RMS does not have either translocation. The specific translocations (or lack thereof) do not appear to correlate well with histologic features (31). In the future, monitoring for these fusion products with sensitive techniques such as reverse transcriptase polymerase chain reaction may be useful for detecting minimal residual disease during or after treatment, and for guiding therapy (32,33).

Embryonal RMS often is characterized by loss of heterozygosity at 11p15.5, suggesting the presence of a tumor suppressor gene (34).

Genomic amplification also differs in alveolar and embryonal RMS. It is rare in embryonal RMS, whereas gains of whole chromosomes (particularly of chromosomes 2, 8, 12, and 13) and hyperdiploidy are common (35–38). In alveolar RMS, gene amplification is common, as is near-tetraploidy.

Cell Cycle Control

Myogenesis involves differentiation of the mesenchymal fibroblast into skeletal muscle and is under the control of a series of gene products including the MyoD protein family (myogenin, MYF5, and MYF6) (39). These gene products also halt cell cycling. Expression of the MyoD proteins, which can be determined by an anti-MyoD antibody, has demonstrated that malignant cells have characteristics of skeletal muscle differentiation and therefore represent RMS. It is possible that some tumor suppressor factor is present in the normal fibroblast that, when combined with the RMS cell and the MyoD gene product, can drive the cell toward differentiation and halt cell proliferation.

Proto-Oncogenes

The *myc* gene can contribute to uncontrolled cell proliferation via several pathways including insertion mutations, translocations, retroviral transductions, and amplification. Two reports involving 20 patients showed that 50% of those with alveolar RMS had n-*myc* amplification, in contrast to its uniform absence in patients with embryonal RMS (40,41). Impressively, among the patients with alveolar RMS, n-*myc* amplification predicted a fatal outcome.

Tumor Suppressor Genes

Tumor protein p53 mutations can be demonstrated in a significant proportion of childhood RMS (42). In the presence of damaged DNA, normal p53 produces G1 arrest and prevents the cell with damaged DNA from undergoing any proliferation. In

conjunction with *myc*, p53 drives such damaged cells toward apoptosis. This might explain why some forms of RMS, which escape cure by radiochemotherapy, become progressively more virulent: they generate resistant clones of tumor cells.

CLINICAL PRESENTATION

RMS occurs in any anatomic location where there is skeletal muscle and in some locations where skeletal muscle is not normally found (Fig. 11.2) (10). The most common locations are the genitourinary sites and the head and neck. Genitourinary sites include the bladder, prostate, vagina, uterus, urethra, and paratesticular region. Head and neck lesions are divided into parameningeal sites (nasopharynx, nasal cavity, paranasal sinuses, middle ear and mastoid region, infratemporal fossa, and pterygopalatine and parapharyngeal areas) and other head and neck sites (parotid region, cheek, masseter muscle, oral cavity, oropharynx, larynx, hypopharynx, scalp, face, and pinna) (43).

RMS commonly presents as a mass with poorly defined margins, but specific presentations relate to the primary disease site. A mass in the genitourinary system may cause urinary tract or rectal obstruction. On occasion, the mass may protrude from the cervix, vagina, or urethra. When the protruding tumor has the gross appearance of a cluster of grapes, it is called botryoid (grapelike) sarcoma. Prostate and bladder RMS may also have a botryoid appearance and protrude into the lumen of the bladder. Hematuria, urinary frequency, or retention with subsequent renal failure may occur. Paratesticular RMS presents with a mass and may be confused with a hydrocele, incarcerated hernia, or testicular torsion. In the extremities, RMS often is palpable and causes pain or limits motion. Parameningeal RMS may present with airway obstruction or a palpable mass. As the tumor grows, it can erode the base of the skull and cause cranial nerve palsies. Penetration into the brain can occur and mimic an intracranial mass, with headache, vomiting, and diplopia. RMS of the cheek or larynx causes obstruction of the aerodigestive track or a discernible mass; other symptoms or signs referable to the head and neck include hoarseness, polyps, decreased hearing, persistent otitis, otorrhea, rhinorrhea, nasal congestion or obstruction, and headache. Patients with orbital RMS usually present with proptosis, discoloration, or limitation of extraocular motion. RMS of the trunk can present as a mass simulating a hernia or hematoma, or causing a classic superior vena cava syndrome. In the retroperitoneum, RMS can cause gastrointestinal discomfort or other mass-related symptoms.

Diagnostic Evaluation

The history and physical examination should focus on the extent of local disease and the possible presence of metastases. RMS may extend locally and infiltrate along fascial planes and into surrounding tissues. Tumor margins often are indistinct. Depending on the site, the local tumor generally is imaged by some combination of computed tomography (CT), magnetic resonance imaging (MRI), and plain radiography. Genitourinary RMS often is investigated initially by ultrasound and barium enema, and voiding cystourethrogram, cystoscopy, or pelvic examination under anesthesia occasionally is indicated. The draining lymphatics, particularly in genitourinary and extremity primary sites, are evaluated with CT and often surgery

Table 11.1
International Classification of Rhabdomyosarcoma

	Frequency (%)	Actuarial 5-Year Survival (%)
Superior prognosis		
Botryoid rhabdomyosarcoma	6	95
Spindle cell rhabdomyosarcoma	3	88
Intermediate prognosis		
Embryonal rhabdomyosarcoma	79	66
Poor prognosis		
Alveolar rhabdomyosarcoma	32	54
Undifferentiated sarcoma	1	40
Other	9	

Data from Newton WA Jr, Gehan EA, Webber BL, et al. Classification of rhabdomyosarcomas and related sarcomas. Pathologic aspects and proposal for a new classification: an Intergroup Rhabdomyosarcoma Study. *Cancer*. 1995;76:1073–1085.

(44,45). The most common sites of metastases are lung, bone, bone marrow, and locoregional lymph nodes (21). Chest CT is the optimal imaging method for lung metastases. A nuclear medicine bone scan is performed to detect bony metastases but is not reliable in determining skull base involvement in parameningeal tumors, which is evaluated with CT or MRI. Bone marrow aspirate and biopsy are performed, and examination of cerebrospinal fluid (CSF) cytology is indicated if the tumor is in a parameningeal site (46). An MRI is used to evaluate spinal cord–related symptoms. Positron emission tomography (PET) scan is also being used with increasing frequency and is effective at detecting regional lymph node involvement and identifying distant metastases (47).

Prognostic Features

Histology

Most RMS are soft, fleshy tumors with variation in the extent of both invasion and necrosis. Immunohistochemical stains, including antidesmin, antivimentin, and anti-muscle-specific actin, are used routinely to help ascertain the muscle origin of the tumor cells, and the detection of the muscle regulatory gene *MyoD1* may be even more sensitive than desmin (48).

Four histological subtypes of RMS are classically described: embryonal, alveolar, pleomorphic, and mixed (Fig. 11.2). However, the lack of agreement in classification among pathologists and the need to develop a single system that is prognostic prompted formation of an international panel to devise a new system, the International Classification of Rhabdomyosarcoma (Table 11.1) (49–51). Classification on the basis of histological features remains a challenge and current COG clinical trials utilize central pathologic review to ensure uniform pathological diagnosis since stratification schema and guidelines vary by histology (52).

Favorable: Embryonal, Botryoid, and Spindle Cell Variants

Embryonal RMS is the most common histological subtype. Embryonal RMS accounts for 60–70% of RMS in childhood and typically arises in the head and neck region and genitourinary tract (49). This form is composed of blastemal mesenchymal cells that tend to differentiate into cross-striated muscle cells. Although it resembles normally develop-

ing skeletal muscle in the 7–10 week fetus, great variation in the degree of differentiation can exist. Cellularity is moderate, and the stroma is loose and myxoid in most cases. The cells are generally fusiform or stellate, often admixed with primitive round cell forms. Cross-striations are present in about one third of cases (1). Periodic acid–Schiff staining, actin/desmin-positive reactivity, and Z-band material usually are present. Loss of heterozygosity at 11p15.5 may be identifiable. The pathologic differential diagnosis often includes lymphoma, Ewing's sarcoma, and neuroblastoma (other small, round, blue cell tumors of childhood that have in common their light microscopic appearance and necessitate immunohistochemical evaluation for further characterization).

The botryoid variant of embryonal RMS represents about 10% of all RMS cases and occurs in mucosa-lined organs including the bladder, vagina, nasopharynx, nasal cavity, middle ear, and biliary tree. The stroma is loose with a myxoid character and a condensed tumor cell or cambial layer must be identifiable. The tumor cells may be small or large, with varying degrees of myogenesis. These tumors are generally localized and noninvasive (1,50,51).

The spindle cell variant is composed exclusively of spindle-shaped cells and has a low cellularity. It can be collagen-rich or collagen-poor, with the former having a storiform pattern. Its most common site is paratesticular.

Unfavorable: Alveolar

About 20% of children with RMS have the alveolar subtype that is more common in adolescents and in tumors involving the extremities, trunk, and perianal and perineal region. The alveolar form resembles developing skeletal muscle in the 10–20 week-old fetus. The cells are round, with scanty eosinophilic cytoplasm that is occasionally vacuolated. Cross-striations are quite rare. The name alveolar is derived from the pattern produced by the tendency of cells to line connective tissue septa reminiscent of alveoli. Variable arrangement of trabeculae may cause the tumor cells to be arranged in strands, clefts, sheets, or clusters (1). The characteristic translocations are discussed in the “Biology” section earlier in this chapter. A “solid” variant has been identified, which grows as solid masses of closely aggregated cells with little or no discernible alveolar arrangement.

Table 11.2
Tumor, Node, Metastasis Pretreatment Staging Classification

Stage	Sites	Tumor Invasiveness	Tumor Size	Lymph Node Status	Metastasis
1	Orbit Head and neck (excluding parameningeal) Genitourinary (nonbladder, nonprostate) Biliary tract	T1 or T2	A or b	Any N	M0
2	Bladder or prostate Extremity Head and neck parameningeal Other (e.g., trunk, retroperitoneum)	T1 or T2	A	N0 or NX	M0
3	Same as stage 2	T1D or T2	A B	N1 Any N	M0
4	All	T1 or T2	A or b	Any N	M1

T1, confined to anatomic site of origin; T2, extension; *a*, less than 5 cm in diameter; *b*, more than 5 cm in diameter; NX, clinical status unknown; N0, not clinically involved; N1, clinically involved; M0, no metastasis; M1, metastasis present.

Stage

RMS has been staged according to multiple systems developed in different institutions or multi-institutional groups. With the advent of IRS-III, a pretreatment staging system was developed based on the tumor, node, and metastasis (TNM) system used by SIOP, which reflected the disease characteristics at diagnosis (Table 11.2). IRS-IV, IRS-V, and the current COG trials have used this TNM staging system, which incorporates tumor size and invasiveness (*a* or *b* and T1 or T2, respectively), nodal status, presence of metastasis, and tumor site. Essentially, stage 1 tumors are in favorable sites. Stage 2 tumors are in unfavorable sites but are small (less than 5 cm) with negative lymph nodes. Stage 3 tumors are in unfavorable sites and are large or with positive lymph nodes. Stage 4 tumors are at any site, with hematogenous metastasis. This staging system has been validated with respect to its relationship to patient outcome (53).

Group

Implicit in the discussion of the grouping and staging systems is the importance of accurate identification of prognostic variables. Most of these variables are interrelated. A wealth of data supports the relevance of the clinical group of the patient, which in essence is the postsurgical disease extent at the time chemotherapy is initiated. The clinicopathologic grouping system has been used since the first IRS studies (Table 11.3, Fig. 11.2). The clinical group reflects the absence of microscopic disease (group I, 13% of patients) or presence of microscopic disease (group II, 20% of patients), gross disease (group III, 48% of patients), or metastatic disease (group IV, 18% of patients) (11,20). Clearly, the clinical group also reflects the disease site (ease of resection) and the biologic invasiveness of the tumor. Because therapeutic decisions made before study entry affected the assigned group, this system did not accurately reflect the biology of RMS (53–55). Moreover, the emphasis on surgical reduction of tumor bulk implicit in this system led surgeons to perform unnecessarily morbid surgeries at inappropriate times. In addition, the

surgical approach was not uniformly applied, which obfuscated interpretation of results (54). However, data from all of the IRS studies support the utility of the grouping system, and it continues to be used in conjunction with stage and with careful surgical guidelines in the current trials that are specific to site of disease (Fig. 11.3) (9–11,20).

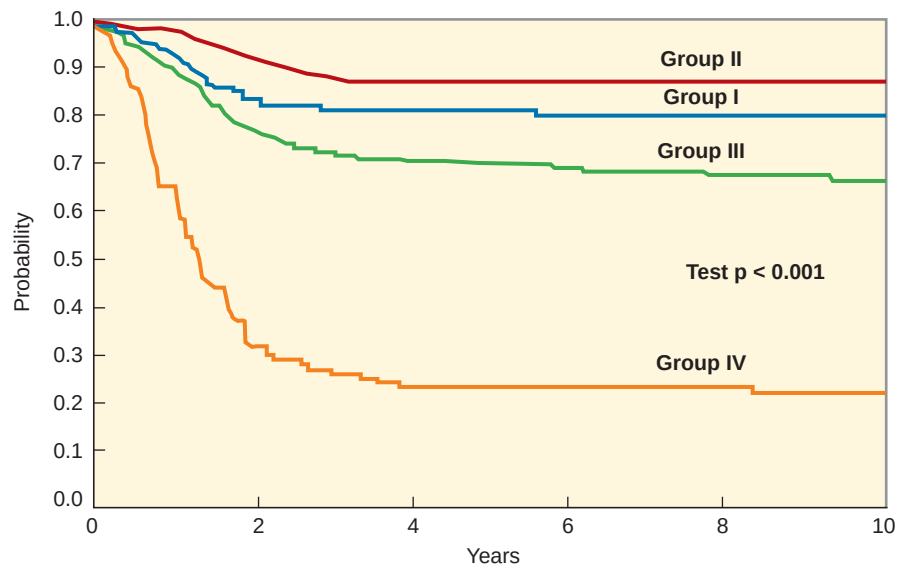
Primary Site

The primary site is a strong determinant of outcome, as verified by data from IRS-II and IRS-III (Fig. 11.4) (9–11,20). This relates, at least in part, to the association of site with other tumor and treatment variables. The primary site generally determines the ability to surgically remove the tumor, which in turn determines the IRS grouping (9). Surgical removal also relates to tumor invasiveness and the morbidity that would attend resection. Most orbital lesions are in group III (73.5% in IRS-I, IRS-II, and IRS-III); this is also true for

Table 11.3
The IRS Grouping System

Group I	Localized disease, completely resected a. Confined to muscle or organ of origin b. Infiltration outside the muscle or organ of origin
Group II	Total gross resection with a. Microscopic residual disease b. Regional lymphatic spread, resected c. Both
Group III	Incomplete resection with gross residual disease a. After biopsy only b. After major resection (more than 50%)
Group IV	Distant metastatic disease present at onset

Figure 11.3 Survival by clinical group for all patients treated in IRS-IV. Improved outcome was seen in group II compared with group I and presumably due to undertreatment of select patients with group I disease. (From Pizzo P, Poplack D, eds. *Principles and Practice of Pediatric Oncology*. Philadelphia, PA: Lippincott-Raven; 2006:984, with permission.)



parameningeal lesions (which are never in group I) and genitourinary bladder or prostate lesions (46,56). Conversely, most genitourinary nonbladder and nonprostate tumors are in group I, and most extremity tumors are in group I or II or are metastatic (group IV) at diagnosis. Other factors are also relevant to the association of primary site with prognosis. For example, the tumor location determines the presenting signs and symptoms, which are often related to the rapidity of diagnosis. Tumor size (up to 5 cm vs. more than 5 cm) is associated with survival time ($p < 0.001$) by multivariate analysis (51). Size is also related to tumor site through presenting symptoms and signs. Primary site influences the propensity for lymphatic spread (Table 11.4) (44,57). Whereas genitourinary, abdominal or pelvic, and extremity tumors commonly involve regional lymph nodes, tumors in the head and neck, trunk, and female genital organs rarely do so. However, the frequency of lymph node involvement is almost certainly underestimated by IRS data because the assessment of nodal status has not been systematic. Data from Stanford and Memorial Sloan-Kettering support the prognostic significance of lymph node involvement. Pedrick et al. (19) showed that 88% of patients presenting with involved nodes had primary tumors that were invasive and extended beyond the site or organ of origin. The more current IRS studies should provide more consistent documentation of lymph node status with improvements in imaging techniques and careful surgical guidelines.

Other Factors

A variety of other factors have prognostic significance, some of which are general and others specific to certain tumor subgroups. IRS data show that lymphocyte count, patient's sex and age are prognostic (20). Although younger age is associated with a better outcome, the specific subgroup of children younger than 1 year old with alveolar histology have a significantly poorer survival than do older children, a finding not seen for infants with the embryonal subtype (58–60). Some site-specific variables influence outcome. In the head and neck, risk factors that predict tumor access to the cranial subarachnoid space (skull base erosion, cranial nerve palsy,

intracranial extension) decrease the likelihood of disease-free survival (51% vs. 81% if no risk factors) (46,61,62). In extremity sites, the presence of lymph node involvement is strongly associated with a high incidence of relapse in metastatic sites and inferior survival. In contrast to many other childhood cancers, early response to chemotherapy has generally not been found to correlate with long-term disease-free control (63).

GENERAL PRINCIPLES OF THERAPY

Currently, the COG studies stratify patients into three risk groups (low, intermediate, and high) on the basis of known prognostic factors and historical outcome (13). The prognostic features incorporated into the risk classification scheme include histology, stage (which in turn incorporates site, tumor size, invasiveness, node status, and metastases), and clinical group. General definitions of the risk groups are as follows:

- **Low risk:** Patients with localized embryonal RMS occurring at favorable sites (stage 1) and patients with embryonal RMS occurring at unfavorable sites with either completely resected disease (group I) or microscopic residual disease (group II)
- **Intermediate risk:** Patients with embryonal RMS occurring at unfavorable sites with gross residual disease (group III) and patients with nonmetastatic alveolar RMS at any site
- **High risk:** Patients with metastatic RMS (group IV, stage IV)

Clearly, this scheme will continue to evolve as treatments improve and new data emerge regarding particular subsets of patients and biologically based prognostic features. The overall goals are to reduce long-term toxicities in patients with a high likelihood of cure and to develop superior and innovative therapies for patients who continue to fare poorly with modern treatment regimens.

The therapeutic struggle for clinicians managing children with RMS, to cure while minimizing functional and cosmetic deficits, is heightened by the difficulty in eradicating both local and systemic disease. The spectrum of locations

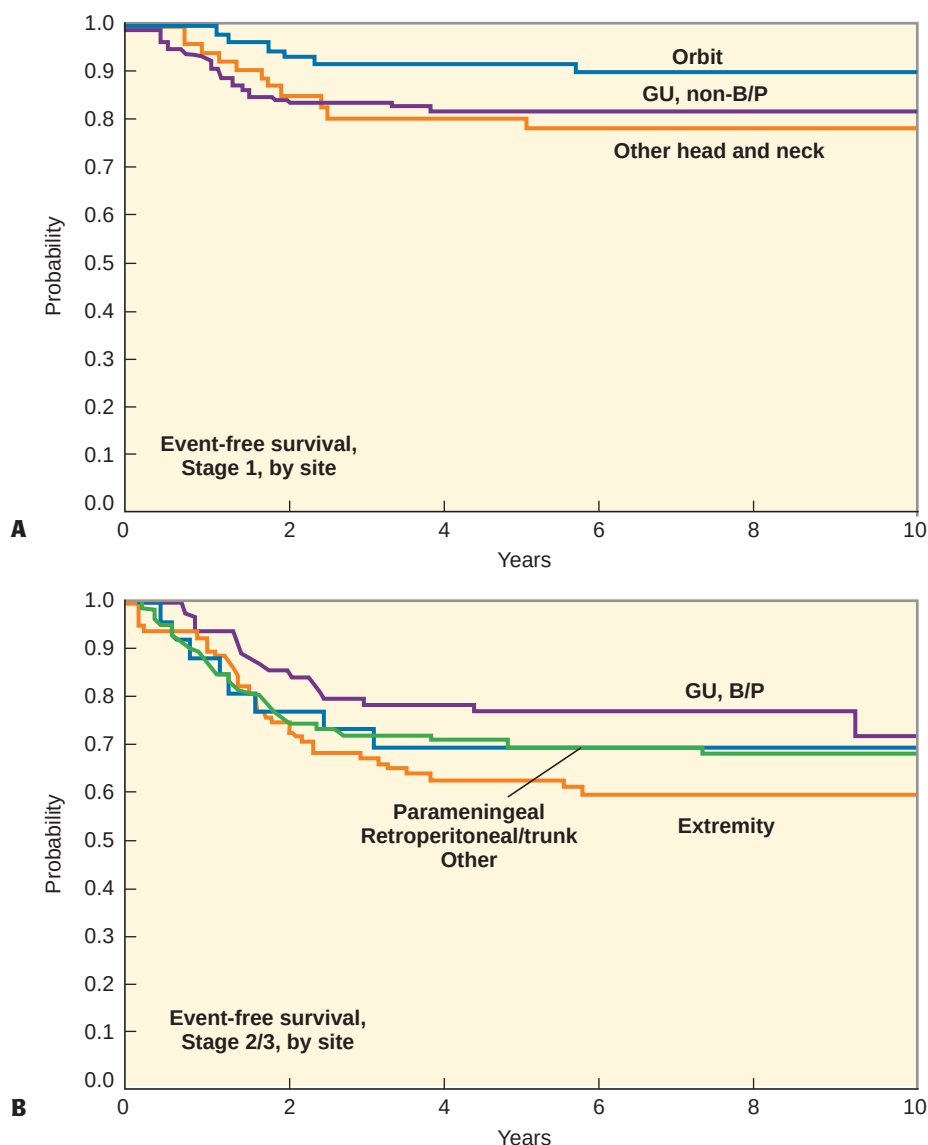


Figure 11.4 Event-free survival of patients treated on Intergroup Rhabdomyosarcoma Study IV by stage and site. **A:** For patients with nonmetastatic “favorable” site tumors (stage 1), the best outcome was seen for orbital primary tumors. **B:** For patients with nonmetastatic unfavorable site tumors (stage 2 or 3), the best outcome was for those with genitourinary (bladder–prostate) tumors, whereas those with extremity tumors had an inferior outcome. GU B/P, genitourinary tract (bladder or prostate); GU non-B/P, genitourinary tract (nonbladder, nonprostate). (From Pizzo P, Poplack D, eds. *Principles and Practice of Pediatric Oncology*. Philadelphia, PA: Lippincott-Raven; 2006:991, with permission.)

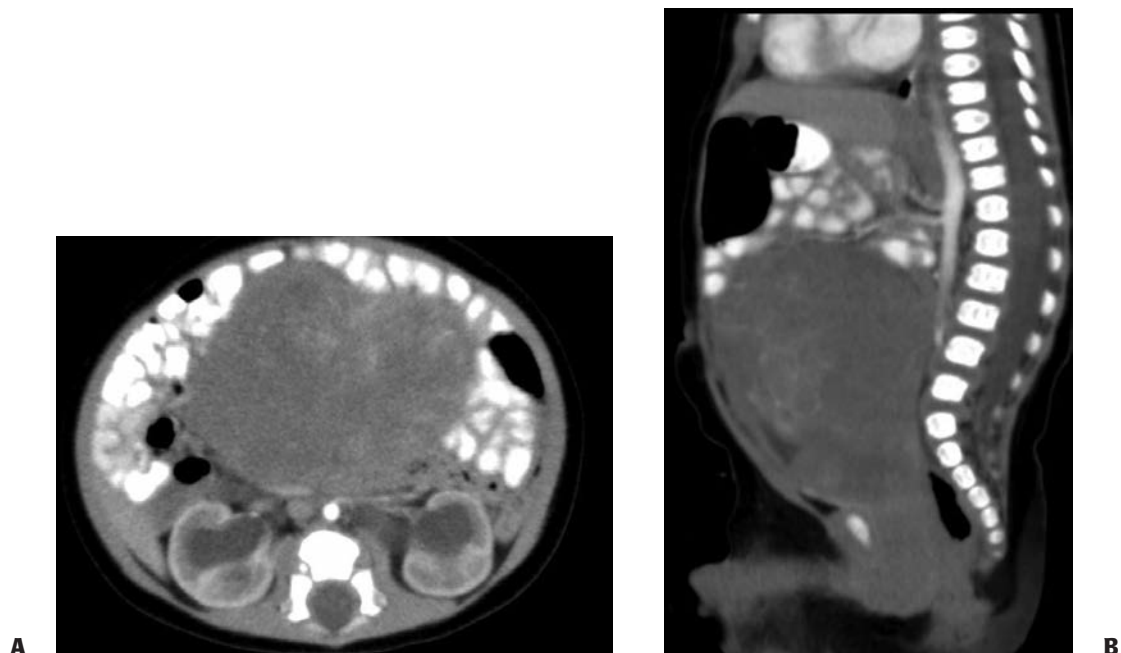
and histologies complicates determination of treatment strategies through differences in the propensity for local and systemic control and treatment sequelae. It is clear that multidisciplinary therapy is necessary. Aggressive surgery and RT alone have been curative in fewer than 25% of children, with the exception of patients with orbital or genitourinary primary sites (17,64). Conversely, chemotherapy alone is associated with high local failure rates, a lesson learned by attempts to manage orbital or genitourinary tumors without radiation (17,65). The judicious use of chemotherapy to eradicate micrometastatic disease and reduce the extent of local disease and RT to increase the potential for local control has led to a decrease in aggressive surgery except in selected situations (8). The current challenge is to develop approaches to additionally enhance the complementary actions of all three treatment modalities in terms of intensity and sequence.

Surgery

Before the advent of radiation and chemotherapy, complete resection of RMS was the clear goal of surgical treatment. This often involved radical surgeries such as pelvic exenteration, radical prostatectomy, cystectomy, amputations, and orbital exenteration. Even so, fewer than 10% of children were amenable to complete resection and curable because of the absence of metastatic disease. Beyond this, most of these children had severely compromised quality of life functionally, cosmetically, and psychologically. Select sites that were more often curable by aggressive surgery included the orbit and bladder. Combined analysis of patients with nonmetastatic disease from IRS-I, IRS-II, and IRS-III showed that only 16% of children had disease amenable to complete resection (group I) and 20% had tumors for which removal of gross disease (group II) was possible (Fig. 11.5). In general, achievement of

Table 11.4**Lymph Node Metastasis by Primary Site for 592 Patients with Visibly Resected Disease^a from IRS-I and IRS-II**

Site	Number of Patients	Number and Percentage with Nodal Metastases
Extremity		
Upper	74	12 (16%)
Lower	107	10 (9%)
Total	181	22 (12%)
Genitourinary organs		
Paratesticular	107	28 (26%) $p = 0.001^b$
Bladder	29	6 (21%)
Prostate	12	5 (42%) $p = 0.03$
Female genital organs	17	1 (6%)
Other	1	N
Total	166	40 (24%)
Head and neck		
Orbit	39	0 (0%)
Other	96	8 (8%) $p = 0.06$
Total	135	8 (6%)
Other		
Anus and perineum	15	2 (13%)
Pelvis and retroperitoneum	22	5 (23%)
Trunk	65	2 (3%) $p = 0.01$
Abdomen and thorax	8	2 (25%)
Total	110	11 (10%)
Totals	592	81 (14%)

^aMicroscopic or no residual disease.^b p values relate to comparison of frequency of nodal metastases for this site compared with the 14% for all 592 patients.From Lawrence W Jr, Hays DM, Heyn R, et al. Lymphatic metastases with childhood rhabdomyosarcoma. *Cancer*. 1987;60:910–915, with permission.**Figure 11.5** Axial (A) and sagittal (B) images of a 10-month-old boy with a group III rhabdomyosarcoma of the bladder/prostate. The tumor displaces the bowel and causes urinary obstruction resulting in hydronephrosis.

local control with organ preservation is the appropriate goal. This is accomplished with appropriate combined-modality therapy. Aggressive surgery remains appropriate in certain situations, particularly for salvage therapy.

Reoperation for microscopic residual disease after an initial excision, or when the first operation was performed without knowledge of the type of neoplasm involved, may be indicated before additional management. Reoperation after chemotherapy as a second-look procedure provides an attractive option for select cases. Many of these patients have had a “pathologic” complete response and have survival similar to that of patients who had an initial complete resection.

The role of lymph node dissection as a component of surgical therapy continues to evolve. Advances in imaging may improve radiographic detection of involved lymph nodes. Current guidelines are site specific because of the variability in the frequency of lymph node involvement and outcome data relating to its significance. Genitourinary and extremity RMS have a high incidence of lymph node metastases (Table 11.4) (44). The high frequency of nodal spread for extremity tumors, often without clinical or radiographic evidence of involvement, has both prognostic and therapeutic implications (66,67). Currently, COG guidelines include surgical evaluation of lymph nodes for RMS of the extremity and for males who are older than 10 years of age with paratesticular tumors. Sentinel lymph node biopsy continues to be explored as an alternative to formal lymph node dissection (68). This topic is considered further in later sections because considerations are site specific.

Overall, the extent and timing of surgical excision depend on the site of tumor and overall treatment strategy, balancing cure with functional outcome.

Chemotherapy

Before the 1960s, the role of chemotherapy in RMS was for the treatment of metastatic disease. Several investigators reported responses to vincristine and actinomycin used alone (VA) or in combination with cyclophosphamide (VAC) (64). Various groups then began to report that the adjuvant administration of chemotherapy for totally or subtotally resected localized disease contributed to an increase in survival probability from

10–40% to 60–80% (69). Heyn et al. (8) randomized 32 children with completely resected RMS to adjuvant therapy with VA or no adjuvant therapy. There were 8 deaths among the 15 children in the control group and 2 deaths in the 17 treated children. All children with microscopic residual disease received chemotherapy, and survival rates were excellent.

With the widespread adoption of chemotherapy as part of the therapy of RMS, several trials were undertaken to establish the optimum drug combinations. IRS-I tested whether VAC was superior to VA in group II disease and whether pulse VAC plus adriamycin was superior to pulse VAC alone in groups II and III (Table 11.5). The study found no benefit to cyclophosphamide in group II diseases, and no benefit to the addition of adriamycin in groups III and IV (9).

IRS-II built on the results of IRS-I (Table 11.6) (10). Patients in group I received VAC or VA. Disease-free survival was similar. IRS-II showed no benefit to pulse VAC compared with cyclic sequential VA for group II. In groups III and IV, pulse VAC was better than a VAC and adriamycin combination but not statistically significantly better.

IRS-III (1984–1991) separated patients by histology into either a favorable (embryonal) or unfavorable (alveolar, anaplastic, and monomorphous) histology. Results based on subgroup are detailed in Table 11.7. Several drug pairs (adriamycin with imidazole carboxamide [DTIC], actinomycin D with VP-16, and actinomycin D with DTIC) appear to have been associated with gain in survival (11).

IRS-IV (1991–1997) used the new staging system to assign drug therapy. Patients with group I paratesticular tumors and group I or II orbital tumors were treated with VA, and all other nonmetastatic patients except those with preexisting renal abnormalities were randomized to receive one of three chemotherapy regimens: VAC; vincristine, actinomycin D, and ifosfamide (VAI); or vincristine, ifosfamide, and etoposide (VIE) (12). Patients with group III tumors were also randomized to receive conventional RT or hyperfractionated RT. VAC, VAI, and VIE were equally effective, and overall the patients with embryonal tumors who received three-drug therapy benefited in comparison to those in IRS-III, where just VA was given. For patients with metastatic tumors, a pilot IRS study looked at the activity of ifosfamide and doxorubicin in

Table 11.5
Design and Results of IRS-I, 1972–1978 (686 Patients)

Clinical Group	Chemotherapy Regimen	Conventional Radiation Therapy	5-Year Survival (%)	Entire Group Survival (%)
I	VAC × 2 years	No	93	83
	VAC × 2 years	Yes	81	
II	Cyclic sequential VA × 1 year	Yes	73	71
	VAC × 2 years	Yes	70	
III	Pulse VAC × 2 years	Yes	53	52
	Pulse VAC + Adr × 2 years	Yes	51	
IV	Pulse VAC × 2 years	Yes	14	21
	Pulse VAC + Adr × 2 years	Yes	26	
Overall			55	

A, actinomycin D; Adr, doxorubicin; C, cyclophosphamide; V, vincristine.

Modified from Mandell LR. Ongoing progress in the treatment of childhood rhabdomyosarcoma. *Oncology*. 1993;7:71–83, with permission.

Table 11.6
Design and Results of IRS-II, 1978–1984 (1003 Patients)

Clinical Group	Chemotherapy	Conventional Radiation Therapy	5-Year Survival (%)	Entire Group Survival (%)
I ^a	VA × 1 year	No	85	81 ^b
	VAC × 2 year	No	84	
II ^a	Cyclic sequential VA × 1 year	Yes	88	80 ^b
	Repetitive pulse VAC × 1 year	Yes	79	
III	Repetitive pulse VAC × 2 years	Yes	66	65
	Repetitive pulse VAdrC–VAC × 2 years	Yes	65	
IV	Repetitive pulse VAC × 2 years	Yes	26	27
	Repetitive pulse VAdrC–VAC × 2 years	Yes	27	
Overall			62	63

A, actinomycin D; Adr, doxorubicin; C, cyclophosphamide; V, vincristine.

^aPatients with alveolar and extremity tumors excluded in groups I and II; treated with repetitive pulse vincristine, actinomycin D, and cyclophosphamide × 1–2 years with or without conventional radiotherapy.

^bIncludes extremity and alveolar tumors treated differently.

Modified from Mandell LR. Ongoing progress in the treatment of childhood rhabdomyosarcoma. *Oncology*. 1993;7:71–83; and Maurer HM, Gehan EA, Beltangady M, et al. The Intergroup Rhabdomyosarcoma Study II. *Cancer*. 1993;71:1904–1922, with permission.

an up-front window and found a response rate of 63% (complete and partial responses) (70). Subsequently, a full randomized IRS trial in 128 patients compared two up-front treatment windows, vincristine and melphalan (VM) and ifosfamide and etoposide (IE), and later therapy consisted of VAC or VAC with the window therapy included if the patient had an initial response (71). Initial response rates were comparable (VM 74% vs. IE 79%), but 3-year failure-free survival (FFS) and overall survival (OS) rates were superior in the patients who received the IE-containing regimen (FFS 33% vs. 19% and OS 55% vs. 27%).

IRS-V used a risk stratification schema very similar to the current system outlined above to assign patients to three risk groups (13). VA or VAC was used in a nonrandomized fashion in the low-risk patients. VA was given to patients with tumors in favorable sites with group I or group II disease, to patients with small, group I tumors in unfavorable sites, and to all patients with orbital tumors (including group III). All other patients meeting the low-risk criteria received VAC. All of the low-risk patients had embryonal histology or one of its variants. For intermediate-risk patients, the gold-standard VAC therapy was compared in a randomized trial to VAC alternating with vincristine, topotecan, and cyclophosphamide (VTC). This group included patients less than 10 years of age with metastatic disease and embryonal histology. Previous studies in both untreated and relapsed patients have shown topotecan to be a very active agent, particularly for patients with alveolar histology. Preliminary results of this trial suggest that there was no benefit to the addition of topotecan (72). For high-risk patients with metastatic disease who historically had poor outcomes with standard VAC therapy, the combination of irinotecan and vincristine was tested in an up-front window and then incorporated into subsequent therapy with VAC for patients who responded (73). Irinotecan has demonstrated significant antitumor activity for patients with both metastatic and relapsed RMS, though it is more active when given in combination with vincristine than as a single agent (74–76).

Currently, COG has open clinical trials for low-risk and intermediate-risk disease as defined above. The low-risk trial uses VAC in a nonrandomized manner for all patients. The cyclophosphamide dose is relatively low at 1.2 g/m² per cycle. Four cycles are given initially with radiation administered at week 13 for patients with microscopic, locoregional, or gross residual disease. Patients receive an additional 4 or 12 courses of VA depending on which low-risk subset they are in. The goal is to increase treatment efficacy by adding in a low cumulative dose of alkylating agent for the lowest-risk patients while shortening the duration of treatment for these patients, and to decrease the risks of both acute and long-term toxicities of treatment (in particular, infertility) for the higher-risk subset by decreasing the cumulative exposure to cyclophosphamide. For intermediate-risk patients, the current trial randomizes patients to standard VAC chemotherapy or VAC alternating with vincristine and irinotecan (VI) cycles. RT is given at week 4 in conjunction with two cycles of VI for patients on the VAC/VI arm. The goal is to improve disease control by administering irradiation earlier than in previous trials and also to look at the possible role of irinotecan as a radiation sensitizer. The high-risk trial recently met its accrual goals and is closed to await results. Because of intriguing results from the comparison of a single-institution trial of vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide to IRS-IV outcomes, this combination was used in the trial (77). Cycles were given in a compressed manner, every 2 weeks instead of the traditional 3-week schedule with the goal of improving outcomes in an analogous manner to a trial for nonmetastatic Ewing sarcoma that used this approach. Until the results of these trials and their predecessor trials mature and become available, VAC remains the gold-standard chemotherapy regimen for most patients with RMS, while the lowest-risk patients have an excellent outcome with the two-drug combination, VA.

The challenge remains to identify the drug combinations with the most favorable therapeutic ratio when used in combination with the other modalities, and to develop innovative

Table 11.7
Therapy and Outcomes According to Specific Patient Subgroups in IRS-III, 1984–1991 (1032 Patients)

Risk Subgroup	Treatment	5-Year Progression-Free Survival (%)	5-Year Survival (%)	Progress (IRS-II vs. IRS-III)
Group I (favorable histology)	VA × 1 year	83	93	C not necessary
Group II (favorable histology)	VA × 1 year + RT	56	54	Need for Adr not proven because of small patient numbers and different histologies compared with IRS-I
	VAdrA × 1 year + RT	77	89	
Groups I and II (unfavorable histology)	VAdrC–VAC + CDDP × 1 year + RT	71	80	Better than IRS-II because of intense chemotherapy
Group II (paratesticular)	VA × 1 year + RT	81	81	C not necessary
Groups II and III (orbit and head)	VA × 1 year + RT	78	91	C not necessary
Group III (except special pelvic, orbit, and head sites)	VAC × 2 years + RT	70	70	Differences not statistically significant but better than IRS-II because of intense induction chemotherapy, second-look surgery
	VAdrC–VAC + CDDP × 2 year ^a + RT	62	63	
	VAdrC–VAC + CDDP + VP-16 × 2 year ^a + RT	56	64	
Group III (special pelvic sites)	VAdrAC–VAC + CDDP + VP-16 × 2 years ± RT ± surgery	74	83	Better than IRS-II because of intense chemotherapy, early RT, second-look surgery; the bladder salvage rate more than doubled (60% vs. 25%)
Group IV	VAC × 2 years + RT	27	27	No significant differences and no better than IRS-II
	VAdrAC–VAC + CDDP × 2 years + RT	27	31	
	VAdrAC–VAC + CDDP + VP-16 × 2 years + RT	30	29	

A, actinomycin D; Adr, doxorubicin; C, cyclophosphamide; CDDP, cisplatin; DTIC, imidazole carboxamide; RT, radiation therapy; V, vincristine; VP-16, etoposide.

^aSecond-look surgery recommended at week 20; if partial response, patients received Adr + DTIC, A + VP-16, or A + DTIC.

Modified from Pappo AS. Rhabdomyosarcoma and other soft tissue sarcomas of childhood. *Curr Opin Oncol.* 1995;7:361–366, with permission.

therapies for the subset of patients who continue to fare poorly despite the advances in therapy that have been made over the past few decades.

Radiation Therapy

The goal of RT today is to provide local and regional control, with or without surgery, in conjunction with chemotherapy. The optimal multimodal strategy would coordinate RT with these other therapies so as not to impair surgical healing or drug administration. Therefore, major considerations would include the primary site of the tumor, the extent of surgery, the interaction of RT with chemotherapeutic agents, and any emergent contingencies. An analysis of IRS-II data for group III patients underscores the difficulty that still exists in obtaining local and regional control (78).

The responsiveness of RMS to RT was established in the 1940s and 1950s (79). Fifty to 65 Gy was thought to be necessary to achieve local control of the primary tumor regardless of the nature of the surgical procedure. In the setting of postoperative microscopic residual disease, these doses were demonstrated to achieve local control in 90% of cases (69, 80–82). Because RMS was known to extensively infiltrate tissues, large radiation volumes initially were used, as was appropriate and standard for other soft tissue sarcomas. As the efficacy of chemotherapy for micrometastatic disease became established and the risk of normal tissue damage caused by combined-modality therapy was recognized, investigators considered whether equivalent local control rates could be obtained with lower radiation doses and volumes (81). Beyond this, the need for any RT after wide local tumor

resection with negative margins was questioned. The IRS studies attempted to systematically examine the issues of RT dosage and volume within the limits imposed by the many chemotherapy questions that were also asked.

IRS-I patients in group I were randomized to receive postoperative RT or no RT, whereas all other patients were irradiated (Table 11.5) (9). The dose was adjusted to the patient's age and ranged from 40 to 60 Gy. Daily fractions were 1.5–2 Gy, and RT was administered immediately after surgery for group I patients and after 6 weeks of chemotherapy for groups III and IV. At 5 years, approximately 80% of the patients in both group I study arms were without evidence of disease. Overall survival for patients with group I RMS did not differ significantly with RT. For this reason, RT was omitted for group I favorable histology cases for IRS-II. In IRS-I, the dose given for local control was related to patient age and tumor size. Dose–response relationships were examined. A 32% local recurrence rate was seen after doses less than 40 Gy and a 12% local recurrence rate was seen after doses greater than 40 Gy in the subgroup of children older than 6 years; however, this difference was not statistically significant. IRS-I found no dose–response relationship when patients were stratified solely by clinical group. The treatment volume was also analyzed for its impact on local failure. Patients who received RT to less than the entire muscle bundle were compared with those whose RT encompassed the entire bundle. In patients younger than 6 years, local control rates were 84% versus 92%, respectively, and in older children rates were 91% versus 85%; however, these differences were not significant. RT to clinically uninvolved lymph nodes was not encouraged, whereas it was recommended for involved nodal regions. Local control was better in genitourinary sites than in the extremity.

In IRS-II the RT guidelines were modified based on IRS-I results (Table 11.6). Minimum tumor doses were 40 and 45 Gy for younger children (less than 6 years of age) and older children, respectively, but tumors larger than 5 cm received 50–55 Gy (83). Analyses of local and regional failure have been performed for IRS-II, with local failure defined as initial failure to achieve complete response or local relapse after an initial response (10,78,83). Group I patients with an unfavorable alveolar histology had a significantly higher frequency of locoregional recurrence than those with favorable histology. Although the frequency of local failure was only 10% in group II, it was at 20% for group III (excluding “special pelvic” sites) and 41% for group IV. When local relapse was analyzed as a percentage of all relapses, it accounted for 46% of relapses in group I (despite “complete” surgical removal of tumor) and 36%, 53%, and 20% of relapses in groups II, III, and IV, respectively (10,78). Moreover, the local relapse rate was greater and survival rate inferior for patients with unfavorable versus favorable histology (41% vs. 13%) and for lesions larger than 5 cm versus smaller than 5 cm (34% vs. 23%). The predominant pattern of relapse for group III tumors was locoregional (84). Those with lymphatic involvement at diagnosis had a significantly greater risk of relapse (84). The impact of radiation dose on local control was suggested by an analysis by Wharam et al. (43) for patients with nonparameningeal head and neck tumors. An increased relapse rate occurred when a dose less than 40 Gy was delivered. However, these data must be interpreted with caution,

as this study was not randomized to compare dose. Local control for all patients receiving more than 40 Gy was 93%.

In IRS-III, which accrued 1062 patients between 1984 and 1991, therapy was stratified not only by clinical group but also by histology (with unfavorable types comprising those with alveolar, anaplastic, and monomorphous cells or patterns) and primary site (Table 11.7) (11). Postoperative RT was administered to all patients except those in group I with favorable histology tumors and those in group III with special pelvic sites in complete pathologic remission after primary chemotherapy. The RT dose for group I and II patients was 41.4 Gy. For patients with gross residual disease, the dose depended on patient age and tumor size: 41.4 Gy was given for children younger than 6 years old with tumors smaller than 5 cm, 50.4 Gy was given for children older than 6 years old with tumors greater than or equal to 5 cm, and an intermediate dose of 45 Gy was given for children who were either older or had larger tumors, but not both. The overall survival at 5 years was 71%, superior to that in IRS-II (63%) and IRS-I (55%) (11). An update of patients in group I with alveolar or undifferentiated histology confirmed a benefit to the addition of RT for this cohort (85). For group III patients, the rates were 73%, 65%, and 52%, respectively. Although local control rates of 90% were achieved for patients in groups I and II, local recurrence in patients with group III disease remained unacceptably high, as in IRS-II.

IRS-IV accrued 1011 patients between 1991 and 1997 and used the pretreatment TNM staging system to assign chemotherapy and the clinical grouping system to assign radiotherapy (12). Group II patients did especially well (Table 11.8). Because of the unsatisfactory local control rates for patients with gross residual disease (group III) in IRS-II and IRS-III and because of the normal tissue toxicities associated with radiation doses higher than those used in the previous studies, hyperfractionated RT was tested in patients on IRS-IV with group III disease (1.1 Gy twice daily to 59.4 Gy vs. 1.8 Gy daily to 50.4 Gy) (86). Although feasible, no advantage to hyperfractionation was demonstrated. There was no difference in failure-free survival or overall survival between conventional RT and hyperfractionated RT (by actual treatment received *and* when analyzed by age, gender, tumor site, tumor invasiveness, lymph node status, histological features, stage, or tumor site—Table 11.9).

IRS-V looked prospectively at using lower doses of RT for patients with favorable histology; 36 Gy for patients with microscopic residual disease and no regional node involvement, 45 Gy for patients with orbital tumors and gross residual disease, and 36–41.4 Gy for patients with superficial head and neck tumors, biliary tumors, and vulvar or uterine tumors who undergo second-look surgery and have either negative margins or microscopic residual tumor. All patients with alveolar group I tumors received 36 Gy to the primary site. For intermediate-risk patients, IRS-V sought to determine the rate of local failure in patients with gross residual tumor at diagnosis who, after second-look surgery, had response-adjusted radiation dosage reduction (to 36 Gy for complete response and to 41.4 Gy for microscopic residual). It also aimed to determine whether preoperative RT followed by second-look surgery for patients with group III disease and poor response to induction chemotherapy was feasible. Results of this study should be available soon.

Table 11.8**Outcome for Patient with Group II Tumors According to Histology, Primary Site, and IRS Study**

	N	5-Year Failure-Free Survival		5-Year Overall Survival	
		Percentage	p	Percentage	p
Patients with embryonal histology tumors			<0.001		0.0018
IRS-I	105	75		78	
IRS-II	74	73		75	
IRS-III	129	79		86	
IRS-IV	90	93		97	
Patients with alveolar histology or UDS tumors			0.11		0.24
IRS-I	60	53		58	
IRS-II	85	58		70	
IRS-III	68	65		70	
IRS-IV	44	73		64	
Favorable primary site			0.95		
IRS-I and IRS-II	36	75			
IRS-III and IRS-IV	27	71			
Unfavorable primary site			0.01		
IRS-I and IRS-II	109	50			
IRS-III and IRS-IV	85	66			

UDS, undifferentiated sarcoma.

From Smith LM, Anderson JR, Qualman SJ, et al. Which patients with microscopic disease and rhabdomyosarcoma experience relapse after therapy? A report from the soft tissue sarcoma committee of the Children's Oncology Group. *J Clin Oncol*. 2001;19:4058–4064, with permission.

The SIOP has taken a slightly different approach to the management of pediatric RMS. They have investigated the omission or modification of local therapies based on response to systemic therapy in attempt to decrease late toxicities (16,17,87). The SIOP MMT 89 trial omitted RT or surgery for patients achieving a complete response to chemotherapy (87). Overall survival and event-free survival were 71% and 57%,

respectively. Local failure represented the main cause of relapse. The salvage rate after local failure was high, but prolonged follow-up is necessary to confirm durable disease control.

The current COG RMS trials, ARST 0331 and ARST 0531, enroll patients with low-risk RMS and intermediate-risk RMS, respectively. These trials require volume-based planning, but include the use of multiple radiation modalities

Table 11.9**Estimated Cumulative Incidence at 5 Years of Local, Regional, and Distant Failure by Primary Site and Therapy for Patients Who Received Their Randomized Therapy on IRS-IV**

Site	Local			Regional			Distant		
	Total (%)	CFRT (%)	HFRT (%)	Total (%)	CFRT (%)	HFRT (%)	Total (%)	CFRT (%)	HFRT (%)
Orbit	2	4	0	0			2	0	5
Head and neck	12	9	17	0			6	0	17
Parameningeal	16	12	20	1	0	1	11	10	12
Genitourinary (bladder, prostate)	19	25	8	0			15	14	16
Extremity	7	5	10	20	24	10	28	30	27
Other	14	12	16	5	3	6	17	20	14
All sites	13	12	15	3	3	3	13	13	13

p values for differences between CFRT and HFRT were nonsignificant for all subgroups.

CFRT, conventionally fractionated radiotherapy; HFRT, hyperfractionated radiotherapy.

Modified from Donaldson SS, Meza J, Breneman JC, et al. Results from the IRS-IV randomized trial of hyperfractionated radiotherapy in children with rhabdomyosarcoma—a report from the IRSG. *Int J Radiat Oncol Biol Phys*. 2001;51(3):718–728, with permission.

including photons, electrons, protons, and brachytherapy. Radiation is omitted only for patients with group I favorable histology disease. Microscopic residual disease after surgery is treated to a dose of 36 Gy and nodal disease is treated to 41.4 Gy. The dose for group III orbital tumors is 45 Gy; all other group III tumors receive 50.4 Gy. The gross tumor volume (GTV) is defined as the prechemotherapy volume. A margin of 1 cm around the GTV is recommended to define the clinical tumor volume (CTV). Nodal disease is also included in the CTV. A volume reduction after 36 Gy is permitted for those patients receiving 50.4 Gy who have had a substantial reduction in tumor size following systemic treatment. This volume reduction is encouraged for noninvasive or “pushing” tumors, but not for invasive tumors. Enrollment of all patients on available protocols is encouraged. In the setting of treatment off protocol, these parameters provide a guideline for RT.

SPECIFIC SITES

Bladder and Prostate Rhabdomyosarcoma

Bladder and prostate RMS combined represent approximately one half of genitourinary RMS (10). The predilection of bladder RMS for males and the bladder trigone often make it impossible to determine the origin of these tumors, and therefore these sites are generally considered together (88,89). It is important to note that when the site of origin can be determined, most data indicate a more favorable prognosis for bladder RMS (90,91). RMS of this location tends to occur in very young children; most are under the age of 5 at the time of diagnosis. Urinary abnormalities, including dysuria, polyuria, incontinence, and in particular urinary retention, are early signs. The first radiographic evaluation is typically ultrasound. Thin-cut CT scan and/or MRI of the abdomen and pelvis provide greater detail allowing for evaluation of the primary mass and retroperitoneal lymphatics while providing a reliable study to assess response to chemotherapy and/or radiation. Figure 11.5 shows a large RMS of the bladder or prostate (site of origin could not be determined radiographically) in an infant. PET/CT may provide a useful diagnostic tool for evaluation of lymphatics and is being evaluated for its role in this disease (92). CT of the chest should also be performed as a part of the metastatic workup. Endoscopic biopsy via cystoscopy may allow for diagnosis. If adequate tissue cannot be obtained by this method, open biopsy should be performed (93). If urinary obstruction is present at diagnosis, initial management also includes urinary stent placement or urinary diversion to protect renal function. Approximately 80% of tumors in modern series have favorable histology, embryonal or botryoid type. Regional lymph node involvement for this site is not uncommon, particularly when tumors arise from the prostate, and documented in the range of 20–30% (44,57). The hypogastric or external iliac nodes are most commonly involved, although spread to lumboaortic nodes may occur, even in isolation. Only 15% have demonstrable systemic metastases at diagnosis (94).

The therapeutic approach for RMS of the bladder and prostate has progressed over time as documented in North American and European studies. High survival rates have been achieved for decades but, sadly, these survivors have suffered considerable treatment-related morbidity. Management has evolved from pelvic exenteration to less-aggressive organ-

preserving therapy while maintaining high survival rates. At present, the goal of multimodality therapy for these children is to cure with preservation of bladder function. Therefore, up-front radical surgical procedures are no longer performed. If the tumor cannot be removed completely with preservation of bladder and urethral function, definitive surgery is delayed in attempt to achieve a response with chemotherapy $\pm$ RT that will allow for an organ-preserving surgical procedure.

IRS-I (1972–1977) enrolled 64 patients with primary RMS of the bladder or prostate. During the first few years of this protocol, pelvic exenteration, most often anterior exenteration, was the initial treatment for most patients followed by chemotherapy with or without radiation (94). This treatment resulted in high rates of disease control and survival, but the morbidity of surgery led to an effort to find a combination of therapy that might allow for organ preservation. In the later years of this study, many participating institutions adopted more limited surgery in attempt to preserve organ function. Partial cystectomy, if complete tumor resection was accomplished, resulted in excellent rates of disease control (95). Despite a high rate of complete responses, primary chemotherapy and RT, without surgery, resulted in a higher rate of disease recurrence. These patients did not undergo a second-look operation and chemotherapy was less intense than delivered in other series of this time period that evaluated primary chemoradiation for this disease (96). Pelvic exenteration provided salvage for many of these patients. The bladder preservation rate for IRS-I was 23%. Lymph node dissection and adjuvant RT for patients with involved lymph nodes did provide a benefit (57,97).

IRS-II (1978–1984) adopted a strategy using more vigorous primary chemotherapy with the intention of using minimal surgery to remove residual tumor and avoiding the morbidity of pelvic irradiation. RT was added in the setting of residual (postsurgical) disease or if an exenterative procedure would be needed. Almost all patients eventually needed RT, surgery, or both to achieve a complete remission. Although the 3-year survival for these patients (71%) was similar to that in IRS-I (75%), the 3-year disease-free survival rate was significantly lower (52% vs. 70%). Although the bladder preservation rate was initially high in IRS-II (97%), the percentage of patients who retained their bladders and were alive at 3 years was disappointing at only 22%, comparable to 23% in IRS-I (95,98). Low doses of radiation (2500 cGy) utilized in certain cases prior to 1980 and delay of irradiation to week 16 may have decreased the likelihood of local control.

IRS-III (1984–1991) investigators approached the problem of prostate and bladder tumors with a view of what appeared to limit successful bladder preservation in IRS-I and IRS-II; therefore, RT was routinely administered to all patients at week 6 after induction chemotherapy (intensified compared with IRS-I and IRS-II), except those in whom complete tumor removal was possible without total cystectomy. Surgery was then performed to document a complete response or to excise residual tumor while attempting to maintain bladder function. The results of IRS-III have been gratifying: the bladder retention rate at 4 years was 60% and survival was 90% for patients presenting with local or regional disease. An analysis of the 28 group III patients by Heyn et al. showed that 15 (54%) ultimately retained their bladders. Induction chemoradiotherapy induced a complete loss of tumor cells in 46%; in cystectomy specimens, tumor

cellularity was reduced, and tumor cell maturation occurred. Of interest is that cellular maturation was greater in tumor specimens of patients who retained their bladders and two patients with maturing cells did not experience recurrence (99,100). Subsequent studies have also reported mature cells or rhabdomyoblasts and suggest that this finding following therapy may represent a response (100). However, the finding should be viewed with caution and reviewed by an expert pathologist. While radical surgery is not indicated for this finding alone, close follow-up is prudent as recurrences have been documented (100,101).

IRS-IV (1993–1997) enrolled 90 patients with non-metastatic bladder/prostate RMS (102). The recommended treatment regimen continued efforts to maintain bladder function while achieving cure. All patients received alkylating-based chemotherapy. Seventy-four patients received RT. Fifty-three patients had at least one second-look procedure, most after RT. At a mean follow-up of 6 years, overall survival was 82%, failure-free survival was 77%, and bladder preservation was close to 70%. IRS-IV attempted to formally evaluate bladder function through patient questionnaires. Only 40% of all patients on IRS-IV had normal bladder function. Although overall survival remained high with treatment on IRS-IV, there is still room to improve functional outcome. In addition, urodynamic studies can provide a more accurate and objective way to evaluate bladder function and should be obtained for patients with bladder/prostate RMS undergoing treatment with bladder preservation. IRS-IV also evaluated hyperfractionated RT, but found no benefit (86).

Three-dimensional treatment planning is preferred for better visualization and delineation of target volumes and normal structures. MRI may be of benefit for better delineation of soft tissues, while CT provides better visualization of growth plates. MRI–CT fusion may be useful. For patients with large tumors displacing bowel, GTV is defined as the preoperative tumor volume excluding the debulked portion of tumor and accounting for shifting of structures. Critical structures in this region that should be considered include bladder, rectum, bowel, pelvic and femoral head growth plates, penile bulb, and testes. Although four-field techniques may be used, AP/PA or slightly oblique anterior or posterior fields provide the benefit of shielding femoral head growth plates. IMRT may be of benefit for some cases, but care should be taken in designing field arrangement to avoid exposure of tissues that could be spared completely. Growth plates in these young children are sensitive to low doses of radiation (10–20 Gy) and second malignancies are a concern. Protons may provide benefit for some cases (Fig. 11.6).

Paratesticular

Paratesticular RMS is less common than bladder/prostate RMS, accounting for approximately one third of GU RMS and 7% of all RMS (103,104). Intrascrotal paratesticular RMS usually arises in the distal area of the spermatic cord and may invade the testis or surrounding tissues, although primary RMS of the epididymis or tunics can also occur (64,103). Patients generally present with a painless scrotal mass. Scrotal ultrasound is generally the first diagnostic test that confirms a mass in the scrotum that does not illuminate. Biopsy should not be performed and the scrotum should not be violated. An orchiectomy is performed through an

inguinal incision, with a high ligation of the spermatic cord at the level of the inguinal ring. Paratesticular RMS has a relatively high rate of spread to the lymphatics, first to the para-aortic nodes, following the course of the spermatic cord into the renal hilar retroperitoneal space. Histologically, nearly all paratesticular RMS are of the embryonal subtype (104). Thin-slice CT scan of the abdomen and pelvis is recommended to evaluate lymphatics.

IRS-I and IRS-II (1973–1983) enrolled 150 patients with paratesticular RMS (104). The majority had group I disease ($n = 57$) and only 14 had metastatic disease. Ninety-seven percent had embryonal histological subtype. Patients with group I disease were significantly younger. The 3-year overall survival rates by group were 98%, 90%, and 64% for groups I, II, and IV, respectively. There were only four group III patients. Considering the relatively high risk of nodal involvement, surgical evaluation of lymph nodes was performed for most patients. Eighty-one percent of patients underwent exploratory laparotomy and inspection and/or pathological examination of retroperitoneal lymph nodes (RPLN); 67% of patients underwent retroperitoneal lymph node dissection (RPLND). RT was delivered to patients with groups II and III disease, six group I patients received radiation. Doses and volumes varied (hemiscrotum for scrotal violation, 19 of 20 patients involved with RPLN received nodal RT). The results revealed the excellent prognosis for this subset of patients, confirmed that unilateral RPLND was adequate and bilateral RPLND was not necessary, and also indicated age as an important prognostic factor.

One topic of substantial controversy over the past several years has been the necessity of surgical evaluation of RPLN. IRS-III (1984–1991) required ipsilateral RPLND for all patients, but IRS-IV (1991–1997) examined the use of CT scan of the abdomen and pelvis for evaluation of lymphatics in lieu of RPLND (105). The use of CT for staging led to a significant change in the distribution of patients with groups I and II disease in these trials. Sixty-eight percent of patients enrolled on IRS-III had group I disease versus 81% on IRS-IV. This was a result of CT scan failing to detect lymphatic involvement. As a result, failure-free survival for patients with group I disease was inferior on IRS-IV, 81% at 3 years. Failure-free survival was 96% on IRS-III. IRS-IV as well as the Italian and German Cooperative Group discovered the high risk of nodal involvement for children over the age of 10 years (105,106). The IRS concluded that children over 10 years old experienced a superior failure-free survival (100%) on IRS-III compared to IRS-IV (68%) due to recognized group II disease, likely as a result of receiving intensified chemotherapy and RPLN radiation. In contrast, the Italian and German Cooperative Group performed RPLND following negative CT scan and found only 1 patient to have positive lymph nodes; 13 of these patients were older than 10 years of age (106).

CT has been used to detect gross nodal involvement but may fail to demonstrate microscopic infiltration in some patients. Consequently, it has been the practice in the United States to perform a unilateral (trans-abdominal) nerve-sparing RPLND. Twenty-six percent of patients in IRS-I and IRS-II had RPLN involvement at diagnosis, and 16% had positive ipsilateral inguinal nodes; contralateral nodal involvement is rare (44,57). A similar percentage of patients in IRS-III had nodal disease (107). Patients with group II disease on the

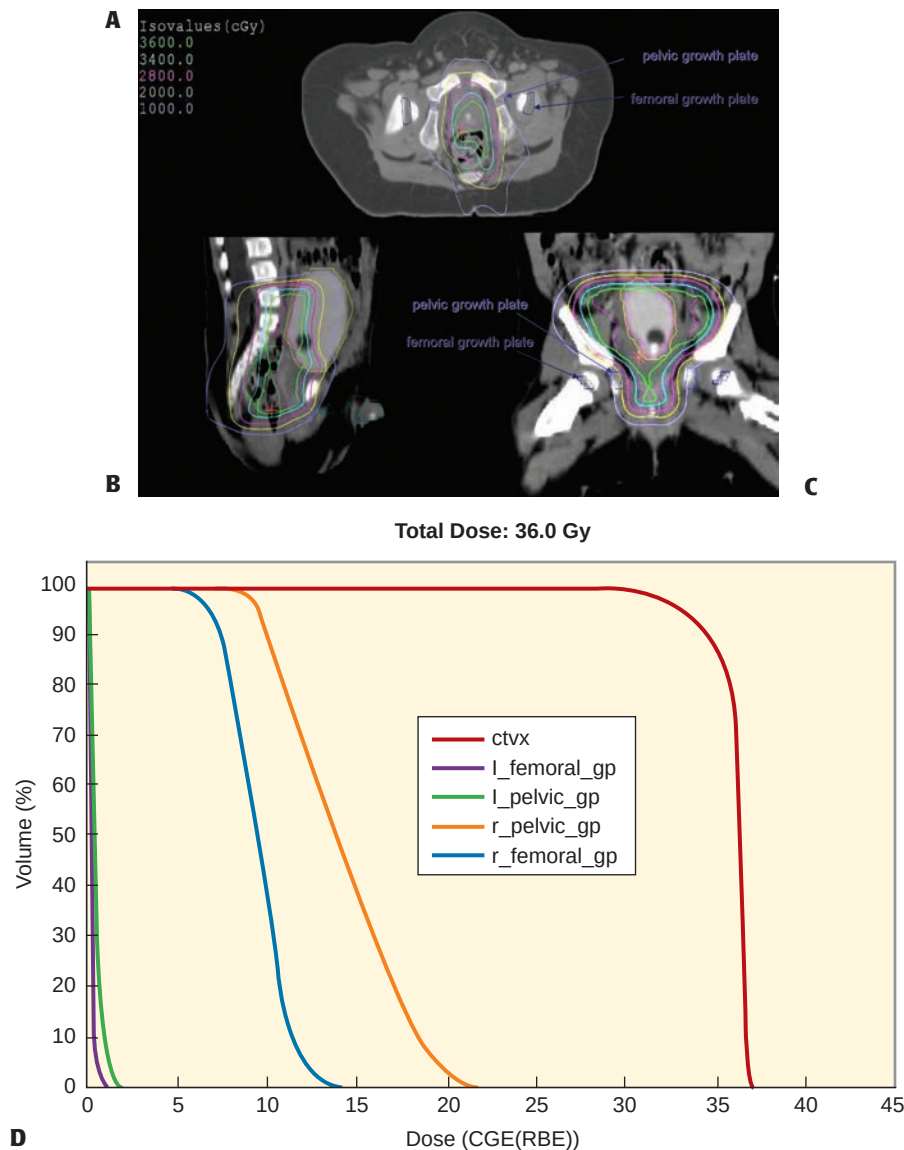


Figure 11.6 Axial (A), sagittal (B), and coronal (C) images of a proton radiation plan for a young child receiving radiation for microscopic disease following chemotherapy and surgical resection. **D**: Bladder–prostate dose–volume histogram displaying growth plates and clinical tumor volume. Additional structures contoured but not shown include bladder, bowel, rectum, penile bulb, and penile shaft. Prescription dose 36 Gy(RBE) to CTV. Femoral head growth plates receive a maximum dose of <3 Gy(RBE); pelvic growth plates receive a range 6–20 Gy(RBE).

basis of positive nodes receive RT to the nodal areas in the IRS studies, in contrast to patients with negative lymph node dissections.

Currently, on the open COG trials, ipsilateral RPLND is required for males diagnosed with paratesticular RMS over the age of 10 years and any patient with suspicious lymph nodes by CT scan. Potential complications of RPLND include bowel, obstruction, lymphedema, and nerve damage (108). Nerve-sparing techniques should be utilized for RPLND. Laparoscopic RPLND has been explored as a minimally invasive technique to evaluate lymph nodes for paratesticular RMS and is the preferred surgical approach at some institutions (109).

If a trans-scrotal biopsy is performed instead of the inguinal approach, then the patient is considered to have group II

disease. Resection of the violated scrotal tissue is recommended and radiation and/or hemiscrotectomy should be considered (45). The contralateral testicle can be transposed laterally into the thigh before irradiation and later re-implanted into the scrotum. The Italian and German Cooperative Group reported no local relapses for 24 patients initially managed with trans-scrotal biopsy that were down-staged to group I with re-excision (106). These patients received only chemotherapy, suggesting that chemotherapy was sufficient to eradicate this microscopic disease.

The most common use of RT for paratesticular RMS is for nodal disease. All patients with nodal disease should receive RT regardless of response. Currently on the COG studies, gross nodal disease present after surgery receives a dose of 50.4 Gy. This may be reduced to 41.4 Gy for microscopic

disease if there is pathologic confirmation of tumor response. Lymph nodes follow the vessels and are generally present within 2 cm of the vessels. Vessels and any involved lymph nodes should be contoured. Anterior and posterior opposed fields are generally used. Structures that are at risk in close proximity include bowel, kidneys, bladder, and bony structures.

Vagina and Vulva

RMS of the vagina and vulva is rare accounting for 3% of pediatric RMS, the majority of these occurring in the vagina (11,110). Vaginal RMS occurs in very young children (90% younger than 5 years of age; mean age for vaginal primaries under 2 years (111). Presenting symptoms include vaginal bleeding, vaginal discharge, and a protruding vaginal mass. Vaginal tumors most commonly arise from the anterior wall, are often multicentric, and can invade the vesicovaginal septum or bladder wall. Regional nodal involvement is uncommon. Vaginal tumors are almost exclusively the embryonal (usually botryoid) subtype (111). Vulvar RMS is encountered even less frequently. Age range is more variable and the mean age of girls with vulvar tumors is 8 years (111). Vulvar inflammation and genital bleeding are the most common presenting signs. On clinical examination, vulvar RMS is most commonly found as a firm nodule embedded in the labial folds or in a periclitoric location. Vulvar tumors may be initially mistaken as an infected Bartholin's gland. It is important that all members of the pediatric oncology team examine the child at the time of diagnosis of a vaginal or vulvar RMS. For the radiation oncologist, this evaluation is crucial for treatment planning as tumors will likely respond rapidly to chemotherapy and imaging may not provide all details needed. MRI and/or CT of the pelvis should be performed at diagnosis and during treatment to evaluate local disease and response. Vulvar RMS may be of any histological subtype, and the alveolar subtype is often seen.

The classic surgical technique for treatment of vaginal tumors was an anterior exenteration with urinary diversion. Surgeries considered less aggressive included vaginectomy with or without hysterectomy. Unfortunately, fewer than 20% of patients could be cured with surgery alone (112). Survival rates improved to 60–80% when chemotherapy was added to surgery, with or without RT. IRS-I (1972–1978) included nine patients with vaginal primaries, eight without metastatic disease (9,113). Six underwent surgery up-front (pelvic exenteration, vaginectomy, or hysterectomy) and two underwent delayed vaginectomy or hysterectomy. All patients received chemotherapy and three patients received radiation. There were high rates of disease-free and overall survival, but surgical morbidity was great. The favorable outcome and chemosensitivity of these tumors were recognized. The major goal of IRS-II (1978–1984) was to maintain outcomes while allowing for organ preservation (98). This study adopted a strategy that included biopsy followed by chemotherapy and organ-preserving second-look surgery at week 8 or 16, depending on the response. The use of RT depended on the completeness of the surgical procedure. Surgical resection was performed with the goal of removing all residual disease with minimal morbidity. Using this treatment approach, 18 of 21 (86%) patients survived at 3 years (98). IRS-III (1984–1988) gave 20 weeks of chemotherapy and then RT to patients who had not achieved a complete remission by that time. Patients

with residual disease underwent surgical resection, most with no pathological evidence of tumor or only rhabdomyoblasts (113). IRS-IV gave RT at week 9, and the cure rate remained high and only 13% of patients underwent surgical resection more extensive than local excision or biopsy (113,114). For female genital tract RMS, the rate of hysterectomy decreased (48% in IRS-I/IRS-II to 22% in IRS-III/IRS-IV) and the use of RT for unresectable tumors increased (23% IRS-II to 45% IRS-IV) (114). Survival rates have remained with better preservation of organ function. For patients that do recur, locoregional failure predominates. It is possible that introducing local therapy at an earlier time point may be of benefit, but chemotherapy as the initial treatment modality has provided superior functional outcomes and high tumor control rates and will remain standard for unresectable disease (114). Salvage rates for patients who experience local failure is higher for female GU sites than for other RMS locations (114). However, longer follow-up is necessary as late relapses may occur.

Current guidelines on COG trials are similar; limited surgery is preferred, and radical surgery is inappropriate except in the setting of persistent or recurrent disease. Surgery is currently performed if feasible as a second-look procedure at week 13. Tumors that are not resectable receive radiation at this time. For those that can be resected, radiation dose is based on margin status. No radiation is given for negative biopsies or completely resected disease and lower RT doses are used for patients with microscopic residual tumor postoperatively. Distal vaginal tumors may not require hysterectomy. Proximal lesions may require hysterectomy with partial or total vaginectomy. Irradiation with brachytherapy may also be considered for these patients.

Vaginal and vulvar RMS represent a site that may benefit from brachytherapy. The Institut Gustave Roussy has extensive experience with this technique and they prefer brachytherapy to external beam radiation when feasible (115). In their series, endocavitary brachytherapy was used for vaginal primaries utilizing a customized mold, while interstitial was preferred for vulvar RMS. Prescription dose was 60–65 Gy delivered in one to three applications. They reported excellent local control for 39 females treated with excellent sparing of surrounding critical structures and low rates of toxicity. Figure 11.7 demonstrates an endocavitary brachytherapy plan for a 3-year-old girl with a vaginal RMS.

For treatment planning (external beam or brachytherapy), CT planning should be utilized. Critical structures to consider include uterus, ovaries, rectum, bladder, bowel, and bony structures. Ovarian transposition may be necessary to avoid dose to the ovaries as they can be affected by doses as low as 2 Gy (116). Vaginal stenosis and fistulas are other potential side effects of treatment.

Uterus and Cervix

Uterine and cervical RMS are less common than vaginal RMS. They occur predominantly in adolescent girls near puberty with a mean age of 13 (111). Patients may present with a pedunculated polyp protruding from the cervix or with diffuse intramural involvement of the uterus and/or cervix and even invasion of adjacent organs; bleeding is common (111,117,118). When uterine tumors occur in younger children, distinction from a vaginal tumor may be difficult. The predilection of uterine and cervix tumors for adolescents and of vaginal tumors for the very

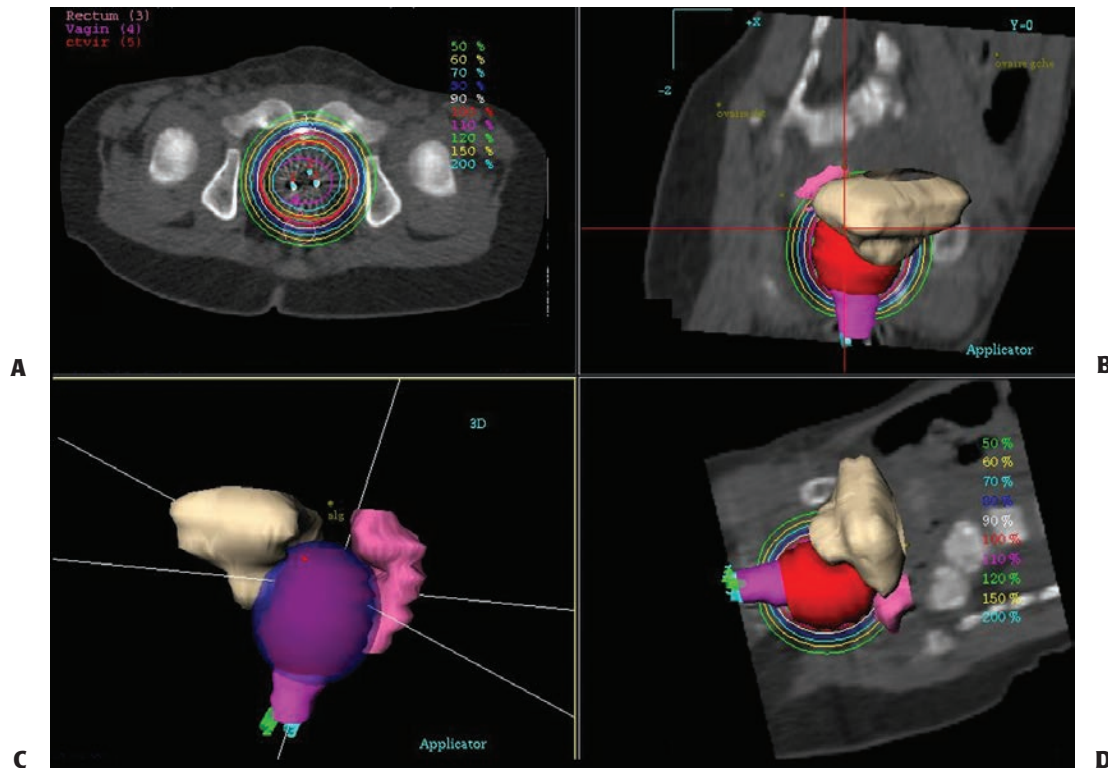


Figure 11.7 Depicts a brachytherapy plan for a vaginal rhabdomyosarcoma. This 3-year-old girl relapsed after chemotherapy alone. Prescription dose delivered was 60 Gy. **A:** Axial CT treatment planning image showing percent isodose prescription lines. This plan demonstrates rapid fall off allowing for sparing of the pelvic growth and femoral growth plates as well. **B:** A multiplanar view. **C,D:** Sagittal DRRs with and overlay of treatment volumes, normal structures, isodose lines. (Courtesy of Christine Haie-Mader, MD.)

young helps to predict the site of origin, but anatomical determination is often possible only after regression of the tumor after chemotherapy. Tumors of this location are generally of the embryonal histology, most often botryoid subtype.

In IRS-I and IRS-II, 10 patients had uterine or cervical primaries. In patients who presented with localized polypoid tumors, polypectomy and adjuvant chemotherapy was highly curative (111). When hysterectomy or vaginectomy successfully removed all gross tumor, cure was also achieved. Conversely, all patients with infiltrative or metastatic RMS died of disease within 11 months of diagnosis (111). Brand et al. (118) reviewed 21 cases of botryoid sarcoma of the uterine cervix. Most patients received chemotherapy, and eight underwent pelvic irradiation. Eighty percent of these patients survived.

Currently, treatment of uterine and cervical RMS is intended to preserve pelvic organs when possible. Patients with initially resectable disease are placed in group I or II by surgery, followed by chemotherapy, and then RT if microscopic residual disease is proven to persist, or hysterectomy with no RT. For those with group III disease, primary chemotherapy is given, followed by a second-look laparotomy. If there is gross residual tumor that cannot be completely resected with hysterectomy, or if microscopic disease is found after resection, the patient then receives RT and continues on chemotherapy. If the second-look exploration shows no demonstrable tumor or tumor that is completely resected, then no radiotherapy is given, and the patient continues on chemotherapy alone. Survival rates for nonmetastatic uterine and cervix RMS should approximate those of patients with

RMS of the vagina and vulva, but response to chemotherapy may be less (114).

The SIOP approaches tumors of the female genital tract with initial chemotherapy and local therapy only for those patients with tumors that do not completely respond to chemotherapy, regardless of initial tumor characteristics (119). They reported 5-year overall survival of 91% and event-free survival of 78% at 5 years for 38 females with RMS of the vulva, vagina, and uterus treated in this manner (119).

Extremity

Extremity RMS comprises approximately 20% of pediatric RMS. Despite intensification of therapy, tumors of this location continue to have a poor prognosis compared to other sites. Overall survival rates have improved from 47% in IRS-I to just over 70% at 3 years in IRS-III and IV, but relapses requiring salvage treatment remain high (FFS at 3 years in IRS-IV was only 55%).

The prognosis for patients with extremity RMS is compromised by the high frequency of the alveolar subtype, of lymphatic metastasis at diagnosis, and of metastasis to any site at diagnosis (27% vs. 18% in all patients with RMS) (120). Approximately 50–70% of these lesions are alveolar RMS, an unfavorable histology (67). Regional lymph node involvement occurred in 17% and 12% of patients on IRS-I and II, respectively (44,57).

Although there is no evidence that amputation is more often curative than wide local excision, this procedure retains a role in patients where limited excision and high-dose irradiation would produce unacceptable functional results, in

patients with distal (alveolar) extremity lesions where gross removal is otherwise impossible, and in patients with massive local recurrences after conservative therapy (67,121). The preferred operative procedure for primary management is wide excision with negative margins.

Efforts to improve detection of involved lymph nodes in hopes of appropriately identifying patients that will benefit from intensified chemotherapy and nodal radiation has been a goal of recent research efforts. Clinical examination, MRI, and CT scan can identify involved lymphatics, but small amounts of nodal disease may go unnoticed with these techniques. On IRS-IV, 76 of 139 patients underwent surgical evaluation of regional lymph nodes. Fifty percent of these patients were found to have lymphatic involvement. Of those patients that had clinically negative lymph nodes, but underwent lymph node sampling, 17% had microscopic lymph node involvement. PET and PET/CT have been explored in small studies for its use in RMS and specifically extremity RMS (122). The current COG RMS studies are trying to evaluate its utility on a larger scale. Sentinel lymph node biopsy is now routinely used for breast cancer and melanoma. Although the experience for pediatric RMS is limited, its use should be explored further as it may prove an accurate method of identifying microscopic nodal involvement with less morbidity than lymph node sampling or full dissection (123). Current COG studies require systematic lymph node sampling for extremity tumors.

Chemotherapy is always given a component of therapy for extremity RMS. RT is omitted only for patients with completely resected favorable histology tumors with negative nodes. The tumor is treated with a 1.5 cm margin on the current COG protocols (but discretion should be used to avoid circumferential irradiation and irradiation of the joint space). Regional lymph nodes are treated only when involved. A strip of soft tissue along the extremity should be spared to avoid lymphedema. Three-dimensional conformal RT using opposed fields (AP/PA or obliques) generally results in optimal dose distribution. Figure 11.8 demonstrates a three-dimensional conformal radiation plan for an extremity RMS using opposed oblique fields.

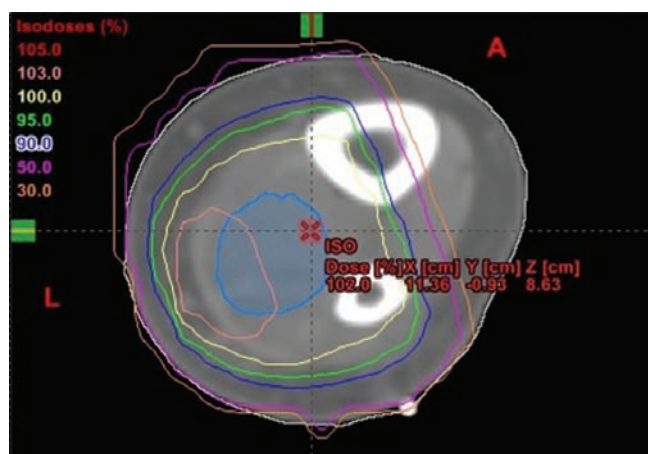


Figure 11.8 Axial image of a 3D-conformal photon plan for a lower extremity sarcoma. Note that a strip of soft tissue is completely spared in effort to avoid lymphedema. (Courtesy of Karen Marcus, MD.)

Parameningeal

Parameningeal (PM) RMS account for approximately 15% of pediatric RMS and 40–50% of head and neck RMS (11). They arise in sites adjacent to the meninges, as the name implies, and have the potential to extend intracranially and spread through the CSF. The four main subsites of PM RMS include the middle ear, nasal cavity/paranasal sinuses, nasopharynx, and infratemporal fossa/pterygopalatine fossa/parapharyngeal area. Middle ear tumors originate medial to the tympanic membrane. They may extend anteriorly and laterally and present as a palpable mass in the region of the parotid, break through the tympanic membrane into the external ear canal, or spread through the posterior mastoid to the posterior cranial fossa. The three paranasal sinuses include the ethmoid, maxillary, and sphenoid sinuses. They surround the nasal cavity and the true site of origin is often difficult to determine. These tumors can invade the orbit or extend through the basal of skull in the region of the cavernous sinus to the temporal lobes or through the cribriform plate to the frontal lobes. The nasopharynx is located superior to the pharynx and is bounded by the nasal septum/nasal cavity, sphenoid sinus, pharyngeal walls, and soft palate. Invasion of the base of the skull is not infrequent and may involve the cavernous sinus causing cranial nerve palsies. Although lymph node involvement can occur, modern series report fewer than 20% of PM RMS as having positive lymph nodes (44,124). Approximately 80% of these tumors are of embryonal histology; the remaining 20% are alveolar. Meningeal penetration and leptomeningeal tumor cell seeding should be assessed in patients diagnosed with PM RMS. Because PM RMS can invade locations such as the orbit and parotid gland, it is sometime unclear if the site of origin is truly PM. When this distinction is not clear, the tumor should be considered PM as this dictates more aggressive therapy and invasion from more favorable sites into the sinuses, middle ear, or parapharyngeal space is less likely.

Complete surgical resection of the primary with a satisfactory cosmetic and functional outcome is rarely possible; the vast majority of patients with PM RMS have group III or IV disease. The role of surgery is generally confined to establishing a diagnosis with a biopsy or a subtotal excision. Cervical lymph node dissection (radical neck dissection) is rarely appropriate because of the associated morbidity and the low frequency of subclinical nodal involvement; conversely, suspicious nodes should be surgically evaluated. Before the use of chemotherapy, fewer than 20% of patients survived despite aggressive surgery and radiation (69). For patients with PM RMS, the volume and timing of RT are critical. The radiation volumes for PM tumors have been modified over the years as a result of the lessons learned through the IRS studies (125).

IRS-I (1972–1977) enrolled 57 patients with PM RMS (126). Thirty-five percent had evidence of meningeal involvement within 12 months of diagnosis. This was almost universally fatal, as 90% of these patients died of their disease. RT on this protocol was delivered to the tumor plus a 2 cm margin at week 6. Poor outcomes led to a revision of the IRS-I protocol in 1977 near its conclusion and helped form guidelines for IRS-II. Patients considered at high risk of meningeal dissemination defined as those with intracranial extension, cranial nerve palsy, skull base erosion, or positive CSF received whole-brain or craniospinal radiation (61). Intrathecal

chemotherapy with three agents was also advised. Additionally, the timing of RT was changed with whole-brain RT delivered week 0 and spinal RT at week 6. After the conclusion of IRS-II, patients treated with intensive chemotherapy and craniospinal radiation were compared to those treated with less-intensive therapy and without spinal irradiation (125). The risk of meningeal dissemination did not differ and radiation to the spine was not advised on IRS-III (61).

In IRS-III, if there was no evidence of intracranial extension, CSF cytology was negative, and bone erosion or cranial nerve palsies were absent, then the primary lesion was irradiated with a 5-cm margin, including treatment of the adjacent meninges. Patients not meeting these criteria received intrathecal chemotherapy. If the CT or MRI demonstrated discontinuity intracranial extension of the primary tumor, but the CSF cytology was negative, prophylactic whole-brain RT without spinal RT was given along with treatment to the primary tumor. Finally, for positive CSF cytology, craniospinal irradiation was given. Results are as follows: 69% 5-year progression-free survival, 15% local failure for group III patients, and a 4.7% incidence of contiguous CNS relapse (46,127). IRS-IV reduced the radiation margin to 2 cm, and only patients with diffuse intracranial meningeal extension or multiple sites of brain parenchymal disease were treated to the entire cranial cavity (127). RT was given at the beginning of the treatment course when there was clear evidence of intracranial extension, defined as positive CSF cytology results or any imaging evidence (by MRI) that tumor touches, displaces, invades, distorts, or otherwise causes a signal abnormality of the dura. Otherwise, chemotherapy was given first, with RT given at week 12. RT was omitted only for patients with completely resected, favorable histology tumors with

negative nodes. Intrathecal chemotherapy and craniospinal irradiation were no longer used. The extent of surgery was determined by the potential cosmetic and functional outcome, and second-look procedures were allowed (128). IRS-V adopted the same guidelines for radiation. For all of the above IRS studies, the prechemotherapy volume has been used to define the GTV. There has been interest in evaluating a lower dose of radiation to the prechemotherapy volume and then coning down to the postchemotherapy volume in attempt to decrease toxicity (Fig. 11.9). The underlying principle supporting this theory is that areas of disease no longer seen radiographically represent microscopic disease and thus should be controlled with a dose of radiation for microscopic dose (36 Gy). At the University of Pennsylvania it has been their practice since 1992 to cone down to the postchemotherapy volume. They reported favorable results for patients treated in this manner (129). ARST 0531 defines the CTV as the GTV plus 1 cm and continues to define the tumor volume as the prechemotherapy volume, but allows for a cone down to the postchemotherapy volume after 36 Gy. All radiation starts at week 4 to allow time for more complex planning and CT planning is required. There is often reluctance to adhere to radiation guidelines for very young children. The SIOP demonstrated the significant and substantial value of RT for these patients (124). RT should not be omitted and the COG encourages adherence to RT guidelines even for patients of 24 months of age. The radiation oncologist should be involved at diagnosis to allow for evaluation of tumor prior to chemotherapy and to allow adequate time for treatment planning. Advanced techniques including IMRT and proton radiation can provide improved sparing of normal tissues in this complex site (130). Figure 11.10 shows a proton plan for a 5-year-old boy with a PM RMS of the left infratemporal fossa.

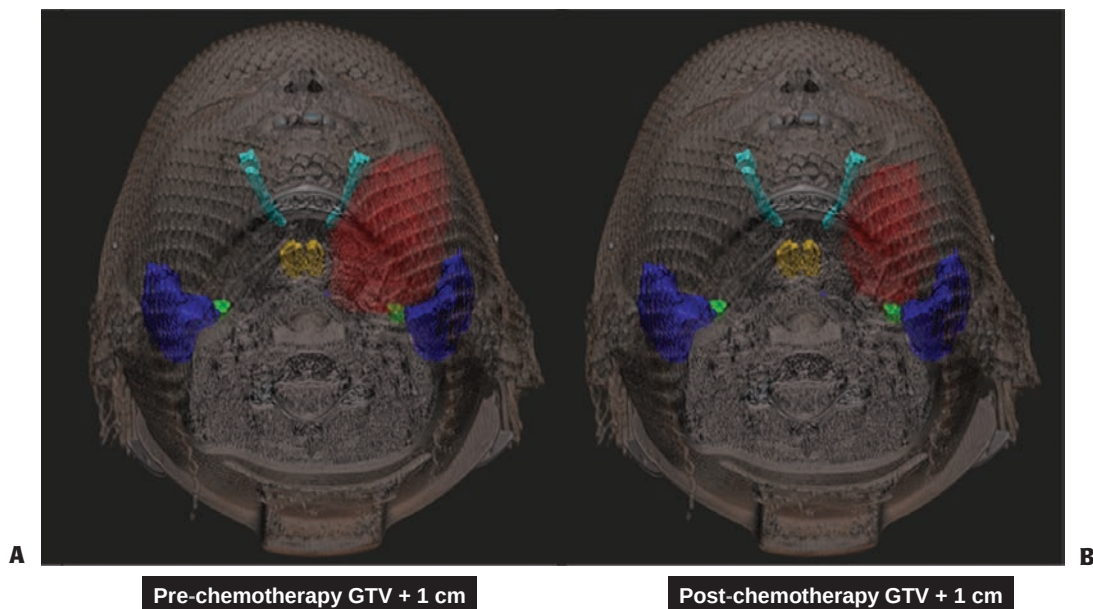


Figure 11.9 High-definition volume rendering (Courtesy of Fovia, Inc., and Justin Lee.). Treatment volumes for parameningeal rhabdomyosarcoma. Recommendations on the current COG protocols are for treatment of the prechemotherapy tumor volume (GTV) plus 1 cm to form the CTV. **A:** Although all IRS and the current COG studies recommend the use of the prechemotherapy volume, postchemotherapy volumes with a margin of 1 cm may be used for a cone down (although not encouraged for invasive tumors) and have been explored in institutional studies as well as European studies. **B:** The postchemotherapy volume plus 1 cm (after 4 weeks of chemotherapy). Red, CTV; dark blue, parotid glands; cyan, optic nerves; green, cochlea; yellow, hypothalamus and pituitary.

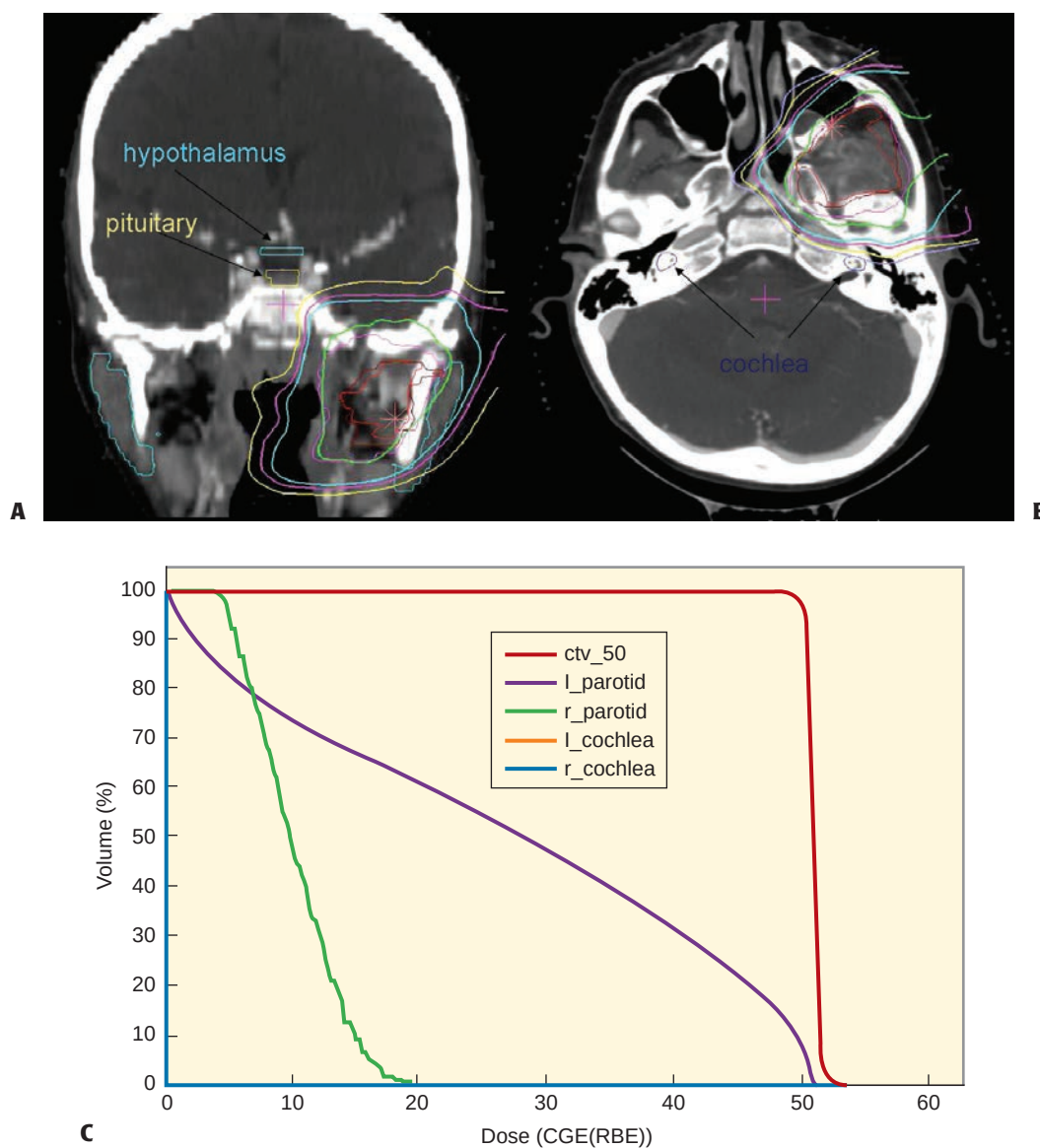


Figure 11.10 Coronal (A) and axial (B) images for a proton plan for treatment for a parameningeal rhabdomyosarcoma. C: Dose-volume histogram for proton plan for parameningeal rhabdomyosarcoma. Advanced planning techniques are particularly useful for sparing normal tissues in this region.

Orbit

Orbital RMS comprises approximately 10% of pediatric RMS (20). Because of the accessibility of the orbit to examination and the sensitivity of ocular function to mass effect, orbital RMS often is diagnosed early. Eyelid swelling and globe displacement are common presenting signs. Orbital exenteration was the standard treatment until the mid-1960s, but local disease control was rarely achieved. In the late 1960s, Cassady and coworkers (7,131) observed that RT afforded local control in five of five patients after a biopsy. RT has now assumed a major role in the treatment of orbital RMS. Approximately two thirds are group III orbital RMS. Treatment generally consists of biopsy, chemotherapy, and RT. The volume need not include the entire orbit if the tumor is small. For patients treated on IRS I & II, local control was 94% with RT and was increased to 98% with surgical salvage (82). Of note, orbital

RMS can also invade meninges via erosion of the superior orbital fissure. An analysis of IRS data suggested a relationship of histology to outcome. For the 84% with embryonal histology, the 5-year survival was 94%. However, for the 10% of children with alveolar RMS, this rate was 74%, and all five infants with alveolar disease died (56). Current COG protocols dictate a prescription dose of 45 Gy for both embryonal and alveolar RMS. However, alveolar orbital RMS (group III) are considered intermediate risk and receive more intensified chemotherapy on ARST 0531, while embryonal orbital RMS are treated on the favorable-risk protocol ARST 0331. Because of the favorable outcome of patients with orbital RMS and substantial late toxicity, the SIOP attempted to use chemotherapy alone (132). Local control was compromised by this strategy. An international workshop evaluating a total of 306 patients from four large cooperative groups found no difference in overall survival

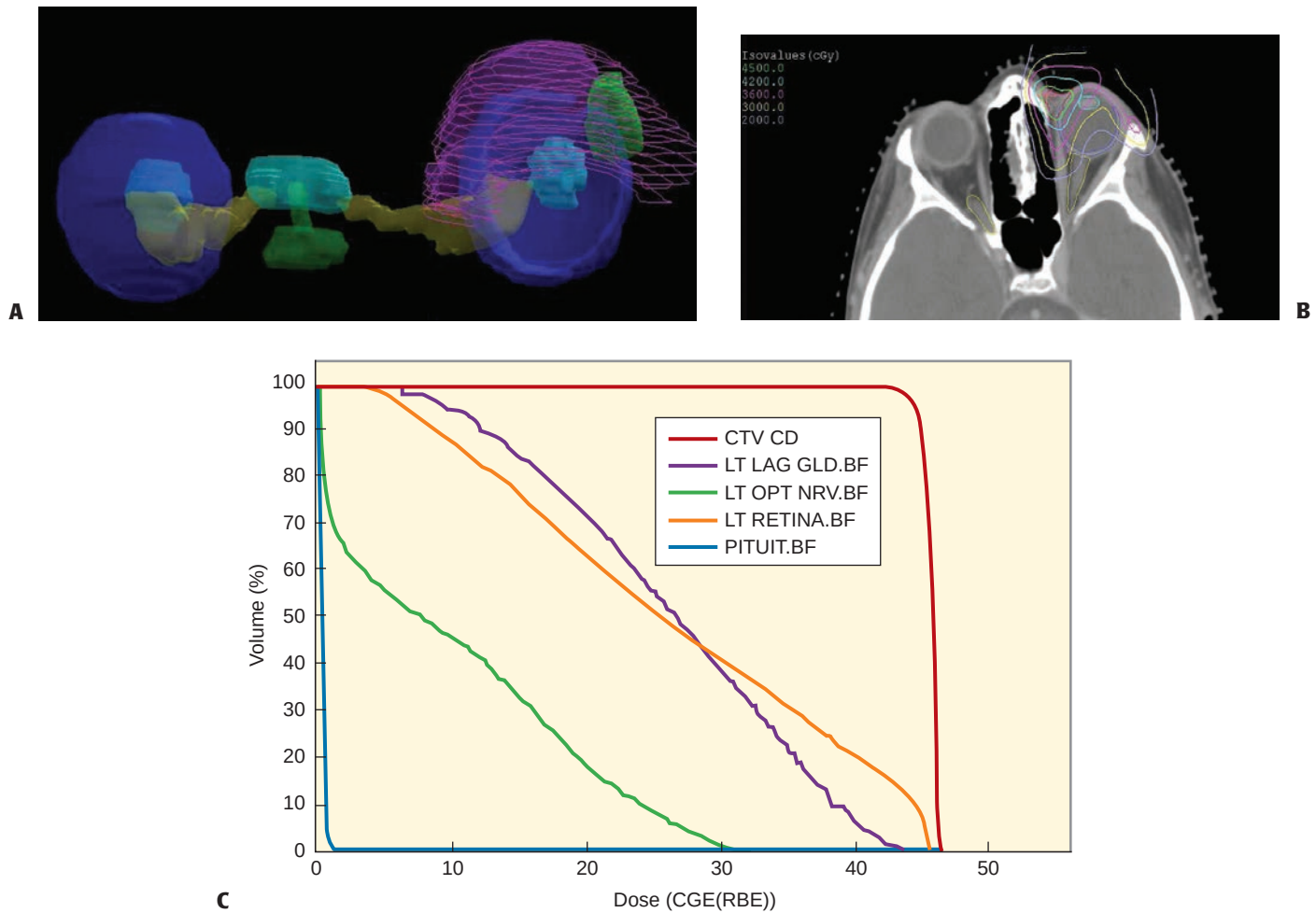


Figure 11.11 Proton treatment for an orbital rhabdomyosarcoma. **A:** A multiplanar view of a large orbital rhabdomyosarcoma involving the superior orbit and invading lacrimal gland. **B:** Axial view of proton plan. **C:** Dose–volume histogram.

based on delivery of RT at diagnosis, but a significant difference in local control (82% with RT vs. 53% without RT) (133).

The functional and cosmetic late adverse effects of orbital irradiation are considerable because of the close proximity of several critical structures. Three-dimensional planning should always be utilized. The RT plan should be designed to deliver 45 Gy to the tumor volume while taking into consideration the doses delivered to the lens, lacrimal gland, cornea, retina, optic nerve, bony structures, and brain (134). Treatment with the eye open to avoid the bolus effect of the lids, unless the lids are involved, may be preferred. Advance photon techniques should be considered. Proton therapy allows for substantial sparing of normal tissues for patients with this disease and may help decrease late effects in the orbit (Fig. 11.11) (135,136).

Other Head and Neck Sites

Parotid region, oral cavity, oropharynx, scalp, and larynx RMS comprise the head and neck sites outside of the paraneural region and orbit. They make up approximately 10% of RMS and have a favorable prognosis. They are generally of embryonal histology; however, cheek and scalp lesions

have a higher frequency of alveolar histology (82). Superficial lesions may be marginally or, at times, widely resected with satisfactory cosmesis and function, a situation that less often pertains for deeper tumors. Narrower resection margins (less than 1 mm) are acceptable because of anatomic restrictions. Optimal cosmesis with excellent disease control may best be obtained with a marginal resection and subsequent RT. For the deeper tumors (oral cavity, buccal mucosa, larynx, parapharyngeal, or parotid region), RT is generally necessary. Because of the favorable outlook for patients with nonparaneural head and neck tumors, most patients have been classified as stage I or II in IRS-IV and IRS-V and are now eligible for ARST 0331 and therefore receive less-intense chemotherapy than do those with PM head and neck tumors (137).

Although the early experience with head and neck RMS suggested that lymph node involvement was uncommon (8% in IRS-I and IRS-II), this may have resulted from less than thorough assessments. In fact, lymph nodes were positive in 20% of patients in whom lymph node status was reported (82). Donaldson et al. (69) reported a similar incidence. A CT scan of the neck with thin slices should be performed for all

patients with head and neck RMS. Even with this study, detection of lymphatic involvement can be difficult. PET/CT may improve detection of lymph nodes for this group of patients and is encouraged on the current COG trials (92). Involved lymph nodes groups may be treated with surgery and radiation. Similar to PM RMS and orbital RMS, tumors are in close proximity to critical structures and advanced radiation techniques may be of benefit in avoiding normal tissues (138,139).

Trunk

Truncal sites include the chest wall, paraspinal area, abdominal wall, and diaphragm in decreasing order of frequency. Scapular and buttock lesions are considered to be extensions of the extremity, and retroperitoneal and perineal tumors are considered separately. An early IRS report focused on 30 children with soft tissue sarcoma of the trunk (140). Ten of the 14 children with chest wall primaries had group I or III disease, and 5 were long-term survivors. None of the four children with metastases at diagnosis survived. Improvements in outcomes were seen in IRS-IV. Five-year failure-free and overall survival was 68% and 78%, respectively (compared with 30% and 40%, respectively, for IRS-I) (141). A recent report from the Children's Oncology Group reported overall outcomes on the impact of surgical excision for chest wall cases. They found no difference in failure-free or overall survival based on the degree of resection.

Paraspinal tumors were rare (3.3%) in IRS-I and IRS-II. They tended to be greater than 5 cm in diameter, often invaded the spinal extradural space, and were commonly of an undifferentiated or extrasosseous Ewing's subtype. Survival at 5 years was approximately 50% in both studies (142). Local and distant relapses were common, and patients with embryonal subtypes fared no better than others.

RMS of the diaphragm is typically unresectable and/or metastatic at diagnosis. A total of only 15 patients were enrolled on IRS studies I–IV (143). Although complete remission was achieved in 10 patients (67%), only 5 (33%) were alive without disease at a median follow-up of 9 years.

Current guidelines include as wide a surgical resection as is feasible, either at diagnosis or after chemoradiotherapy as a second look. For patients with an initial excision that was less aggressive than feasible or of an uncertain nature, a re-excision should be considered. RT is given to all patients except those with completely excised small, favorable histology tumors and uninvolved lymph nodes. RT fields encompass the original disease extent, and chemotherapy is always used (140,142).

Retroperitoneal

Retroperitoneal tumors comprise 11% of RMS. Children usually present with abdominal pain, back or lower extremity pain, and/or an abdominal mass (144). Median age at diagnosis is approximately 6 years. The majority of patients have embryonal subtype, but alveolar histological subtype is seen (145). Retroperitoneal tumors are larger and have a higher rate of distant metastases at diagnosis compared to tumors of other sites likely due to the ability of tumors to grow in the abdominal or pelvic cavity without causing symptoms. They often compress or invade abdominal or pelvic organs and/or major vessels and are usually not amenable to up-front resection. In addition, lymph node involvement is common (23% in IRS-I and IRS-II; 28% in IRS-IV) (44). Delivery of RT is also prob-

lematic due to the size and proximity of normal organs of patients. In the IRS-I and II, advised RT was not delivered in 39% (144). This very high number of RT protocol violations was attributed to the difficulty in delivering the prescribed dose while respecting normal tissue tolerance. IRS-IV, similarly, had a high number of protocol violations for this subsite (145). All these factors combine to render the prognosis for retroperitoneal RMS worse than for most other sites. Five-year survival was approximately 40% in IRS-II and 4-year survival was 60% on IRS-III (146). IRS-IV demonstrated improved outcomes reporting estimated failure-free and overall survival at 5 years of 70% and 75%, respectively, for tumors of the retroperitoneum and non-GU pelvis tumors (145). Locoregional recurrence continues to be problematic in this disease. Embryonal subtype and age <10 years were found to predict improved prognosis in IRS-IV (145). Debulking of >50% may improve outcomes, but it is also possible that debulking may appear to improve outcome due to selection bias (smaller tumors are amenable to debulking) (146). A debulking procedure should be strongly considered if feasible (145). In addition, gastrointestinal toxicity is frequently encountered in long-term survivors (147). Guidelines are essentially the same as those noted previously for truncal tumors. Because of normal tissue tolerance, RT usually involves multiple reductions in field size. CT planning should be used. IMRT may be of benefit. Proton radiation using fields entering from posterior may be useful for sparing structures anterior to the tumor volume for selected cases.

Perineal

Perineal tumors are rare (2% of RMS) and carry a poor prognosis (148,149). These tumors include nongenitourinary tumors of the perineal and perianal tissue located outside of the pelvis and between the pubic symphysis and coccyx. Tumors of this region are more often of alveolar histology than embryonal and lymph node metastases are common (148,149). The 3-year survival reported for IRS-I and IRS-II combined was 59%, which was somewhat inferior to that of patients with disease in other sites (64% for other sites) (20,148). The 5-year failure-free and overall survival rates for IRS-I to IRS-IV reported collectively was only 45% and 49%, respectively (150). When extent of disease was controlled for, only age less than 10 predicted for an improved outcome. Based on the high incidence of lymph node involvement, the authors recommended surgical evaluation of both the iliac and inguinal lymphatics for accurate staging and to determine radiation fields. A recent analysis of 29 patients from Japan also reported poor outcomes for these patients (149). The approach to these patients also entails as complete a resection as functionally acceptable, followed by chemotherapy and RT as appropriate. Figure 11.12 demonstrates an IMRT plan for a child with perineal RMS involving regional lymph nodes.

Hepatobiliary Tree

Hepatobiliary RMS is rare, often of botryoid subtype, and generally occurs in very young children. The common bile duct, the common, right, or left hepatic duct, and the ampulla of Vater may be sites for RMS. A recent IRS report reviewed the experience of the 25 patients in IRS-I to IRS-IV with RMS of the biliary tract (151). The majority of patients presented with intermittent obstructive jaundice with or without abdominal distention, fever, pain, and loss of appetite. Imaging

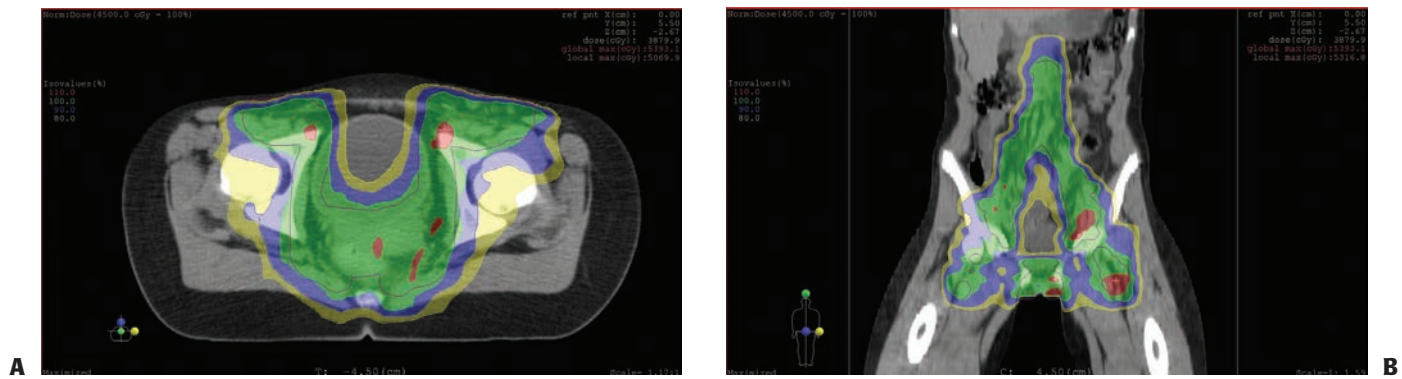


Figure 11.12 Axial (A) and coronal (B) images of an intensity-modulated photon therapy plan for a child with a perineal rhabdomyosarcoma with nodal involvement. (Courtesy of Arthur Liu, MD.)

was inadequate for the identification of regional metastases. Despite aggressive surgery, gross total resection at diagnosis was possible in only six cases, two of which had negative surgical margins. However, the 5-year survival rate was 78%, and much of the mortality was related to infectious complications associated with external biliary drains. The biliary tract is considered a favorable site, and current recommendations

include conservative surgery (without bile drainage) to establish an accurate diagnosis and determine the extent of regional disease, followed by chemotherapy and RT. Delivery of RT may be challenging given young age and volume and dose tolerances of the liver and kidneys. Proton therapy may be of benefit, particularly for large tumors and when constraints cannot be met with other RT modalities (Fig. 11.13).

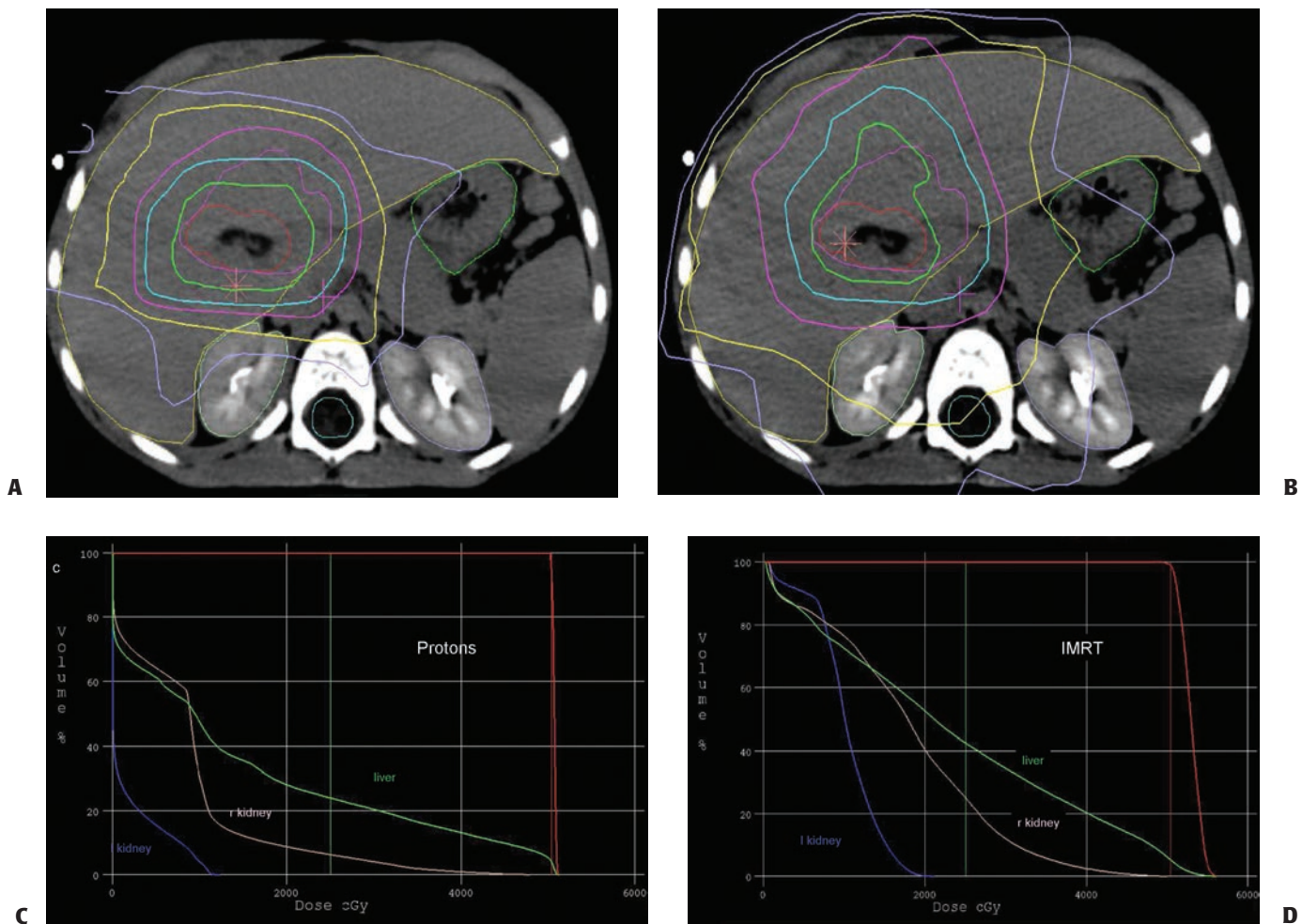


Figure 11.13 Axial images for a proton (A) versus an intensity-modulated photon plan (B) for a 3-year-old child with biliary rhabdomyosarcoma. The properties of proton radiation allow for increased sparing of liver and kidneys as seen in images and dose-volume histograms (C).

Metastatic Disease

Approximately 15% of patients with RMS present with metastatic disease (14). Failure-free survival at 3 years for this group of patients is only 25%. An analysis of IRS-IV patients with metastatic RMS showed a favorable subgroup of patients with embryonal histology and two or fewer metastatic sites with a 3-year failure-free survival of 40% and overall survival of 47% (29). Patients with metastatic disease that does not involve the bone marrow are also more likely to survive (25–30%) (14,19,29). A separate report examined outcomes for patient with pulmonary metastases only (152). The majority of these patients had multiple lung nodules, but most patients did not have biopsy to confirm metastatic disease. Thirty-five percent of patients did not receive radiation to the lungs. Fewer lung recurrences were seen in patients who did receive lung RT, but there was no significant impact on survival. Overall survival for patients with disease metastatic to the lung did not differ from those with other single-site metastases.

Chemotherapy is the main treatment for children with metastatic RMS. Surgery and/or radiation are used for local control of both primary and metastatic disease. Although long-term survival is poor, data suggest the use of local therapy can improve outcome (153).

RECURRENT DISEASE

Unfortunately, the prognosis for most patients with recurrent RMS is poor, although there is a subset of patients with favorable salvage rates (154). These patients are those with favorable histology who initially presented with stage I or group I disease and whose recurrence is local or regional. The 5-year survival rates are 50–70% for this group, whereas most other children have an extremely poor prognosis. Despite the poor long-term outlook for patients with recurrent disease, many can still achieve a durable second remission with salvage therapy, and there are several active chemotherapy regimens, including ifosfamide with etoposide and cyclophosphamide with topotecan (155,156). The COG has been investigating a risk-based approach to salvage treatment in which favorable-risk patients were treated with doxorubicin and cyclophosphamide alternating with ifosfamide and etoposide. Unfavorable-risk patients with measurable disease received vincristine and irinotecan (with a randomization to two different drug administration schedules), followed by the alternating schedule, or the aforementioned regimen with the addition of a new agent, tirapazamine, for patients without measurable disease. This trial met its accrual goals and a new trial for patients with recurrent disease is under development. RT is often used for local control or palliative treatment, and aggressive surgery may improve outcomes in the setting of recurrent disease. Unfortunately, high-dose cytotoxic therapy with bone marrow rescue has not proven to be effective for patients with metastatic or recurrent disease (157).

FUTURE

While it is clear that there has been tremendous progress over the past several decades, largely attributed to the efforts and dedication of cooperative groups, patients, and families, we

must continue to improve outcomes for children diagnosed with RMS. Advances in radiology and technical advances in radiation oncology should allow for better detection of involved areas of disease and avoidance of healthy tissues while assuring adequate delivery of radiation. Molecular profiles will indicate which patients may have more biologically aggressive disease and are likely to play a larger role in determining what patients may benefit from intensified treatment and/or new targeted agents. Continued improvements in systemic therapy may allow us to avoid RT in some patients, while adding to the benefit for others in whom local control becomes of increased importance due to eradication of systemic metastatic disease. We are optimistic that developments in radiation oncology along with advances in the cancer disciplines of surgery and medicine will allow for increased survival as well as an improvement in the quality of life for our patients.

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Soft Tissue Sarcomas Other Than Rhabdomyosarcoma; Desmoid Tumor

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The word *sarcoma* is derived from the Attic Greek word *σάρκωμα* or *sarkoma* meaning a fleshy excrescence (1). The term was used by Galan with particular reference to a nasal growth (2). An early English language dictionary from 1657 continued this definition of sarcoma as a “flesh growing in the nostrils like the proud flesh in a sore” (3). In modern usage, however, soft tissue sarcomas are defined as all malignant tumors of nonepithelial, extraskeletal tissues including the peripheral and autonomic nervous system but excluding the hematopoietic system, glia, and supporting tissues of specific organs and viscera. Soft tissue sarcomas constitute approximately 6.5–7% of childhood cancer. Within this 6.5–7%, approximately one half are rhabdomyosarcoma (4–6). Because the distribution of the types of other soft tissue sarcomas in children is distinctly different from that in adults, Spunt and Pappo have advocated the term “nonrhabdomyosarcoma soft tissue sarcoma” (NRSTS) (7). This group of soft tissue sarcomas constitutes 3–3.5% of childhood cancers (8), affecting approximately 500 children less than 20 years of age in the United States each year. NRSTS has not received the same focus of attention as rhabdomyosarcomas—though similar in incidence—perhaps because they have proved to be more resistant to conventional chemotherapy and radiotherapy (RT). While the surveillance, epidemiology and end results (SEER) database does not distinguish among rhabdomyosarcomas and NRSTSs, pediatric soft tissue sarcomas in the United States have been associated with improving survival over time. For patients less than 16 years of age diagnosed with a soft tissue sarcoma in 1975–1977, the adjusted 5-year survival was 61%. For those diagnosed in 1996–2004, there was a statistically significant improvement in 5-year survival at 74% (9,10). But to what degree this simply reflects improvements in rhabdomyosarcoma management is difficult to know. Moreover, very few patients with NRSTSs have been enrolled in cooperative group clinical trials. For instance in the United States prior to the 2006 Children’s Oncology Group (COG) ARST0332 trial, less than 200 patients had been enrolled in only three prospective clinical trials in the United States (11–13).

For most children with NRSTS, the origin or cause of the tumor is unknown. Some cases may be traced to prior radiation exposure (see Chapter 20), chemical exposure, iatrogenic or disease-caused immunosuppression, and neurofibromatosis, with the latter group having a 7–10% lifetime risk of developing malignant peripheral nerve sheath tumor (MPNST, historically called a neurofibrosarcoma or malignant schwannoma). The association of sarcomas with neurofibromatosis indicates that some sarcomas are associated with chromosomal deletions and translocations

and the presence of abnormalities of tumor suppressor genes. Homozygous gene deletions occur in both the long and short arms of chromosome 17 in neurofibromatosis type 1. Candidate tumor suppressor genes include *17q11* (the NF tumor suppressor gene) and *p53* (*17p13*) (4). Rhabdomyosarcoma and NRSTS also occur as part of the familial Li–Fraumeni syndrome. More generally in adult and pediatric soft tissue sarcomas, cytogenetic abnormalities are common with a mixture of simple translocations or point mutations giving rise to fusion genes or oncogenes and more complex genetic instability with a multiplicity of chromosome aberrations (14–31) (Table 12.1). Gastrointestinal stromal tumors are of particular interest albeit rare in children since its associated *c-kit* oncogene is a successful therapeutic target with imatinib, a prototype tyrosine kinase inhibitor (32). While not yet tested in pediatric NRSTS, there are a variety of other molecular targets and associated agents under investigation in adult soft tissue sarcomas including platelet-derived growth factor receptor-A (sunitinib), *Raf* kinase (sorafenib), *mTOR* (rapamycin), vascular endothelial growth factor (bevacizumab), heat shock proteins, *hedgehog*, histone deacetylase, and nucleotide excision repair (31).

PATHOLOGY

The frequency of the different histologic subgroups of NRSTS of childhood varies between reporting institutions (Table 12.2). These differences may be attributable to variations in referral patterns and to the small numbers in each series. In addition, NRSTSs often are difficult for pathologists to classify, and there is wide intraobserver variation (33). In an M. D. Anderson Hospital series of sarcomas of the head and neck in children and adolescents, histologic diagnoses were changed in 22% of patients (34). Several other studies have assessed discrepancy rates between the original diagnosis of soft tissue tumors and the diagnosis made by expert reviewers when patients are referred to specialty centers for entry in therapeutic trials. About 5–10% of cases having the original diagnosis of sarcoma are revised to nonsarcoma, and for 16–32% of patients with a sarcoma, the histologic subtype is revised. Where grade was analyzed, there was disagreement in up to 40% of the cases (35). For example, malignant fibrous histiocytoma (MFH) was first described as a separate entity in the 1960s and by the 1970s was widely accepted by pathologists, identifying this entity as the most common soft tissue sarcoma subtype. Therefore during this time decades ago, the reported incidence of MFH in adults sharply increased while that of fibrosarcoma fell (36). Historically, MFH has been unusual in childhood. But with general advances

Table 12.1

Common Cytogenetic Changes in Nonrhabdomyosarcoma Soft Tissue Sarcomas

Histologic Type	Characteristic Cytogenetic Events	Genes Involved
Alveolar soft-part sarcoma	t(X;17)(p11;q25)	ASPSCR1-TFE3 (ASPL-TFE3) fusion
Aggressive fibromatosis (desmoid tumor)	Trisomies 8 and 20 Deletion of 5q	APC inactivation
Lipoma (typical)	12q15 rearrangement	HMGA2 (HMGIC) rearrangement
Well-differentiated liposarcoma	Ring form of chromosome 12	
Myxoid/round-cell liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	FUS-DDIT3 (FUS-CHOP) fusion EWSR1-DDIT3 (EWS-CHOP) fusion
Lipoblastoma	Rearrangement of 8q11–13	PLAG1 gene rearrangements: HAS2/PLAG1, COL1A2/PLAG1
Pleomorphic liposarcoma	Complex abnormalities	
Malignant fibrous histiocyoma	Complex abnormalities	
Myxoid malignant fibrous histiocyoma	Ring form of chromosome 12	
Low-grade fibromyxoid sarcoma	t(7;16)(q34;p11)	FUS-BBF2H7 fusion
Leiomyoma (uterine)	t(12;14)(q15;q24) or deletion of 7q	HMGA2 (HMGIC) rearrangement
Leiomyoma (extrauterine)	Deletion of 1p	
Leiomyosarcoma	Deletion of 1p Other complex abnormalities	
Monophasic synovial sarcoma	t(X;18)(p11;q11)	SS18-SSX1 (SYT-SSX1) or SS18-SSX2 (SYT-SSX2) fusion MYCN overexpression
Biphasic synovial sarcoma	t(X;18)(p11;q11)	SS18-SSX1 (SYT-SSX1) fusion MYCN overexpression
Benign schwannoma	Deletion of chromosome 22	NF2 inactivation
Malignant peripheral nerve sheath tumors, low-grade	None	
Malignant peripheral nerve sheath tumors, high-grade	Complex abnormalities	
Primitive neuroectodermal Tumor	t(11;22)(q24;q12) t(21;22)(q12;q12) t(11;22)(p13;q12)	EWSR1-FLI1 (EWS-FLI1) fusion EWSR1-ERG (EWS-ERG) fusion EWSR1-WT1 (EWS-WT1) fusion
Desmoplastic small round-cell tumor	Ring form of chromosomes 17 and 22	COL1A1-PDGFB fusion
Dermatofibrosarcoma protuberans	t(17;22)(q21;q13)	
Endometrial stromal tumor	t(7;17)(p15;q21)	JAZF1-SUZ12 (JAZF1-JJAZ1)
Gastrointestinal stromal tumor	Monosomies 14 and 22 Deletion of 1p	KIT of PDGFRA mutation
Fibrosarcoma, infantile	t(12;15)(p13;q26) Trisomies 8, 11, 17, and 20	ETV6-NTRK3 fusion
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12) t(9;17)(q22;q11)	EWSR1-NR4A3 (EWS-NR4A3) fusion TAF15-NR4A3 (TAF2N-NR4A3) fusion
Inflammatory myofibroblastic tumor	2p23 rearrangement	ALK fusion to TPM3, TPM4, clathrin, and other genes
Clear cell sarcoma	t(12;22)(q13;q12)	EWSR1-ATF1 (EWS-ATF1) fusion
Malignant rhabdoid tumor	Deletion of 22q	HSNF5 (INI1) deletion or mutation

Gene symbols are those provided in the Human Genome Nomenclature Database (<http://www.genenames.org>). Previous names of genes are given in parentheses.

Adapted from Skubitz KM, D'Adamo DR. Sarcoma. *Mayo Clinic Proc.* 2007;82(11):1409–32; and Spunt SL, Skaepk SX, Coffin CM. Pediatric nonrhabdomyosarcoma soft tissue sarcomas. *Oncologist.* 2008;13(6):668–678.

in pathologic categorization based on immunohistochemistry, ultrastructural studies, and cytogenetics, the diagnosis of MFH has been questioned as a distinct entity (37). At least in adults, this is no longer a common diagnosis, and when undifferentiated it is generally considered the same as a high-grade pleomorphic sarcoma. Figure 12.1 shows the histologic appearance of an MFH or pleomorphic sarcoma.

Many of the childhood NRSTSs have characteristic cell types (Table 12.3). The WHO classification uses lines of differentiation to categorize tumors into adipocytic, fibroblastic/myofibroblastic, “so-called” fibrohistiocytic, smooth muscle, pericytic (perivascular), and vascular types, as well as tumors of uncertain differentiation (49). Of course, other sarcomas include the skeletal muscle

Table 12.2

The Most Common Types of Childhood Nonrhabdomyosarcoma Soft Tissue Sarcoma in Recent Clinical Series^a

Histology	St. Jude Children's Research Hospital ^b (6,83,223)	Harvard Joint Center for Radiation Therapy ^c (56)	Children's Hospital of Philadelphia (224)	Baylor/Texas Children's Hospital (8)	Children's Hospital and Medical Center Seattle ^d (4)	M. D. Anderson Hospital and Head Neck Sarcomas (34)	SEER ^e Data (66)	Italian Cooperative Study of Childhood Soft Tissue Sarcoma (147)	Pediatric Oncology Group (225)	Rambam Medical Center (68)	Mayo Clinic (48)	Instituto Nazionale Tumori Milan (226)	University of Iowa (162)
Primitive neuroectodermal tumor and extrasosseous Ewing sarcoma and Askin tumor	11%/18%	30%	38%	9%	32%	40%	36%	5%					
Neurogenic sarcoma and neurofibrosarcoma	28%/15% 6%/12%	16%	10% 2%	6% 2%	10%	17% 4%	10%	15%	10%	2%	16%	3%	
Synovial sarcoma	14%/12%	11%	15%	30%		4%	15%	8%	12%	5%	36%	24%	
Alveolar soft part sarcoma													
Sarcoma not otherwise specified													
Malignant fibrous histiocytoma													
Hemangiopericytoma	—/4%				2%			4%	5%	2%	1%	4%	
Liposarcoma	—/4%			2%				1%	5%	2%	3%	8%	5%
Dermatofibrosarcoma protuberans						4%		5%		2%	1%	2%	
Fibrosarcoma	11%	9%	18%	4%	20%	17%	48%	14%	13%	33%	15%	5%	21%
Mixed mesenchymoma			2%	6%		4%		3%		<2%		2%	6%
Angiosarcoma and hemangiosarcoma	—/8%		2%					2%		<2%		8%	6%
Epithelioid sarcoma	5%/8%		8%					3%				1%	3%
Extrarenal rhabdoid sarcoma	—/8%							2%				5%	2%
Clear cell sarcoma	5%/8%							1%				2%	6%
Leiomyosarcoma								1%	4%	5%	2%	7%	13%
Other	20%/16%		20%		4%				12%			6%	

^aIn each series, the most common histologic types are indicated by bold type.^bThe number to the left of the slash is the number of surgically resectable patients; to the right are patients with metastatic disease.^cThis series does not include children with metastatic disease.^dThis series combines dermatofibrosarcoma protuberans with fibrosarcoma.^eSurvival, epidemiology, and end results.

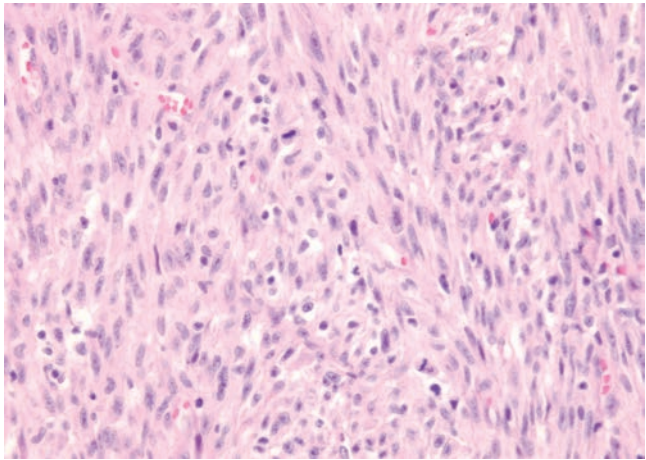


Figure 12.1 The histologic appearance of a malignant fibrous histiocytoma on hematoxylin and eosin staining, original magnification $\times 40$. Many pathologists now categorize this lesion as a pleomorphic sarcoma. Note the spindle cell proliferation (long, narrow rodlike cells) with frequent mitoses, enlarged hyperchromatic and pleomorphic nuclei, and a storiform pattern of growth (fascicles of cells radiating from a central point). There is also some tendency toward a herringbone pattern in this example, characteristic of a fibrosarcoma.

tumors/rhabdomyosarcomas and bone/cartilaginous tumors discussed elsewhere in this textbook.

Malignant peripheral nerve sheath tumor (MPNST) has also been known as neurofibrosarcoma, neurogenic sarcoma, malignant schwannoma, or malignant neurilemmoma. It is a malignant neoplasm that arises in a peripheral nerve sheath. In children, from one fifth to two thirds of cases of MPNST are associated with neurofibromatosis type 1 (NF1) (50–52). The morphology is characterized by fascicles of spindle cells with a herringbone or storiform pattern. One may observe evidence of schwannian differentiation (53). There can be areas of significant nuclear hyperchromatism and abundant mitotic figures (54). These tumors usually are positive for S-100, vimentin, and neuron-specific enolase. In about 2–16% of patients with NF1, nodular and plexiform neurofibromas transform to MPNSTs. NF1 is transmitted as an autosomal dominant with variable penetrance. However, almost 50% of cases are sporadic mutations (1). People with NF1 are 1.2 times more likely to have a malignant neoplasm listed on their death certificates than

those who do not have the disease. These include MPNST, optic gliomas, and pheochromocytomas (55). NF1 is also called the von Recklinghausen disease. Friedrich Daniel von Recklinghausen (1833–1910) was born in Gutersloh, Westphalia, Germany, and studied medicine at the Universities of Bonn, Würzburg, and Berlin. He was a professor in Königsberg, Würzburg, and Strasbourg. Also known for coining the term “hemochromatosis,” he published a monograph in 1882 that first described NF1 and the accompanying benign neurofibromas having a histologic appearance of disordered peripheral nerves and fibrosis.

Biphasic *synovial sarcoma*, the more common type, also has spindle-shaped cells. These are mixed with oval and keratin-positive epithelial cells. Pseudoglandular spaces or slits and clefts mimic synovium (56). About one third of synovial sarcomas in children are the monophasic type (57). About two thirds of cases involve the lower extremity and one third the upper. Synovial sarcomas differ from other NRSTSs in that they have a significant risk of lymph node metastases (57,58). The monophasic type may have a better prognosis, but this is debatable (57,46). Synovial sarcomas commonly have a $t(x;18)(p\ 11.2;q11.2)$ translocation that may result in two different fusion genes (*SYT-SSX1* and *SYT-SSX2*). Controversy exists as to the prognostic importance of these fusion genes. Initial reports suggested that *SYT-SSX1* fusion was associated with improved survival and less potential for metastasis (59,60). But in a contradictory small series, the *SYT-SSX1* fusion was associated with a 42% 5-year metastasis-free survival, compared with 89% for the *SYT-SSX2*. The *SYT-SSX1* fusion is also associated with a higher cell proliferation rate as assessed by Ki-67 staining (61). Yet another recent report suggests tumor grade rather than fusion gene subtype in synovial sarcoma is the more important prognostic factor (62).

Liposarcomas originate from primitive mesenchymal cells rather than from mature adipose tissue. Some have a myxoid appearance, whereas others resemble benign lipomas. The pleomorphic type may resemble fibroblastic, myoblastic, or synovial sarcoma. *Angiosarcoma* should always be considered high grade with an aggressive behavior, a high rate of local recurrence, a propensity to metastasize, and a poor prognosis (63).

Leiomyosarcoma originates from smooth muscle. The well-differentiated lesions usually have a centrally located blunt-ended nucleus (“cigar-shaped”).

Fibrosarcoma is an infiltrative, fibrous neoplasm composed of interlocking bundles of spindle cells (64,65). The tumor usually stains positive for vimentin. There are two clinically different

Table 12.3 Cells of Origin of Nonrhabdomyosarcoma Soft Tissue Sarcoma of Childhood	
Cell of Origin	Sarcoma
Fat	Liposarcoma
Blood and lymphatic vessels	Angiosarcoma, hemangiopericytoma
Fibroblasts	Fibrosarcoma, malignant fibrous histiocytoma
Smooth muscle	Leiomyosarcoma
Nervous tissue	Malignant peripheral nerve sheath tumor
Synovial	Synovial sarcoma
Chondrocytic	Extraskeletal chondrosarcoma
Epithelial	Epithelioid sarcoma
Melanocytes	Clear cell sarcoma of tendons and aponeuroses
Myofibroblasts	Myofibrosarcoma

Based on Pappo AS, Parham DM, Rao BN, et al. Soft tissue sarcomas in children. *Semin Surg Oncol*. 1999;16:121–143.

forms of fibrosarcoma in children. One is a lesion appearing in the first 5 years of life with a low rate of distant spread. This type of fibrosarcoma, called the congenital type, is generally treated by excision (4,33,40). In children younger than 5 years of age this tumor may also be called infantile fibrosarcoma (Figure 12.2). The other occurs in children older than 5 years and has a more ominous prognosis with behavior similar to that of adult forms (65). This classic or adult-type fibrosarcoma is treated according to the principles outlined for other NRSTSs. Infantile fibrosarcoma has a rapid initial growth but generally indolent behavior. Local recurrence is common, metastases are rare, spontaneous regressions have been reported, and RT is rarely used. Infantile and adult fibrosarcomas are histologically identical. There is no routine microscopic, immunohistochemical, or ultrastructural way of distinguishing the two clinical types (64). *Low-grade fibromyxoid sarcoma* is an indolent tumor that rarely occurs in children. It consists of spindle and stellate cells with uniform nuclei arranged in a whorled pattern with alternating areas of fibrous and myxoid stroma (66). True *malignant fibrous histiocytomas* are pleomorphic sarcomas as noted above, often characterized by a whorled growth pattern. They are thought to arise from histiocytic cells acting as facultative fibroblasts. *Hemangiopericytomas* arise from pericytes, the modified smooth muscle cell with contractile function located on the internal surface of venous capillaries and postcapillary venules (67). The *malignant mesenchymoma* has two or more cell types, any of which, taken by itself, might be considered a malignant neoplasm (68,69); however, the term is losing favor as a clinicopathologic entity as such sarcomas can usually be classified in other ways (70). *Ectomesenchymomas* are felt to be of neural crest origin with multidirectional differentiation exhibiting combinations of neuroblastoma, ganglioglioma, schwannoma, embryonal rhabdomyosarcoma, benign melanocytic proliferation, and bone or cartilage elements. These rare tumors may have a dominant rhabdomyosarcomatous element with clinically similar response to chemotherapy and RT (71) (Figure 12.3).

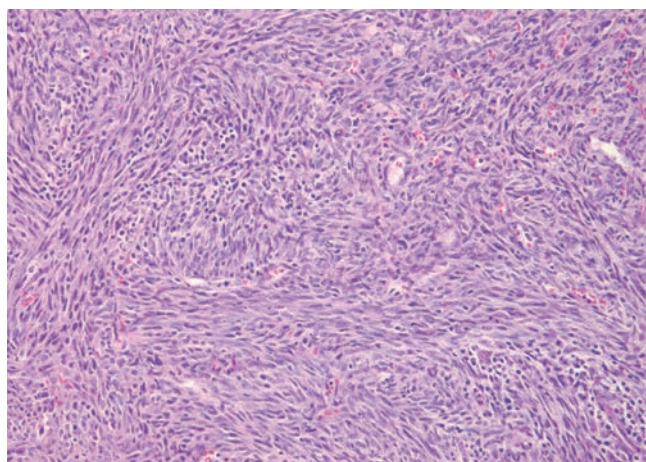


Figure 12.2 Example of microscopic pathology of an infantile fibrosarcoma, original magnification $\times 20$. This is another fibrous spindle-cell proliferation as in the example of an MFH. While histologically aggressive in appearance, when this fibrosarcoma occurs in the first several years of life there tends to be a benign biologic behavior with little potential for metastatic spread. Local excision is the primary management. In unresectable cases chemotherapy can be used to promote regression and subsequent surgery.

There are several childhood NRSTSs that have a characteristic microscopic picture, but the cell of origin is uncertain. The *epithelioid sarcoma* is a tumor of the subcutaneous tissue, tendons, and fascia, usually of the upper extremity, including the hand. There is a nodular arrangement of plump, polygonal to round, epithelioid cells interspersed with spindle-shaped cells (5,72). Central degeneration or necrosis is often present. The tumor tends to spread within fascial planes or aponeuroses and may grow along the neurovascular bundle and encroach on large vessels or nerves. Regional lymph node metastasis may occur in association with high-grade tumors and tumors larger than 5 cm (73). The tumor generally stains positive for keratin.

Alveolar soft part sarcomas have a characteristic crystalline material seen with periodic acid–Schiff (PAS) stain (74,42). The tumor tests positive for vimentin on immunohistochemistry. The tumor cells typically have an organoid or nestlike arrangement. Vascular invasion is always seen. Of 11 children with alveolar soft part sarcoma seen at St. Jude Children's Research Hospital in a 32-year period, 6 had localized disease and 5 had unresectable or metastatic disease. Cytogenetic studies indicate that 17q25 abnormalities are common (42). In 19 patients seen in Italy, 4 had metastatic disease at presentation. The 5-year survival for all 19 patients was 80% (75). A slow doubling time of the tumor may explain its very late occurrences (sometimes more than 10 years) (37,45).

Extraskelatal (or extraosseous) Ewing sarcoma (EOES) and peripheral primitive neuroectodermal tumor (PNET) are characterized by cohesive, uniform, small hyperchromatic cells in a fibrous background. Dense clumping of chromatin, mitotic figures, and rosette formation are typical of PNET. On immunohistochemistry analysis, EOES are generally positive for vimentin and HBA-17. PNET is generally positive for neuron-specific enolase and other neuron-related markers such as S-100 protein, neurofilament, or HNK-1. Both PNET and EOES are associated with a particular chromosome translocation $t(11;22)(q24;q12)$. The progenitor cell for these two small, round, blue cell NRSTSs is not established. They may arise from neural crest, primordial germ cells, or perhaps mesenchymal stem cells (4,76). When PNET or EOES arises in the thoracic cavity it is called the *Askin tumor*.

Desmoplastic small, round, blue cell tumor is a rare intraperitoneal malignancy occurring predominantly in adolescent boys. It is characterized by a reciprocal translocation $t(11;12)(p13;q12)$ associated with the *EWS-WT1* gene fusion transcript. Cells often stain positive for desmin, keratin, and neuron-specific enolase. The predominant pattern of relapse is intraperitoneal (77). Patients generally are treated with surgical debulking, alkylator chemotherapy, and whole abdomen irradiation or intra-abdominal P-32. The relapse-free survival rate is approximately 20% (78,79) (50,51). PET scanning may be useful in follow-up for early diagnosis of recurrence (80). Figure 12.4 depicts a rare instance of this disease occurring outside the peritoneum.

Clear cell sarcoma is characterized by ovoid or polygonal cells with abundant clear cytoplasm, indistinct borders, large nucleoli, and abundant intracytoplasmic glycogen. Immunocytochemistry often is positive for S-100 protein, neuron-specific enolase, and melanocyte-associated antigen HMB-45. A specific chromosomal translocation $t(12;22)(q13;q12)$ involving the DNA transcription factors ATF-1 on chromosome 12 and the *EWS* gene on chromosome 22 has been described in 60–75% of clear cell sarcoma cases (81,82).

A fair proportion of NRSTSs show no cellular differentiation. These are called *undifferentiated sarcomas* or *sarcomas not otherwise specified*.

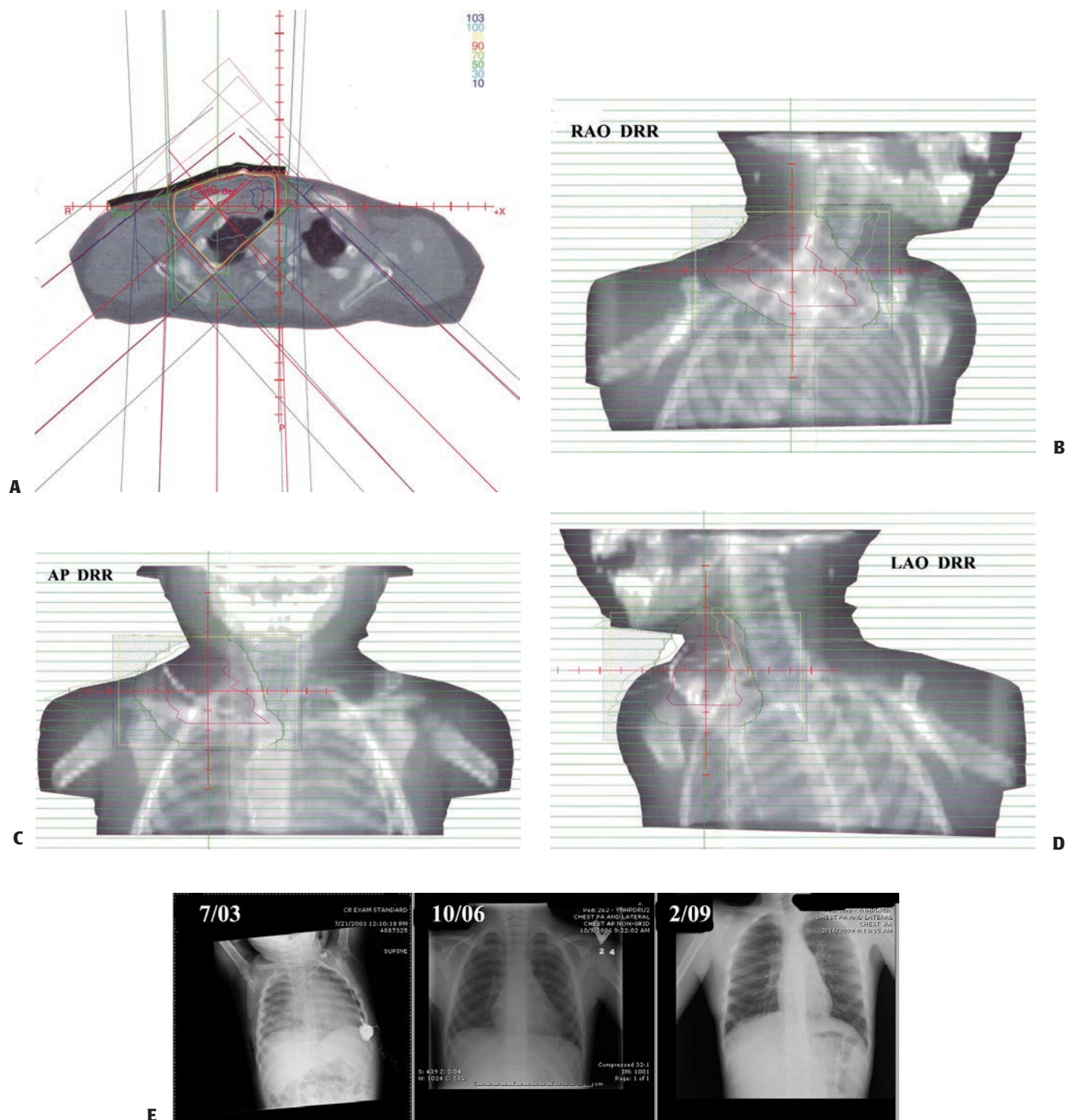


Figure 12.3 This 10-month-old boy developed a 2.5 cm superficial mass in the right supraclavicular fossa. After ultrasound showed this to be a solid lesion, a marginal excision was performed in February 2003. An ectomesenchymoma was diagnosed having immature cartilage separated by bands of collagen in a myxoid background with cellular areas having primitive ovoid and spindle cells. The dominant cellular pattern had features of an embryonal rhabdomyosarcoma. Surgical margins were positive. There was no evidence of metastasis in an adjacent lymph node or on CT imaging. As a wider excision was not possible due to tumor abutting clavicle, lung apex, and carotid artery, postoperative RT was indicated. Along with VAC chemotherapy as per rhabdomyosarcoma management, the patient received 3060 cGy in 17 fractions using a four-field technique (AP, PA, RAO, LAO fields) facilitated by daily general anesthesia with IV propofol. Shown is the radiation treatment plan and digital reconstructed radiographs (DRR) of three of the fields. The treatment plan minimized the volume of distal clavicle, spine, and shoulder girdle being treated to full dose. In last follow-up at age 7 years without evidence of disease, there is negligible bony asymmetry seen on chest x-rays correlating with normal physical examination. Panel **A**: radiation treatment plan. Panel **B**: RAO DRR. Panel **C**: AP DRR. Panel **D**: LAO DRR. Panel **E**: follow-up CXRS in 2003, 2006, and 2009.

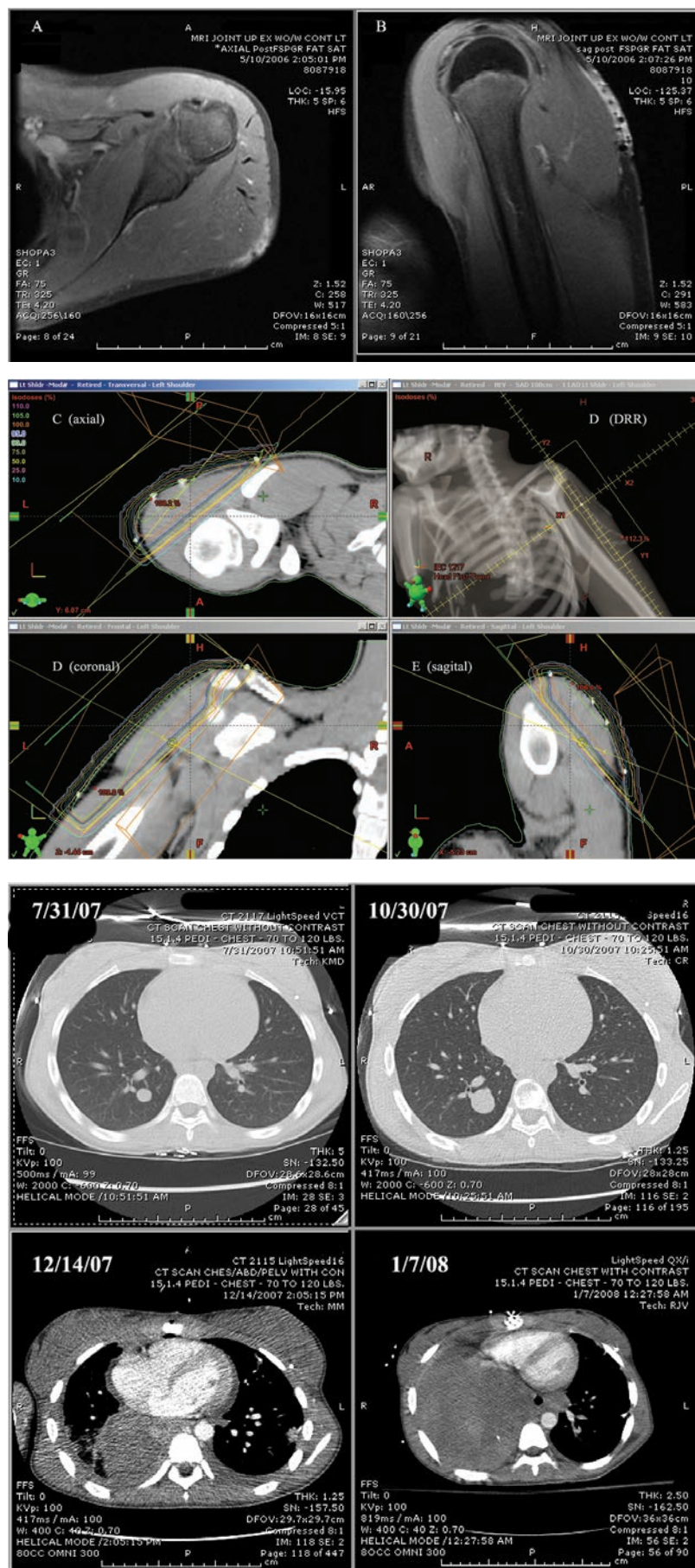


Figure 12.4 This 12-year-old female presented with a subcutaneous mass over the left shoulder that was marginally excised. Pathology showed a desmoplastic small, round-cell tumor with a classic $t(11;12)$ translocation on cytogenetics. This case represents an unusual extra-abdominal presentation of this rare sarcoma. MRI scan showed contrast enhancement in the surgical bed (upper panel). Re-excision, axillary node dissection, bone marrow biopsy, and CT scans were negative for other sites of disease. The patient was treated with an Ewing sarcoma type chemotherapy protocol with involved-field RT to 45 Gy in 25 fractions (middle panel of axial, coronal, and sagittal CT images with superimposed radiation dose distribution). Despite local control of the primary tumor, the patient unfortunately developed progressive pulmonary metastases shortly after completing vincristine/doxorubicin/ cyclophosphamide alternating with ifosfamide/ etoposide chemotherapy. (See bottom panel of four serial CT images showing progression of lung metastasis over 6 months.) Despite surgical excisions of lung nodules and salvage chemotherapy, the patient ultimately succumbed to her disease.

PRESENTATION, WORKUP, AND STAGING

Most NRSTSs present as a painless swelling but may also present with signs and symptoms of vascular compression, neurologic impairment from nerve compression, or bowel dysfunction when tumors arise from the retroperitoneum.

The radiographic workup begins with the plain radiograph. One looks for evidence of soft tissue mass, calcification, and destruction of adjacent bone. Radionuclide bone scanning is used to assess metastatic bone involvement, activity in bone adjacent to the tumor, and active vascular activity in the tumor itself. Arteriography is advocated for its delineation of the tumor's blood supply, a matter of concern to the surgeon or to the direct infusional chemotherapist. Computed tomography (CT) and magnetic resonance imaging (MRI) are the essential studies for clear definition of tumor extent, patterns of infiltration, evaluation of adjacent bone, and planning surgical and radiotherapeutic approaches. MRI often shows a larger area of involvement than does CT (Fig. 12.5). The evaluation for distant metastasis focuses on the most common site, the lungs, with chest radiograph and thoracic CT scanning (51,52,56,83–85). Metabolic scanning techniques, such as thallium scans and positron emission tomography (PET), are being used with increasing frequency. PET measures glucose utilization rate in sarcomas and may be used to assess lesion grade and to monitor neoadjuvant therapeutic response (Fig. 12.6) (86,87).

NRSTS in childhood may be staged by one of two systems. A few investigators still use the rhabdomyosarcoma grouping system, although their number is shrinking (see Table 11.2). This system is convenient and relies on surgical resectability as an important prognostic factor. There is no doubt that tumor size and resectability are important in predicting outcome in NRSTS of children. In fact, a retrospective analysis of NRSTS from the

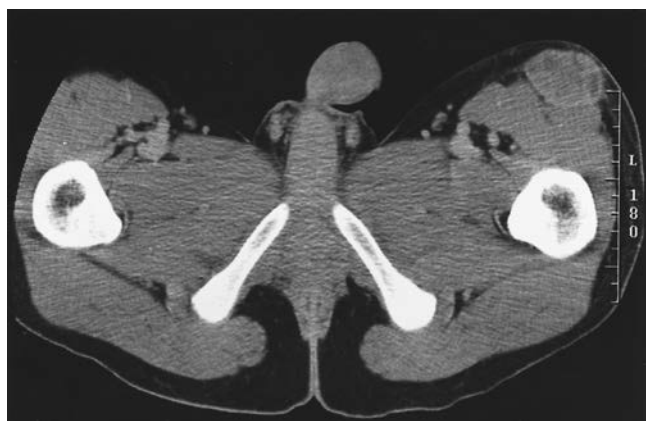


Figure 12.5 This 17-year-old white boy presented with a 7-month history of a mass, noted on self-examination, of the left thigh. The mass eventually grew to 4 cm in size. Magnetic resonance imaging demonstrated a mass without the involvement of bone. Positron emission tomography showed increased metabolic activity. On pathology, the tumor was “hypercellular highly vascularized neoplastic proliferation of generally small round to oval nuclei with evenly distributed chromatin and small nucleoli. Immunohistochemical stains are positive for vimentin, negative for leukocyte antigen; most consistent with extra skeletal Ewing’s sarcoma/primitive neuroectodermal tumor.” The patient was treated with tumor excision, involved-field irradiation, and systemic chemotherapy.

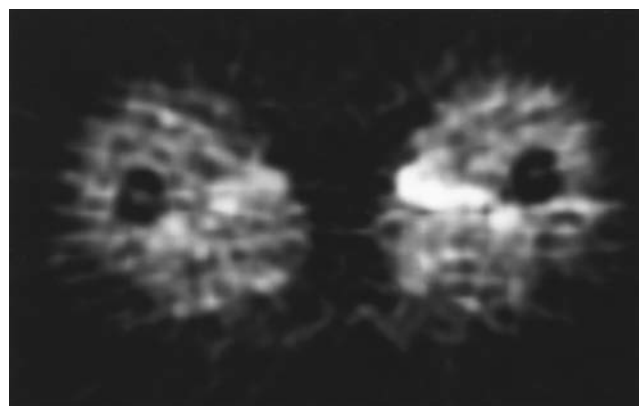


Figure 12.6 A positron emission tomography scan showing increased metabolic activity in a limb involved by primitive neuroectodermal tumor.

St. Jude Children’s Research Hospital has crudely identified three distinct risk groups: (1) grossly resected nonmetastatic disease (89% 5-year survival); (2) initially unresectable, nonmetastatic disease (56% 5-year survival); and (3) metastatic disease (15% 5-year survival) (38,88,89) (Fig. 12.7). Adverse risk factors include metastatic disease, tumor size >5 cm, high grade, positive surgical margins, intra-abdominal primary tumor site, and omission of postoperative RT in localized disease. Regarding tumor size as a prognostic factor in sarcoma patients (including rhabdomyosarcoma and NRSTS), a recent report suggests that there should be an adjustment for overall patient size (90). The authors noted, for example, that the mortality risk associated with a patient with a body surface area of 1.75 m² and a 5-cm tumor was the same as for a 0.6 m² child with a 2.8-cm tumor.

Histologic tumor grade, however, is of considerable importance and is not directly considered in the rhabdomyosarcoma grouping system (33,91–93). Sarcoma grade assessment incorporates pleomorphism, spontaneous necrosis, and number of typical and atypical mitoses per 10 high-power fields. Building on the first tumor grading system (squamous cell carcinoma of the lip) in 1920, Broders and colleagues at the Mayo Clinic published a grading system for sarcomas in 1939 based on the degree of mitosis, tumor giant cells, and fibrous stroma (94,95). In 1969, the American Joint Commission (AJC) on Cancer Staging described a staging system for soft tissue sarcoma that uses grade, tumor size, nodal involvement, and presence of metastases as the determinants of stage (Table 12.4). First validated by Russell et al. in 1977, the AJC system incorporates in the sarcoma staging system both TMN and tumor grade components (96). Grade is determined by evaluation of the degree of cellularity, cellular anaplasia or pleomorphism, mitotic activity, expansive or infiltrative growth, and necrosis (72). Frequency of distant metastases increases and the survival probability decreases with increasing size of the primary tumor (92). About 15% of patients have metastatic disease at presentation (4).

Histologic grading is an important way to predict the outcome of NRSTS. Moreover, as treatment decisions may often hinge on grading, the clinician should be aware of the criteria and uncertainties inherent in pathologic interpretation. There are various strategies for grading. One system, developed by the Pediatric Oncology Group (POG), labeled grade 1 as tumor that has little propensity for malignancy. Grade 2 tumors are those with fewer than 5 mitoses per 10 high-powered fields or less than 15% geographic necrosis, and grade 3 tumors are those known to be

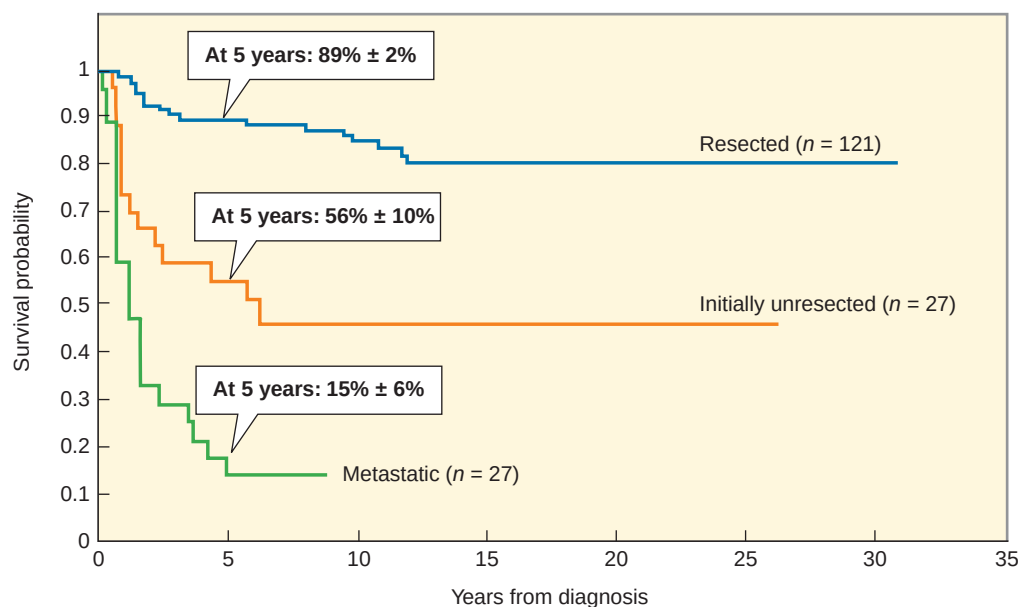


Figure 12.7 Risk stratification of nonrhhabdomyosarcoma soft tissue sarcomas. (From Spunt SL, Hill DA, Motosue AM, et al. Clinical features and outcome of initially unresected nonmetastatic pediatric nonrhhabdomyosarcoma soft tissue sarcoma. *J Clin Oncol*. 2002;20:3225–3235, with permission.)

Table 12.4

The 2010 American Joint Committee on Cancer Staging System for Sarcoma of Soft Tissue^a

T: Primary tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor less than or equal to 5 cm in greatest dimension
T1a	Superficial tumor ^b
T1b	Deep tumor ^b
T2	Tumor more than 5 cm in greatest dimension
T2a	Superficial tumor ^b
T2b	Deep tumor ^b
N: Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph nodes metastasis
M: Distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
G: Histopathologic grading^c	
Gx	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
Stage^d	
Stage IA	T1a/b N0 M0 G1 or Gx
Stage IB	T2a/b N0 M0 G1 or Gx
Stage IIA	T1a/b N0 M0 G2 or G3
Stage IIB	T2a/b N0 M0 G2
Stage III	T2a/b N1 M0 G2
	T2a/b N0 M0 G3
Stage IV	M1

^aThis staging system does not apply to Kaposi sarcoma, gastrointestinal stromal tumors (which has its own classification), fibromatosis (desmoids tumor), infantile fibrosarcoma, or sarcomas arising in dura mater or brain, parenchymal organs, and hollow viscera. Staging system now includes dermatofibrosarcoma (previously excluded), angiosarcoma, and extraskeletal Ewing sarcoma.

^bSuperficial, above superficial fascia without invasion of the fascia; Deep, located either beneath the superficial fascia or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep.

^cAJCC now recommends a three-tier system. The FNCLCC (French) system is the preferred grading system.

^dNew in seventh edition of *AJCC Cancer Staging Manual*: There is now a staging distinction between G2 and G3, at least for tumors >5 cm.; N1 is now Stage III instead of Stage IV; Stage I is divided into IA and IB. Stage II is divided into IIA and IIB; clinical versus pathologic staging is designated cT versus pT; deep or superficial location of tumor is no longer a factor in overall stage.

From Edge SB, Byrd DR, Compton CC, et al., eds. *AJCC Cancer Staging Manual*, 7th ed. New York: Springer, 2010, with permission from AJCC.

Table 12.5
POG Grading System for Pediatric Nonrhabdomyosarcoma Soft Tissue Sarcomas

Grade	
1	Liposarcoma: myxoid and well differentiated Deep-seated dermatofibrosarcoma protuberans Fibrosarcoma: well differentiated or infantile (<5 yr) Hemangiopericytoma: well differentiated or infantile (<5 yr) Well-differentiated malignant peripheral nerve sheath tumor Angiomatoid malignant fibrous histiocytoma
2	All NRSTSs not in grades 1 or 3; <15% of tumor shows geographic necrosis, or mitotic index is <5 mitoses/10 high-power fields
3	Fibrosarcoma with >15% of tumor with geographic necrosis or mitotic index >5 mitoses/10 high-power fields Liposarcoma: pleomorphic, round cell Mesenchymal chondrosarcoma Extraskeletal osteosarcoma Malignant triton tumor Alveolar soft part sarcoma

Based on Pappo AS, Parham DM, Rao BN, et al. Soft tissue sarcomas in children. *Semin Surg Oncol.* 1999;16:121–143.

clinically aggressive by virtue of histologic diagnosis and with more than 4 mitoses per 10 high-powered fields or more than 15% geographic necrosis (97) (Table 12.5). One review of this POG grading system found a 73% mortality in grade 3 lesions and 15% mortality in grade 1 and 2 tumors (98).

The more common sarcoma grading systems that one is more likely to encounter in clinical usage are the National Cancer Institute (NCI) system and the French Federation of Cancer Centres (FNCLCC) system despite being largely based on adult cases (99). Both are a three-tiered grading system. The aforementioned POG system is a variation of the NCI classification scheme. In the NCI system (100), certain types of sarcomas are deemed low or high grade based on the histological subtype. A typical liposarcoma is low grade while epithelial or synovial sarcomas are always high grade, for instance. For those subtypes that are not automatically allocated to a grade, the degree of necrosis is the most important factor distinguishing intermediate versus high grade. Minor pathologic factors include the degree of mitosis, pleomorphism, cellularity, and stromal matrix. Necrosis as a prognostic marker is categorized by being minimal (0–15%), moderate (15–30%), or marked (>30%). Thus, when degree of necrosis is key to determining grade, the significant cutoff value is 15%. A grade 2 soft tissue sarcoma (e.g., a fibrosarcoma or an MFH) has up to 15% necrosis, while grade 3 disease is simply determined by greater than 15% necrosis.

The FNCLCC has similarities to the NCI system, but has a point scoring system based on tumor histology, necrosis, and mitosis that has a certain clinical appeal in its reproducibility and

simplicity (101). The main criticism, however, is that some histologic subtypes (e.g., MFH, alveolar soft parts sarcoma) do not have attributes that recapitulate normal tissues and cannot be easily scored in terms of differentiation (Tables 12.6 and 12.7). Worldwide, the French system predominates.

Comparisons between the NCI and FNCLCC system show up to one third of cases have grading discrepancies, but the latter system may be a slightly better determinant of prognosis, albeit not for every NRSTS subtype (99,102). The current COG protocol on NRSTS has central pathology review; one of its aims will be to directly compare the POG and the FNCLCC grading systems for pediatric sarcomas. To date, the WHO or other pathology associations have not endorsed any particular grading schema.

Table 12.6
Tumor Differentiation Scores of Sarcoma in the French Federation of Cancer Centres System of Grading Soft Tissue Sarcomas

Diagnosis	Differentiation Score
Well-differentiated liposarcoma	1
Well-differentiated fibrosarcoma	1
Well-differentiated MPNT	1
Well-differentiated leiomyosarcoma	1
Well-differentiated chondrosarcoma	1
Myxoid liposarcoma	2
Conventional fibrosarcoma	2
Conventional MPNT	2
Well-differentiated malignant hemangiopericytoma	2
Myxoid MFH	2
Typical storiform/pleomorphic MFH	2
Conventional leiomyosarcoma	2
Myxoid chondrosarcoma	2
Conventional angiosarcoma	2
Round-cell liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Poorly differentiated fibrosarcoma	3
Epithelioid malignant schwannoma	3
Poorly differentiated MPNT	3
Malignant triton tumor	3
Conventional malignant hemangiopericytoma	3
Giant cell and inflammatory MFH	3
Poorly differentiated/epithelioid/pleomorphic leiomyosarcoma	3
Synovial sarcoma	3
Rhabdomyosarcoma	3
Mesenchymal chondrosarcoma	3
Poorly differentiated/epithelioid angiosarcoma	3
Extraskeletal osteosarcoma	3
Extraskeletal Ewing sarcoma/PNET	3
Alveolar soft part sarcoma	3
Malignant rhabdoid tumour	3
Clear cell sarcoma	3
Undifferentiated sarcoma	3

MPNT, Malignant peripheral nerve tumor; PNET, primitive neuroectodermal tumour; MFH, malignant fibrous histiocytoma. Modified from Guillou L, Coindre JM, Bonichon F, et al. *J Clin Oncol.* 1997;15:350, with permission.

Table 12.7

French Federation of Cancer Centres System of Grading Soft Tissue Sarcomas

Parameter		Criterion
Tumor differentiation	Score = 1	Sarcoma histologically very similar to normal adult mesenchymal tissue
	2	Sarcoma for defined histological subtype (e.g., myxoid MFH)
	3	Sarcoma of uncertain type, embryonal and undifferentiated sarcomas
Mitosis count	Score = 1	0–9/10 HPF
	2	10–19/10 HPF
	3	≥20/10 HPF
Microscopic tumor necrosis	Score = 0	No necrosis
	1	≤50% tumor necrosis
	2	>50% tumor necrosis
Histological grade		
Grade 1		Total score 2 or 3
2		Total score 4 or 5
3		Total score 6, 7, or 8

MFH, malignant fibrous histiocytoma; HPF, high-power field.

Modified from Guillou L, Coindre JM, Bonichon F, et al. *J Clin Oncol*. 1997;15:350, with permission.

While the clinician may rely on sarcoma grading to make treatment decisions, one must be aware of the degree of uncertainty in pathologic diagnosis. This problem has a bigger dimension as the pathologist is increasingly forced to evaluate smaller biopsy specimens rather than the whole tumor as newer treatment algorithms involve preoperative RT or chemotherapy. With smaller specimens, there is an increasing danger of sampling errors as necrosis, mitotic activity, differentiation, pleomorphism, and other grading aspects have geographical variability within a particular tumor. Despite advances in molecular biology, identification of cytogenetic or particular DNA or RNA lesions has not yet supplanted tumor grading to aid clinical decisions for NRSTS.

SELECTION OF THERAPY

Surgery

Every biopsy should be planned to be consistent with the treatment plan. The two techniques for the biopsy are either via needle or open incisional. Needle biopsy techniques include fine-needle aspiration (of variable accuracy and dependent on the experience of the cytopathologist) or core needle biopsy (4). The incision for an open incisional biopsy should be the minimum that is technically feasible and homeostasis should be secure. Incisions on the extremity should be in the long axis (85). Muscle compartments should not be crossed; one does not want to contaminate adjacent areas with tumor. The biopsy should be placed so that the entire surgical tract will be removed at the time of the definitive operation.

Complete surgical excision is the mainstay of therapy. NRSTS may infiltrate widely. Sarcomas tend to expand and infiltrate adjoining tissue spaces, producing a pseudocapsule made up of compressed normal tissue intermingled with microscopic extensions of the tumor. A system for assessing the adequacy of surgical margins in sarcoma surgery was described by Enneking et al. (103). An *intralesional* surgical margin is through tumor, with gross or microscopic contamination. A *marginal resection* is through the reactive or inflammatory zone. A *wide excision* is through normal tissue outside the inflammatory zone. A *radical excision* is outside the anatomic compartment containing the tumor. A wide excision or amputation often is needed to obtain the microscopic-free margin needed for control. Clinical experience, primarily in

adults, has shown that the local failure rate for simple excision of malignant soft tissue sarcomas is 60–90% (51,52,56). This failure rate falls to 18–30% when simple excision is replaced by radical resection, radical compartmental resection, or amputation above the proximal joint (6,33,85,104–107). In a pediatric series, the 5-year survival rate was higher for complete tumor excision than for partial excision (45). For low-grade lesions, wide excision with negative margins may be curative as the sole treatment (8,105). Surgical margins of at least 1.0 cm around gross tumor is preferred for optimal local control (108). In cases of positive margin or unanticipated finding of NRSTS on marginal excision, a re-excision should be strongly considered (109).

There are some patients for whom limb-sparing treatments may be considered (106,107,110–112). Limb-sparing surgery removes a soft tissue sarcoma while preserving the extremity with a satisfactory functional and cosmetic result. To achieve results comparable to those of radical procedures, most limb-sparing procedures involve the planned use of preoperative or postoperative external beam irradiation, brachytherapy, or intra-arterial or systemic chemotherapy. But regardless of adjuvant RT or chemotherapy, resection with negative surgical margins is critical for optimal local control (113). In the presence of planned RT, resection margins may be relatively tight within millimeters, but if surgery alone is planned margins greater than 1.0 cm are likely required along with an en bloc resection beyond any tumor pseudocapsule (114). For tumors abutting bone, stripping off the periosteum en bloc is usually sufficient in the absence of any direct bone invasion; however, the addition of RT in thigh sarcomas may entail a higher risk for later development of femoral bone fractures (115). Other investigators have observed an increased risk of bone fractures as simply a function of high radiation dose delivery and not necessarily related to periosteal resection (116,117). Sarcomas that involve neurovascular bundles are challenging clinical problems, in which surgical and adjuvant radiotherapeutic management must be individualized regarding the sacrifice of blood supply or nerves.

Limb-sparing is clearly not appropriate for some patients. These patients include young children who may deal better with an amputation than with the limb-length discrepancy that may occur with limb-sparing procedures, those with extremity lesions

where it is not possible to acquire adequate surgical margins and where RT may produce major long-term complications, those with lesions that involve major vessels or nerves where resection will severely compromise function, and those in whom a fracture has resulted from tumor and the limb is useless and painful (104,110). Simply put, in the skeletally immature patient, due consideration must be given to the possibility that inappropriate or incorrectly administered RT may produce a stiff, painful, shortened, or disfigured extremity and engender a risk of second malignant neoplasm. Therefore, in some situations amputation may be preferred.

The role of regional node dissection in NRSTS is evolving. Overall, the incidence of nodal involvement is about 4%, ranging from close to 0% for grade 1 to 12% for grade 3 (6,58). It is reasonable to biopsy enlarged regional nodes in high-grade primary tumors. Certain histologic subtypes are more prone to lymphatic spread, including epithelial and synovial sarcomas, while others are not. Kayton has published a small series using sentinel node biopsies in pediatric tumors suggesting its utility in NRSTSs that are at risk for lymphatic spread (118).

Surgery also plays a role in managing NRSTS in the treatment of pulmonary metastases (119,120). With proper patient selection, long-term survival is possible for those undergoing removal of pulmonary metastases. Preoperative evaluation with chest radiograph and thoracic CT scanning is performed to determine the number and location of the metastases. Tumor may be resected via a median sternotomy or lateral thoracotomy, generally with double-lumen endotracheal anesthesia. Two studies in the literature, both of which included adult and pediatric patients, evaluated the important prognostic factors predicting survival after pulmonary metastasectomy. Higher survival rates appear to be associated with complete resection of all metastases, the presence of few lesions (i.e., 1–3), and a long disease-free interval before the development of metastases. Patients rendered free of disease in the series of Jablons et al. (121) had a median survival of 26.8 months. A similar group in the series of Casson et al. (122) had a median survival of 28 months. It is only fair to note that there are no randomized series in the literature comparing surgery with observation or with chemotherapy without resection. Therefore, it cannot be proven that the apparent prolongation of survival after surgery is attributable to the surgical therapy as opposed to good tumor biology (121). As an alternative to surgical resection of oligometastatic disease, there is an evolving experience with so-called body radiosurgery (123). In essence, high-dose ablative and hypofractionated conformal RT is administered. With some of these radiosurgical techniques, the surgeon may be asked to assist

with the placement of radio-opaque fiducial markers into the tumor mass to facilitate precise radiation dose delivery with minimal normal tissue exposures.

Radiotherapy

We have previously noted that the local control rate for NRSTS increases as the extent of surgical resection increases. This is undoubtedly because more radical surgery extirpates microscopic extension of tumor. It is well known that radiation can also sterilize microscopic extensions of tumor (124). We may infer that radiation can be used to accomplish that which is achieved by increasing the extent of surgery (85). The judicious combination of limited surgery and RT should be able to achieve local control rates equivalent to those of radical surgery, with a superior functional result in many cases. Most of the available data support this line of reasoning (85,112,124–126).

POG protocol 8653 was designed to study the role of adjuvant chemotherapy in children with resectable NRSTS (127). Local therapy was standardized to include surgery only for patients with wide or radical margins and surgery with postoperative irradiation for marginal excisions. Protocol guidelines were imperfectly followed. The results indicate higher local control rates with RT for marginal excisions in high-grade tumors (128) (Table 12.8). There will be situations in which radical surgery is not recommended for children or is recommended and declined because of unacceptable functional, cosmetic, emotional, or psychological consequences. RT may play a crucial role for these patients by allowing more conservative surgery with equivalent rates of local control.

In retrospective reviews of adult patients with NRSTS, treatment with conservative surgery and postoperative irradiation for microscopic extension of tumor yields local failure rates of 10–20%, comparable to those of radical surgery (85,106,107). In an analysis of 132 patients, largely adults, treated with preoperative radiation and conservative resection at the Massachusetts General Hospital (MGH), the local control results were 97% for patients with negative surgical margins and 82% for those with positive margins (129). In a series confined to children, the local control rate for patients who had no or microscopic residual disease after surgery and who were treated with postoperative irradiation was 79% (40). Tumor grade and size are the most important predictors of local failure in these series. The randomized prospective National Cancer Institute (NCI) trial, including adults and children, compared limb-sparing surgery and postoperative irradiation with amputation. The 5-year disease-free survival rate for the limb-spared group was 69% and was 72% for the amputated group

Table 12.8

POG Protocol 8653: Local Control by Surgical Margins and Radiotherapy

Surgical margins	IRS Group	Low grade		High grade	
		Surgery alone n (%)	Surgery + Radiotherapy n (%)	Surgery alone n (%)	Surgery + radiotherapy n (%)
Marginal	II	2/2 (100%)	10/11 (91%)	1/4 (25%)	10/11 (91%)
Wide	I	18/18 (100%)	3/3 (100%)	14/16 (88%)	2/2 (100%)
Radical	I	1/1 (100%)	No data	6/6 (100%)	No data

Modified from Marcus RJ. Current controversies in pediatric radiation oncology. *Orthop Clin North Am.* 1996;27:551–557, with permission.

($p = 0.7$). The local failure rate was higher in the limb conservation group, and several patients had to undergo salvage surgery (107,130). Psychological tests indicate that the amputees fared as well as those having limb-sparing surgery (131).

In addition to survival as an endpoint, one should also consider the functional outcome of limb-sparing surgery with RT for NRSTS. A retrospective review of a large number of NCI patients who underwent limb-sparing surgery with RT for extremity NRSTS indicates that the most common long-term complications are contracture, limb edema, decreased range of motion, and decreased muscle strength. Certain RT technical factors were associated with a higher risk of complications: inclusion of more than 50% of a joint in the portal, dosages over the equivalent of 63 Gy at 1.8 Gy per fraction, and large portals that encompassed more than 75% of the extremity diameter (132). Bertuccio et al. (133) analyzed 30 patients with extremity sarcomas who were younger than 21 years at diagnosis and received RT as part of a limb-sparing treatment. Of the 30 patients, 11 had NRSTS, 8 had rhabdomyosarcoma, and 11 had the Ewing sarcoma. On follow-up 50% of the patients had no limitation of limb function and 40% had full function but had a mild limp or needed a shoe lift, compression device, or pins or rods.

Four retrospective reviews of the St. Jude Children's Research Hospital clinical experience with NRSTS, published in 1999–2002, considered the role of adjuvant RT (6,38,88,89,108). In completely resected disease (clinical group I), postoperative irradiation appeared to reduce local recurrences only in high-grade disease. In patients with positive surgical margins (clinical group II), RT reduced local recurrences ($p = 0.001$) (Table 12.9). Several retrospective reviews, confined to children, have suggested a role for postoperative irradiation of NRSTS. RT has been used, in accordance with the standards of the Intergroup Rhabdomyosarcoma Study, in patients with group II (grossly complete tumor resection with microscopic residual disease or involved but completely resected regional nodes) and group III (incomplete resection with gross residual disease) NRSTS (5,51,52,56,40,93,134). In a series of 40 patients with generally high-risk, initially unresectable (group III) tumors, there was a

trend that combined chemotherapy, RT, and surgical resection improved outcomes in a subset of 27 patients with a 33% long-term event-free survival (88).

While there are considerable concerns with delivering high-dose RT to children with NRSTS due to developmental defects and an increased risk for secondary cancers, the role of RT for high-grade, incompletely resected, or recurrent soft tissue sarcomas in adults is well established. There is one randomized trial of surgery alone versus surgery and postoperative RT for extremity soft tissue sarcomas. In this small study from the NCI, 91 patients with high-grade lesions were randomly assigned to surgery plus postoperative chemotherapy with or without postoperative adjuvant RT. Another 50 patients with low-grade lesions were randomized to surgery plus adjuvant RT or surgery alone (135). RT to 45 Gy in 25 fractions was delivered to a wide field followed by a boost for an additional 18 Gy to the tumor bed. Among the patients with high-grade lesions, there were no local recurrences in the patients who received RT, while for patients receiving only adjuvant chemotherapy, the actuarial local failure rate was 22% at 10 years of follow-up. For patients with low-grade sarcomas, the local relapse rates were 4% versus 33% for those receiving postoperative RT and resection alone, respectively. As half of the "low-grade" patients had myxoid liposarcoma (possible undergraded) or desmoid tumors (known to respond to RT), this small randomized trial is not definitive. Indeed, other retrospective studies of low-grade soft tissue sarcomas with a wide resection generally have very low local recurrence rates especially for superficial tumors. Regardless, within this NCI trial there was no influence of postoperative RT on overall survival for either high- or low-grade tumors.

The other randomized RT trial that suggests a benefit for high-grade extremity sarcomas is the brachytherapy study from the Memorial Sloan-Kettering Cancer Center (MSKCC) (136). After complete resection of either extremity or superficial trunk soft tissue sarcoma (45 low-grade, 119 high-grade), patients were randomized to surgery alone versus low dose rate brachytherapy using afterloaded Ir-192 to deliver a dose of 45 Gy to the tumor bed. In patients with high-grade sarcomas, the 5-year local control

Table 12.9

Factors Affecting Local Relapse in NRSTS in the St. Jude Children's Research Hospital Retrospective Reviews

Group	Grade	Margin	Radiotherapy	Local Recurrence Ratio (%)	p value, favoring RT
I	Low	<1 cm	Yes	1/5 (20%)	$p = 0.37$
		<1 cm	No	1/5 (20%)	
		≥1 cm	No	2/44 (5%)	
	High	<1 cm	Yes	0/7 (0%)	
		<1 cm	No	3/7 (43%)	
		≥1 cm	No	4/20 (20%)	
II ^a	All	Positive	Yes	DNG/21	$p = 0.001$
		Positive	No	DNG/19	
I-II ^a	All	Negative	Yes	DNG/31 (3%)	$p = 0.043$
		Positive	No	DNG/90 (16%)	

^aThe trend favoring radiotherapy in groups I and II is the result of a likely benefit in high-grade, close margin group I and all group II.

DNG, data not given; RT, radiation therapy.

From Spunt SL, Poquette CA, Hurt YS, et al. Prognostic factors for children and adolescents with surgically resected nonrhabdomyosarcoma soft tissue sarcoma: an analysis of 121 patients treated at St. Jude Children's Research Hospital. *J Clin Oncol*. 1999;17(12):3697–3705 and Blakely ML, Spurbeck WW, Pappo AS, et al. The impact of margin of resection on outcome in pediatric nonrhabdomyosarcoma soft tissue sarcoma. *J Pediatr Surg*. 1999;34:672–675.

rates were 91% with brachytherapy compared to 70% with surgery alone. There was no benefit to brachytherapy for the low-grade tumors. Moreover, there was no difference among the patient groups from brachytherapy in terms of distant metastasis or disease-specific survival.

The other major phase III study in adult sarcoma patients compared preoperative versus postoperative RT (137). The theoretical advantage of preoperative RT is a smaller volume as well as a lower dose of RT that must be employed. The RT need only be directed at the gross tumor with a several centimeter margin rather than having to encompass the larger surgical resection bed. In the postoperative setting, higher radiation doses are generally employed to counter any potential incremental tumor hypoxia or clonogenic repopulation during the healing phase after surgery. Thus, preoperative RT in this setting tends to employ a radiation prescription of 50 Gy compared to 64–70 Gy in the postoperative setting. The major disadvantage of preoperative RT is a relative impairment of wound healing with a higher risk of dehiscence and infection. Nevertheless, the concept of preoperative RT for NRSTS has not been extensively studied. Certainly, there could be an improvement in function and lower risk of secondary cancers with this approach.

More specifically, this Canadian trial comparing preoperative and postoperative RT enrolled 190 patients, most more than 50 years old. The trial was open from 1994 to 1997 and included patients with limb MFH, liposarcoma, leiomyosarcoma, and other spindle-cell sarcoma histologies. Half received 50 Gy of preoperative RT and a 16- to 20-Gy postoperative boost for a positive margin. Patients in the postoperative group received 50 Gy and a 16- to 20-Gy boost. In a planned interim analysis, the study was terminated early due to higher wound complications (defined as secondary wound surgery, hospital admission for wound care, or the need for deep packing or prolonged wound dressings within 120 days of tumor resection) with the preoperative as opposed to postoperative RT (35% vs. 17%) (137). In subsequent publications, the local recurrence rate, regional or distant failure rate, progression-free survival, and functional outcome did not differ between the groups with local control rates at over 90% in both treatment groups at 7 years of follow-up (138,139). Of interest, the postoperative RT patients have experienced greater late toxicity particularly with greater functional problems due to fibrosis within the irradiated volume. There were also trends toward more lymphedema and joint stiffness in this group contributing to adverse functional outcomes (140).

In conclusion, acceptable indications for RT in childhood NRSTS are localized, incompletely resected tumor with gross residual disease; palliation of metastasis (palliation of pain or compressive syndromes requires 35–50 Gy; however, conventional RT is rarely effective for gross lung metastases) (6,104); as part of a planned limb-sparing procedure; and after an attempt at gross total tumor removal when there is microscopic residual tumor or positive regional lymph nodes. More attention to preoperative RT in pediatric NRSTS is likely to become an active area of further investigation based on the evolving experience in adult soft tissue sarcomas. For oligometastatic disease, there is recent enthusiasm for body radiosurgery or high dose, hypofractionated conformal RT as an alternative to surgery resection (123).

Chemotherapy

The use of adjuvant chemotherapy in childhood NRSTS initially was defended on the basis of the significant risk of metastatic disease and local recurrence in high-grade lesions, retrospective

comparisons, and the success of chemotherapy in rhabdomyosarcoma. The most active single agents are adriamycin and ifosfamide (141). Other active agents are dacarbazine, actinomycin D, vincristine, etoposide, and cyclophosphamide (6,33,51,56,83, 93,105,130,142,143). In this section of the chapter we will review the most pertinent larger-scale studies.

Cooperative Group Studies of Chemotherapy and NRSTS Exclusive of PNET, EOES, and Askin Tumor

POG protocols 8653 and 8654 were open to patients younger than 21 years at diagnosis with any biopsy-proven soft tissue sarcoma other than rhabdomyosarcoma, EOES, or undifferentiated round cell sarcoma. Children who were treated with surgical resection with complete extirpation of tumor; surgical excision of the tumor with postoperative irradiation; or biopsy, preoperative irradiation, and secondary surgery obtaining complete resection were randomized to receive postoperative adjuvant vincristine, adriamycin, and cyclophosphamide (VAdRC) or observation. This randomization, constituting protocol 8653, would be analogous, were one to use the rhabdomyosarcoma grouping system for NRSTS, to randomizing patients in groups I–III, including those rendered resectable by radiation (127).

Protocol 8654 was for patients who were judged to have inoperable tumors or for those with metastatic disease. These patients were randomized to receive either VAdRC or those three agents plus dacarbazine. Involved-field radiation was administered to the primary tumor site (11). Study 8653 was open from June 1986 to May 1992. Study 8654 was open from June 1986 through April 1994. However, there was approximately a 1-year period in which all patients in Study 8654 were treated with vincristine, actinomycin, and cyclophosphamide because of a shortage of dacarbazine. There were 81 eligible patients for protocol 8653. Only 30 patients accepted randomization: 15 received chemotherapy, and 15 were observed. Of the remaining 51 patients, 19 elected adjuvant chemotherapy, and 32 elected observation. For the total group of 81 patients, the 5-year overall survival was 85%, and the event-free survival (EFS) was 72%. The 5-year EFS for randomization patients was 69% for the chemotherapy arm and 87% for the observation arm (Fig. 12.8). A grade 3 tumor conferred a significant disadvantage with respect to EFS. The 3-year EFS was 75% for grade 3 and 91% for grades 1 and 2 ($p = 0.018$). Therefore, there was no discernible benefit to the use of chemotherapy. For study 8654, 75 patients enrolled this trial; the 4-year EFS for patients receiving vincristine, actinomycin D, cyclophosphamide, and adriamycin (VACA) was no different from that for patients receiving the four drugs plus dacarbazine. The 4-year overall survival and EFS were 31% and 18%, respectively (Fig. 12.4) (6,12,144). Not surprisingly, nonmetastatic and low-grade disease had better outcomes relative to metastatic and high-grade disease.

POG 9553 was a phase II trial of vincristine, ifosfamide, and doxorubicin in unresected or metastatic NRSTS (13). Surgery was considered at week 7 with RT thereafter. Radiation doses were age dependent: 54 Gy if under the age of 6 years and 64 Gy for those older. Pulmonary metastasis management included low-dose whole lung RT, although this is currently a controversial practice. Doxorubicin was withheld during RT. Results were reported for 39 patients. The 3-year overall survival and progression-free survival rates ($\pm$ standard deviation) for eligible patients were $59\% \pm 8\%$ and $44\% \pm 7\%$, respectively. There was a suggestion that synovial cell sarcomas responded better to chemotherapy compared to other histologies.

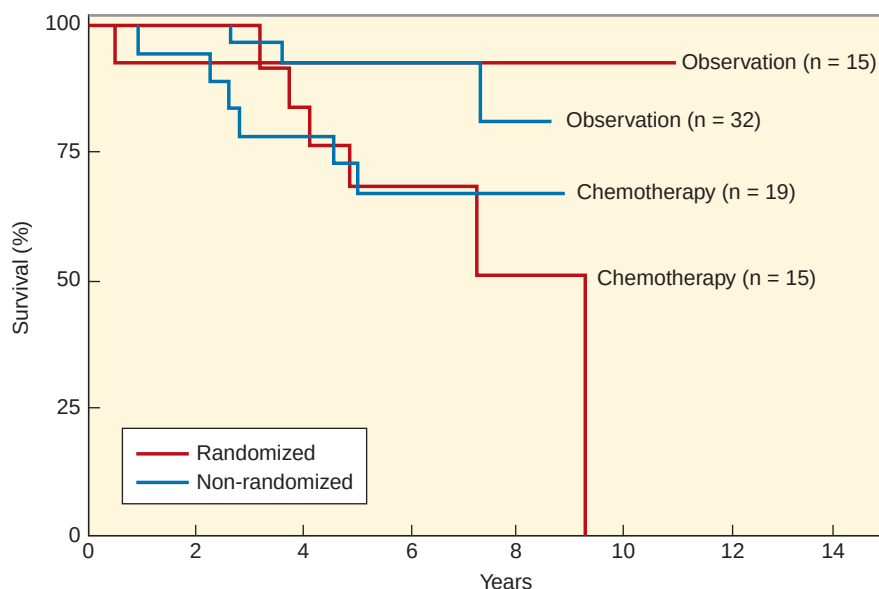


Figure 12.8 Pediatric Oncology Group protocol 8653 randomized children with intergroup rhabdomyosarcoma study groups I–III nonrhabdomyosarcoma soft tissue sarcoma to observation or vincristine, cyclophosphamide, adriamycin, and actinomycin D. Of the 81 eligible patients, 15 were randomized to observation, 15 were randomized to chemotherapy, 19 elected chemotherapy, and 32 elected observation. The four survival curves show no benefit to chemotherapy. (From Pratt CB, Pappo AS, Gieser P, et al. Role of adjuvant chemotherapy in the treatment of surgically resected pediatric nonrhabdomyosarcomatous soft tissue sarcomas: a Pediatric Oncology Group study. *J Clin Oncol* 1999;17:1219–1226, with permission.)

The German soft tissue sarcoma study CWS-81 was initiated in 1981 under the auspices of the German Society of Pediatric Oncology. This study was open to children with rhabdomyosarcoma, undifferentiated sarcoma, EOES, synovial sarcoma, leiomyosarcoma, peripheral PNET, fibrosarcoma, hemangiosarcoma, neurofibrosarcoma, and liposarcoma. For the purposes of this chapter, we will confine our discussion to the results concerning NRSTS exclusive of EOES and PNET. Patients with localized disease, completely resected, received vincristine, actinomycin D, cyclophosphamide, and adriamycin. Patients with grossly resected tumor, microscopic residual disease, and no evidence of regional node involvement received the same chemotherapy but also had involved-field irradiation. These patients were then treated with vincristine, actinomycin D, and cyclophosphamide. Patients with grossly resected tumor with microscopic residual disease and regional nodal involvement or those with incomplete resection or biopsy with gross residual disease received four-drug chemotherapy initially. Those who were good responders continued on this chemotherapy and received involved-field irradiation; ultimately, the adriamycin was dropped. Those who were poor initial responders received involved-field irradiation, but ifosfamide was substituted for cyclophosphamide. Patients who had stage IV disease received vincristine, actinomycin D, ifosfamide, and adriamycin. In 1984, ifosfamide was also added for patients with stage III disease who did not respond to preoperative chemotherapy. Detailed information is available concerning the 30 children and adolescents with synovial sarcomas treated on this study (145). A survival rate of 70% was observed, with a median observation time of 34 months. Patients with synovial sarcoma of the extremities had a disease-free survival rate of 88%. Six of eight patients who had their tumors resected with no residual disease are disease-free survivors, seven out of nine patients who had their tumor resected with microscopic residual disease are disease-free survivors, six of eight patients who have had their tumor resected with gross residual disease are disease-free survivors, and three of five patients

with metastatic disease at presentation (stage IV) were disease-free survivors. Obviously, the German study was not a head-to-head comparison of chemotherapy and observation, and it is not clear what the survival would have been if patients were treated with local therapy alone.

The International Society of Pediatric Oncology (SIOP) has conducted two protocols for NRSTS. The treatment program consisted of a primary complete tumor excision if feasible without mutilation. For patients who were not resectable initially, neoadjuvant chemotherapy was administered. Initial chemotherapy was ifosfamide, vincristine, and actinomycin D. Second-line chemotherapy on study MMT84 was cyclophosphamide and doxorubicin, and in study MMT89 it was epirubicin, doxorubicin, carboplatin, and VM26. Patients were then taken to surgery if possible. RT was used for macroscopic residual tumor after surgery. For patients who had initial primary excision, adjuvant chemotherapy was given with ifosfamide, vincristine, and actinomycin D. In nonmetastatic patients an initial complete excision was obtained in 24% of patients, complete response was obtained in 30% of patients by initial partial excision followed by chemotherapy, and a complete response was obtained in 30% of patients by an initial biopsy, neoadjuvant chemotherapy, and second surgery. In 8% of patients a complete tumor response was obtained by surgery, chemotherapy, and RT, and in another 8% of patients complete response was obtained by surgery, chemotherapy, second surgery, and RT. Therefore, 16% of patients received RT. The overall survival rate in study MMT84 was 73% at 5 years for nonmetastatic patients, and in MMT89 it was 84%. Survival was only 15% for metastatic patients. The 5-year survival rate was 60% for fibrosarcoma, leiomyosarcoma, synovial sarcoma, and other classified sarcomas and 50% for PNET and EOES (146,147). Very young patients represent a considerable challenge in which surgery is performed with very tight margins, chemotherapy has to be attenuated due to altered metabolism of drugs, and RT is generally avoided. A report from SIOP that included 38 patients

with NRSTS treated on the MMT84 and MMT89 protocols suggested that patients less than 1 year of age at diagnosis had similar survivals to older patients (75% in infants and 71% in older children, $p = 0.61$) (148). Data was not specified for the subset of nonmetastatic tumors.

In summary, relatively few pediatric patients with NRSTS have been studied in cooperative groups. The small POG study that randomized patients with NRSTS to chemotherapy or observation showed no benefit to chemotherapy. To date, the studies that have randomized patients to various chemotherapy arms have not shown a substantive difference from those results with local therapy alone. Nevertheless, the two major international cooperative groups have adapted similar treatment strategies with their current investigational protocols. The COG represents most centers in the United States. In Europe, the German and Italian cooperative groups have combined their efforts with a series of reports on pediatric soft tissue sarcomas (63,64,81,149,150), although more recently since 2000, a European-wide consortium called the European Paediatric Soft Tissue Sarcoma Study Group (EPSSG) is sponsoring an NRSTS trial open since 2005. The essential strategy in both the United States and Europe is to risk stratify patients based on tumor size, grade, localized versus metastatic, and respectability. Intermediate- and high-risk patients receive ifosfamide and doxorubicin chemotherapy (141). Surgery is emphasized for local management, but with adjuvant or preoperative RT or chemoradiotherapy in a risk-adapted treatment schema. In metastatic NRSTS, the EPSSG has shown some activity from the combination of ifosfamide, doxorubicin, vincristine, and actinomycin D (151).

Large-Scale Studies of Adjuvant Chemotherapy in Adults with NRSTS

There are at least 18 randomized prospective trials of mostly adult patients evaluating adjuvant chemotherapy for NRSTS. These studies include comparisons of observation with doxorubicin as a single agent; with doxorubicin, cyclophosphamide, dacarbazine, and vincristine; with adriamycin, vincristine, cyclophosphamide, dactinomycin, and dacarbazine; with doxorubicin, cyclophosphamide, and methotrexate; with doxorubicin, cyclophosphamide, vincristine, and dacarbazine; and with doxorubicin and ifosfamide. The majority of these studies are equivocal as to the benefit of adjuvant chemotherapy. We will briefly summarize some of the larger published trials of adjuvant chemotherapy for soft tissue sarcoma, largely in adults.

The NCI trial was conducted for patients with stages IIA–IIIB extremity soft tissue sarcoma. Patients underwent either amputation or limb-sparing surgery followed by RT. They were then randomized to observation or adriamycin and cyclophosphamide. After a maximum cumulative dosage of adriamycin, chemotherapy was switched to methotrexate with leucovorin rescue. At a median follow-up of 7.1 years, the 5-year relapse-free survival is better for patients who received chemotherapy ($p = 0.04$); however, the difference in overall survival was not significant (105,110,130).

The Scandinavian Sarcoma Group randomized 240 patients with high-grade sarcomas to receive either adriamycin or no systemic treatment. No significant difference was seen between the adriamycin and the control group with respect to local recurrence, relapse-free survival, or overall survival for the 181 evaluable patients or the 240 randomized patients (152).

The European Organization for the Research and Treatment of Cancer's (EORTC) Soft-Tissue and Bone Sarcoma Group

conducted a phase III trial of chemotherapy after local therapy of histologically proven soft tissue sarcoma in adults with either surgery or RT. Randomization was to treatment with cyclophosphamide, vincristine, adriamycin, and dacarbazine or to observation. Between 1997 and 1998, 468 patients entered the study; 151 patients were considered ineligible. The mean follow-up duration was 80 months. Relapse-free survival with chemotherapy was 56%, compared with 43% for control subjects ($p = 0.006$); local recurrence was lower in the chemotherapy arm (17% vs. 31%, $p = 0.0041$), but overall survival did not differ significantly between the two arms (66% for chemotherapy vs. 55% for observation, $p = 0.64$). In patients with extremity tumors, no significant improvement was seen with chemotherapy in terms of local recurrence, metastases, or survival. In contrast, local recurrence was less with chemotherapy for head, neck, and trunk sarcomas (43). An Italian cooperative group compared adjuvant epirubicin, ifosfamide, sodium mercaptoethane sulfonate (MESNA), and granulocyte colony-stimulating factor (G-CSF) with a control group (153). There was a median disease-free survival of 16 months in the control group, compared with 48 months in the adjuvant group ($p = 0.04$), and an improvement in median survival from 46 to 75 months ($p = 0.03$). There was thought to be an improvement in survival at 4 years in the adjuvant arm on a planned interim analysis of the data. However, a closer analysis of the data showed that the adjuvant chemotherapy group experienced fewer metastatic events at 2 years (28% vs. 45%, $p = 0.08$). By 4 years this difference had disappeared, with 44% of the control group having metastatic disease and 45% in the adjuvantly treated group ($p = 0.94$). The difference in disease-free survival in the groups at 4 years was related to a significantly greater frequency of local failure in the patients in the control group (17% vs. 6% in those receiving chemotherapy).

Several meta-analyses have been published. A widely quoted 1997 analysis included 14 earlier trials of 1568 patients—fewer than 1% of the patients were younger than 15 years—showing an improvement in local control and disease-free survival but not overall survival (154). About two thirds of the analyzed patients had high-grade tumors, and one-half received RT (154–156). With several more recent trials emphasizing the addition of ifosfamide to doxorubicin, an updated 2008 meta-analysis of 1953 patients shows an overall survival advantage in a subset analysis (157). More specifically, the odds ratio for local recurrence and overall recurrence were 0.73 and 0.67, respectively, in favor of chemotherapy. These statistically significant values were similar to the earlier meta-analysis, but in this update the odds ratio for overall survival was 0.56 (0.36–0.85, 95% confidence interval) in favor of doxorubicin and ifosfamide combination chemotherapy. Doxorubicin alone (OR 0.84, 0.68–1.03, 95% CI) was not associated with a statistically significant overall survival benefit. The absolute risk reduction for ifosfamide/doxorubicin was 11% (30% vs. 41% risk of death). The major caveat to these findings is that two large EORTC trials of adjuvant ifosfamide/ doxorubicin chemotherapy in 819 patients were not included in this updated meta-analysis; the preliminary analysis of these additional trials does not show a survival advantage (158). The meta-analyses have demonstrated a trend that the most benefit to chemotherapy is seen in patients with bulky and high-grade tumors. Particular histologic subtypes were not found to be more chemo-sensitive, although a variety of individual reports suggest otherwise. For instance, there is a school of thought that synovial cell sarcomas and round-cell/mesenchymal liposarcomas may be more responsive to chemotherapy.

Patients with metastatic disease are infrequently cured. A recent study of adults with NRSTS from institutions participating in the Scandinavian Sarcoma Group described a highly select group of 38 patients with metastatic NRSTS or locally advanced disease and who had achieved a complete response with chemotherapy alone or chemotherapy followed by surgery. The drug programs used were either vincristine, ifosfamide, MESNA, and G-CSF (VIG), VIG with doxorubicin, or ifosfamide, vincristine, doxorubicin, dacarbazine, and MESNA. The 2-year disease-free survival, even in this select group, was only 34%. In general, the complete response rate to chemotherapy in advanced NRSTS is less than 10%, and the combined complete and partial response rate is less than 50% (159).

The drugs used for the adjuvant treatment of NRSTS, particularly doxorubicin, have significant toxicities. With the data currently available, chemotherapy probably is not the appropriate adjuvant therapy for low-grade NRSTS treated with appropriate local therapy. As already noted, for high-grade lesions, trials are ongoing to evaluate drug combinations such as doxorubicin and ifosfamide. It has been argued that improved staging and better local control techniques have been the major contributing factors to improved survival in NRSTS, as opposed to any benefits of chemotherapy. Adjuvant therapy for NRSTS is best given in the context of a clinical trial. However, chemotherapy often is given as a component of the treatment of metastatic disease.

RADIOTHERAPEUTIC MANAGEMENT

RT for childhood NRSTS may be administered after biopsy but before definitive surgery (preoperatively), postoperatively, or intraoperatively. The arguments for preoperative irradiation include the following. First, preoperative treatment will produce partial regression of the tumor, and the resection may be less extensive than if the surgery had been done initially. Second, preoperative treatment may decrease the risk of autotransplantation of the tumor in the surgical bed and may also decrease the risk of intravascular seeding. Third, in preoperative treatment the clinically and radiographically demonstrable areas of risk are treated. Other tissues are shielded (99,100,160,161). In addition, because postoperative treatment must cover all surgically manipulated areas, the irradiated volume often is larger. Finally, the postoperative surgical bed maybe poorly vascularized. The concern regarding tumor cell hypoxia in this setting has led to higher radiation doses being required. Results of the Canadian randomized trial suggests an equivalence to 50 Gy preoperatively to 66–70 Gy postoperatively (137,138).

Some of the results from single institutions of preoperative RT in combined adult and pediatric series of NRSTS are also promising. Suit and coworkers (85,106) achieved an 88% 5-year actuarial local control rate and a 66% survival with limited surgery and RT in 258 patients with extremity and head and neck primaries. These results have been echoed in other studies (91,162). Eilber et al. (68,112) administered preoperative external beam irradiation and intra-arterial doxorubicin (30 mg per day for 3 days) followed by limb-sparing surgery for extremity sarcomas. The local control rate was 96% for patients who received 35 Gy, 90–95% for those who received 28 Gy, and 82% for those who received 17.5 Gy. Preoperative RT with hyperthermia for NRSTS is being investigated. Local control rates are quite good when thermoradiotherapy is followed by conservative surgery (163). It is not uncommon to find no remaining viable tumor at the time of resection. External microwave hyperthermia generally is appropriate only in older and more cooperative children.

The disadvantages of preoperative therapy include a delay in the start of definitive surgery, loss of ability to examine the whole tumor specimen for stage and grade, and loss of the ability to surgically assess the extent of the disease. Therefore, many radiotherapists and surgeons favor postoperative treatment. Postoperative RT must be delayed until adequate wound healing has occurred (85,106). A retrospective review comparing preoperative and postoperative external beam irradiation from the University of Minnesota for adults with NRSTS found no significant difference in overall or relapse-free survival or local control. However, wound complications were more common in preoperative RT patients (31% vs. 8%, $p = 0.0014$) (160). Several other centers have done retrospective comparisons of preoperative and postoperative irradiation in series of largely adult patients. Some studies favor preoperative treatment (85,164); others do not (165) (104). The aforementioned randomized trial of preoperative versus postoperative RT conducted at the Princess Margaret Hospital for adult patients with soft tissue sarcomas presents the best data supporting preoperative RT (137–140). While there were more problems with wound healing after RT as compared to postoperative RT (35% vs. 17%, $p = 0.01$), proper selection of patients and surgical attention to avoiding tension on the surgical wound may help mitigate this problem. Preoperative RT uses lower radiation doses (50 Gy vs. 66–70 Gy) and smaller treatment volumes. This translates into lower late complications with fibrosis, lymphedema, and joint stiffness. And importantly, the local and distant control of disease is equivalent with the two approaches of preoperative versus postoperative RT.

Most agree that wound complications are higher with preoperative treatment (164,166). When the therapeutic plan includes EBRT and surgery for the local treatment of NRSTS, it is generally preferable to completely excise small lesions and treat with postoperative irradiation when indicated. Small, low-grade lesions resected with good surgical margins may be observed. Resected tumors with high-risk features, including large-size, high-grade, or positive surgical margins should be considered for postoperative RT. High-grade tumors that have been cleanly resected have controversial indications for postoperative RT due to the concerns about late effects. The cooperative group trials are attempting to sort out the indications for postoperative RT with the COG NRSTS 0332 trial opened in 2007 allocating small, high-grade, negative margin tumors to observation. Positive surgical margins (group II disease) are a clear indication for postoperative RT. Paulino published a series of 83 NRSTS patients managed at the University of Iowa (48). Overall local control rates at both 5 and 10 years was 66%. On multivariate analysis, the size of the tumor and postoperative RT were prognostic factors for local control. Twenty-five patients had positive surgical margins. Five-year local control rates were significantly improved with the use of RT, 82% versus 43%, $p = 0.04$. In a subset of 13 group I patients with low-grade, small tumors, surgery alone resulted in no local recurrences. On the other end of the spectrum of localized NRSTS, most large lesions particularly of high grade are better treated with biopsy, preoperative irradiation, or chemoradiation, and then excision.

Volume

Extremity NRSTSs tend to grow in a longitudinal fashion by following muscle groups. Generous proximal and distal margins beyond the tumor volume (5–10 cm) are appropriate. Because the lesions usually do not cross muscle compartments, the circumferential margins may be more modest (107). A limb CT or

MRI scan, followed by a computerized treatment plan, is extremely helpful. The treatment of sarcomas often is a venue for the demonstration of the benefits of intensity-modulated radiation therapy (IMRT), three-dimensional (3D) treatment planning techniques, tissue compensators, wedges, customized blocking, and rigid immobilization for reproducible treatments. One should avoid high-dose irradiation of the entire width of a limb in order to avoid severe lymphedema (radiation-induced elephantiasis) (104). Blocking should be used to avoid the ankylosis attendant to the high-dose irradiation of the full width of a joint (124). Growth plates should be shielded when possible (although it is usually better to fully treat a growth plate and shorten a limb rather than asymmetrically irradiate a growth plate and angulate a limb). There is also an evolving understanding that fractures may be minimized by reducing the volume of bone, especially weight-bearing bones such as the femur, being treated to high doses (116,117). The use of IMRT and proton RT is under investigation in this regard. In nonextremity lesions the tumor volume must be covered with as generous a margin as is feasible. In children with NRSTS, there may be a more compelling reason to use IMRT (or in the future protons) to reduce the exposure of normal tissues. Limiting the high-dose regions to the affected muscle compartment, while reducing dose to adjacent bone, growth plates, joints, other muscle groups, skin, and uninvolved neurovascular bundles may result in better functional outcomes and less developmental toxicities. IMRT also facilitates differential dosing or a dose gradient between gross tumor and adjacent normal tissues, which can be important in limiting toxicities or escalating radiation dose in cases of unresectable disease. For instance, with retroperitoneal sarcomas, investigations are underway in adults to deliver higher preoperative doses within the target volume where a tight surgical margin is anticipated while potentially lower dose to the intestines and kidney. Similar concepts are adaptable to childhood NRSTS. The rational reduction in radial margins with these techniques requires the technical advances of cross-sectional imaging with 3D treatment planning, an anatomic understanding of tissues at risk, and precise immobilization and field verification.

Epithelioid sarcoma and synovial sarcoma may metastasize to lymph nodes in 10–20% of cases (5,56,167–170). Some physicians use elective lymph node irradiation for these lesions, particularly high-grade tumors. Its efficacy is unknown.

Dosage

Modern radiobiologic evidence gives little credence to the assertion that NRSTSs are inherently radioresistant. The available retrospective reviews suggest that a minimum of 40 Gy is necessary for the postoperative control of microscopic NRSTS in children (51,52). At these dosages, however, there is a substantial chance of local failure. More aggressive treatment is generally warranted. Several investigators favor a dosage of 50–60 Gy using a shrinking field technique (40,85,104). In a University of Florida series for excised pediatric NRSTS tumors, 54 Gy appeared to be an adequate total dose (128,171). Although hyperfractionation is out of favor since a negative randomized trial in rhabdomyosarcoma (172), some clinicians have suggested the use of twice-a-day irradiation (i.e., 1.1–1.2 Gy twice daily to 66–72 Gy) (104) (64). In adults, however, a retrospective analysis from the M. D. Anderson Cancer Center suggests that cumulative doses of at least 64 Gy are optimal (173). Another analysis from the University of Chicago suggests 60 Gy is adequate with no benefit to higher postoperative doses when there are negative surgical margins, but poor lower control with lower doses (174).

For preoperative treatment, lower radiation doses may be used on the order of 50 Gy. Additional radiation may be required, however, if there are positive surgical margins. There is limited experience in pediatric NRSTS, however. POG protocol 8653 intended that unresectable (i.e., group III) tumors receive preoperative RT to 55 Gy for children less than 6 years of age and 65 Gy for older children. At least six patients—out of an unclear number of group III patients—had an insufficient response and could not undergo planned resection (12). POG 9553 used either 54 or 64 Gy (depending on the age of the child) following initial chemotherapy in a prospective series of 25 children with group III NRSTS. This preoperative management resulted in a 3-year overall survival rate of 80% and progression-free survival of 60% (13). A retrospective series from St. Jude Children's Research Hospital of 27 patients with localized unresected NRSTS and a 33% 5-year event-free survival included 15 patients who received preoperative RT most often with chemotherapy; the RT doses ranged from 35 to 65 Gy, but these dose tallies included some component of postoperative RT (88). As one of the larger of such series, there is no clarification of optimal radiation doses for group III NRSTS patients such that the adult experience gives the best guidance for the present, pending any results from current cooperative group trials ongoing.

When intraoperative boosts with brachytherapy or electrons are given as part of a combined approach, the dosage usually is 10–20 Gy. Gross residual sarcoma requires 65–72 Gy by external beam and implant (40,106,107). Some adult patients with unresectable lesions have been treated with external beam and intravenous radiosensitizers or external beam plus hyperthermia (8,175).

Brachytherapy and Intraoperative Radiation Therapy

Brachytherapy may play an important role in limb-sparing surgery for NRSTS (176). Brachytherapy is often but not always given in combination with preoperative or postoperative external beam treatment. Brachytherapy has the following potential advantages: Its radiobiologic effectiveness is increased by the administration of a high dosage of irradiation over a few days rather than several weeks; an intense dose is given deep in the tumor bed; surrounding normal tissue and overlying skin are spared through the rapid falloff of the dosage; and the short treatment time is more convenient, avoiding the problems of travel and housing for protracted external beam therapy (125,177,178).

Conventional afterloading brachytherapy is suitable for children capable of doing self-care. It is more complex, from a nursing standpoint, in younger children. Several techniques are available for brachytherapy for NRSTS in children. The most commonly used type is a manually loaded low-dose rate system. Plastic catheters are inserted into the target volume with the aid of hollow needles. These catheters are subsequently loaded with the radioactive sources. Needles may be placed freehand or with the assistance of a custom-built or standardized template. Intracavitary applicators have been developed for use in treating vaginal sarcomas and lesions of the upper aerodigestive track. Most commonly, iridium-192 or cesium-137 is used. When there is particular concern about radiation exposure to nursing personnel or parents, and if the anatomy of the tumor allows, one should consider using a low-energy radioisotope such as iodine-125 or palladium-103. When these isotopes are used, thin sheets of lead applied over the treatment area or a standard lead apron provides a measure of protection for visitors.

In a conventional low-dose rate afterloading procedure, the afterloading catheters are placed at the time of surgical excision. After tumor excision, the radiation oncologist and surgeon inspect the operative bed and plan the implant. Parallel plastic catheters are placed approximately 1 cm apart throughout the entire tumor bed, usually with a 1- to 2-cm margin. For extremity lesions, some radiation oncologists place the catheters parallel to the axis of the limb (i.e., parallel to the incision), whereas others place catheters perpendicular to the axis of the incision and limb. Postoperative radiographs are taken with dummy sources to calculate the dose distribution and rate. Initial wound healing is allowed to begin, and the catheters are afterloaded with iridium-192 (the most commonly used isotope in this situation) until the sixth postoperative day. Earlier loading is associated with a significant risk of wound complications, up to a 44% incidence (179,180). When the situation warrants it, catheters may be placed adjacent to bone or neurovascular bundles. In general, little irradiation is given via the implant to the superficial incision. Figures 12.9 and 12.10 are two illustrative examples of afterloading brachytherapy used as a boost for hand sarcomas (although the second case was ultimately associated with a local recurrence).

The second general technique of pediatric brachytherapy for NRSTS involves permanent interstitial implant. Low-activity iodine-125, gold-198, or palladium-103 seeds are used. They may be placed with the use of a seed gun (a device used for their implantation), placed through individual needles, or embedded in Vicryl suture material and then sewn into the tumor bed. Although the low energy of these radioactive sources lowers the risk to visitors, these implants often are extremely difficult to perform.

The third form of brachytherapy for pediatric NRSTS is remote afterloading. This may be done at a low dose rate, high dose rate, or pulsed dose rate (intermittent use of a high-dose rate machine). The catheters or applicators are inserted into or placed on the tumor site. They are then connected to the afterloader for remotely controlled radioactive loading. The radioactive sources are retracted into the high-dose rate applicator's vault during planned interruptions. The procedure may be done in an outpatient clinic or operating room. Some departments have specially designated rooms for this purpose. Intraoperative high-dose rate brachytherapy is a modification of this general technique (179–184).

In the treatment of NRSTS, brachytherapy may be used as a boost after or before EBRT or as the sole form of irradiation

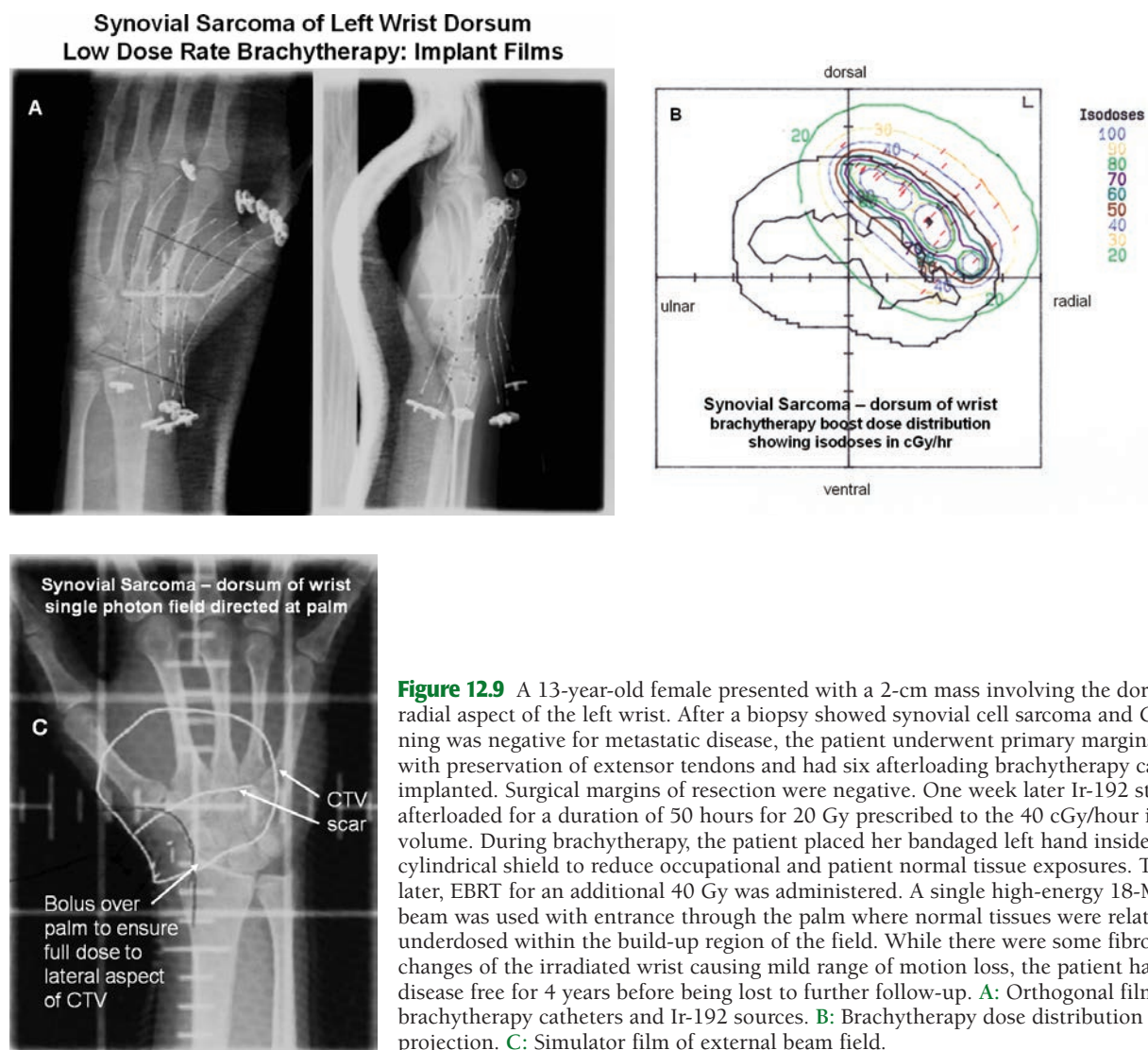


Figure 12.9 A 13-year-old female presented with a 2-cm mass involving the dorsal and radial aspect of the left wrist. After a biopsy showed synovial cell sarcoma and CT scanning was negative for metastatic disease, the patient underwent primary marginal resection with preservation of extensor tendons and had six afterloading brachytherapy catheters implanted. Surgical margins of resection were negative. One week later Ir-192 strands were afterloaded for a duration of 50 hours for 20 Gy prescribed to the 40 cGy/hour isodose volume. During brachytherapy, the patient placed her bandaged left hand inside a lead cylindrical shield to reduce occupational and patient normal tissue exposures. Ten days later, EBRT for an additional 40 Gy was administered. A single high-energy 18-MV photon beam was used with entrance through the palm where normal tissues were relatively underdosed within the build-up region of the field. While there were some fibrotic changes of the irradiated wrist causing mild range of motion loss, the patient has remained disease free for 4 years before being lost to further follow-up. **A:** Orthogonal films of brachytherapy catheters and Ir-192 sources. **B:** Brachytherapy dose distribution in axial projection. **C:** Simulator film of external beam field.

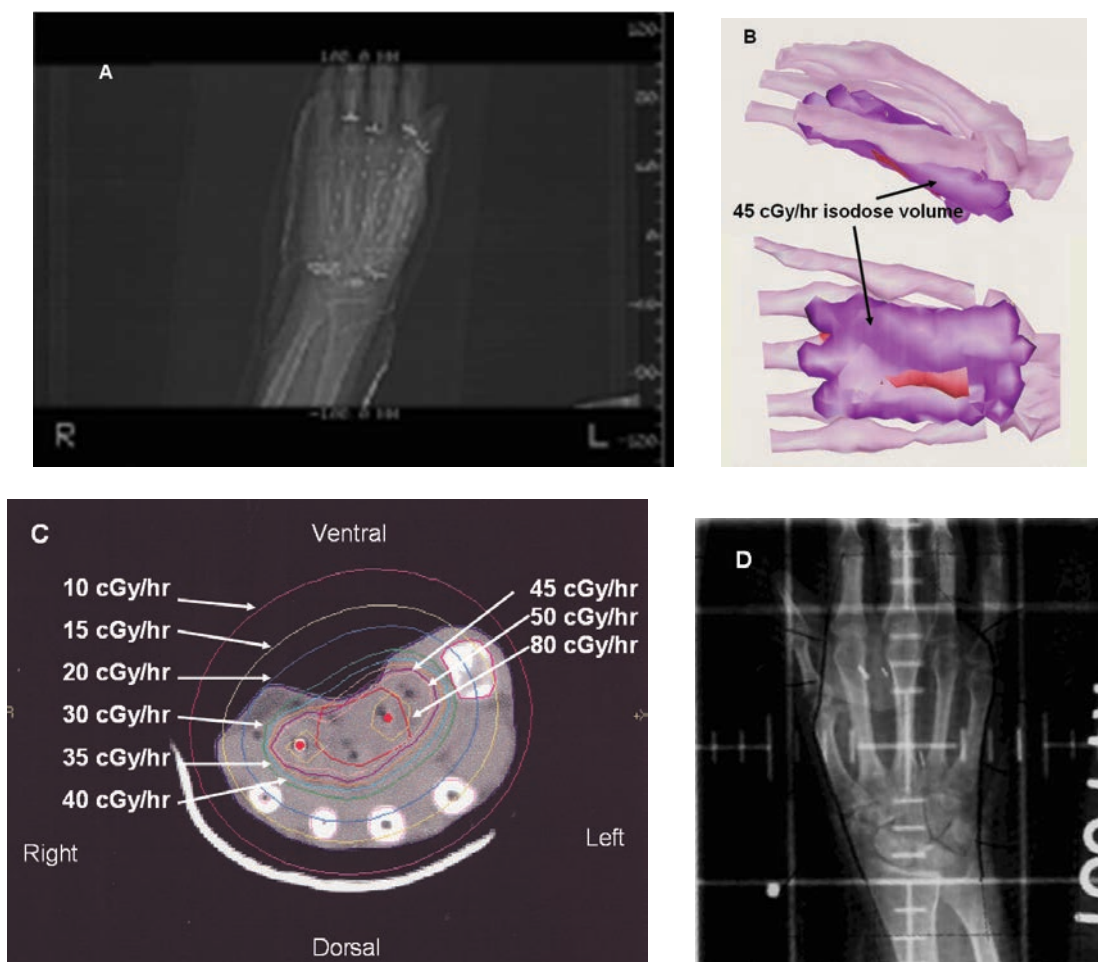


Figure 12.10 At age 15, a fibrotic mass was resected from the right palm with unconfirmed pathology suggesting a desmoid tumor. A local recurrence at the age of 20 gradually enlarged over years resulting in an ulcerative lesion. In May 1999, after an MRI of the right hand showed an infiltrative mass between the second and fourth flexor tendons, marginal resection revealed an epithelioid sarcoma with multifocal deep surgical margins positive for tumor. CT scan of the chest and bone scan showed no metastatic disease. The patient refused amputation. A re-resection and placement of four afterloading brachytherapy catheters was performed in July 1999. With concerns that this particular patient was incapable of managing catheters free of infection for any period of time, Ir-192 strands were afterloaded on postoperative day 1. The implant duration was 56 hours to deliver 25.2 Gy to the 45 cGy/hour isodose volume. Thereafter the patient received 40 Gy in 20 fractions of EBRT with a single field directed at the dorsum of the hand. The patient was lost to follow-up for 2 years, but then returned with complaints of a progressive scar involving the palm. Resection was negative for tumor. Over the next several years, there was progressive loss of flexion of the middle fingers. Then in 2004, new ulcerative lesions over the thenar eminence and distal third finger developed. A forearm amputation was performed for recurrent epithelioid sarcoma occurring both within and at the margin of the RT volume. For at least a year the patient has remained free of recurrent or metastatic disease. Further follow-up is not available. **A:** Ct scout film showing the brachytherapy catheters. **B:** The brachytherapy volume of the 45 cGy/hour isodose relative to the bony anatomy. **C:** The brachytherapy dose distribution in the axial projection. **D:** Simulator film of the external beam field.

monotherapy (88). In general, the planning volume for brachytherapy for NRSTS is smaller than for EBRT. In brachytherapy the volume treated closely approximates the clinical target volume. There is no need to allow for internal organ movement, patient movement, or setup errors. Because the dosage from the radioisotope falls off rapidly, the volume of normal tissue irradiated outside the planning target volume is minimized.

When brachytherapy is the sole form of irradiation to be given, surgical drain sites usually are not implanted. In adult practice, if 45–50 Gy of external irradiation is given as part of a course of treatment, the brachytherapy boost generally is 10–20 Gy at about 50 cGy per hour. If brachytherapy is the sole form of

irradiation used in combination with surgery, then 40–50 Gy in 4 or 5 days is given. The role of brachytherapy in adult NRSTS has been evaluated in several retrospective reviews, but some randomized prospective trials are particularly noteworthy. Between 1982 and 1987, 126 patients, mostly adults, with soft tissue sarcoma were entered into the aforementioned prospective randomized trial at MSKCC (136,185). Patients underwent a grossly complete resection with a limb-sparing operation for NRSTS of the extremity or superficial trunk. Intraoperatively, after the resection was complete, patients were randomized to receive either adjuvant brachytherapy or no adjuvant therapy. Patients who received the implant had a dosage of 42–45 Gy administered with

iridium-192 over a 4- to 6-day period. The median follow-up of this trial was 76 months. The 5-year actuarial local control rate for high-grade tumors was 89% for brachytherapy-treated patients and 66% for control subjects ($p = 0.0025$). There was no local control benefit in the low-grade tumor group.

The improved local control with brachytherapy in high-grade tumors did not translate into an overall decrease in distant metastasis. Even in the high-grade tumor, freedom from distant metastases was approximately 70% at 5 years in both the brachytherapy and control arms (185,186). This trial is of interest not only because it demonstrated a benefit to adjuvant brachytherapy but also because it showed a benefit to a form of therapy that, in contrast to adjuvant external beam irradiation, generally does not irradiate the full surgical scar, does not irradiate the drain site, is shorter in duration (10–14 days of hospitalization vs. 6–7 weeks of outpatient treatment), and is slightly less costly.

The team from MSKCC elected to explore the use of brachytherapy in low-grade tumors in more detail because their initial randomized trial did not include a large number of patients with low-grade NRSTS. From 1982 to 1992, they randomized 45 patients with low-grade tumors to brachytherapy or observation. There was no benefit to brachytherapy in terms of local recurrence (about 76% local control in each arm, $p = 0.60$) or overall survival ($p = 0.38$) (187). In two studies, patients with high-grade NRSTS with a negative margin had 89% and 94% local control rates, respectively, when treated with brachytherapy, compared with 59% and 77% in those with a positive margin. In patients with high-grade tumors and positive margins treated with brachytherapy and external beam irradiation, the local control rate was 90% (179,185,187). In the view of the investigators, these two randomized trials argue in favor of adjuvant brachytherapy for resected high-grade tumors, for surgery alone as the treatment for resected low-grade tumors smaller than 5 cm, and for consideration of external beam for resected low-grade tumors larger than 5 cm because of the remaining high risk of local recurrence in these tumors (i.e., 20–25%). In the early years of the MSKCC trials, there was a substantially higher rate of wound complications in the brachytherapy-treated patients than those in control subjects (44% vs. 14%, $p = 0.0006$). The higher rate of complications has been alleviated by a policy of not loading patients with radioactivity until the fifth postoperative day (186). Burmeister et al. (180), in Australia, obtained slightly less satisfactory results with brachytherapy and external beam therapy in patients with large high-grade sarcomas with close or positive margins. When brachytherapy is used as the only form of RT, some of the local failures result from marginal misses (125,178,185,188). In the Institut Gustave-Roussy series, 14 of 16 local failures were marginal or distant from the high-dose brachytherapy region (188).

Data from approximately 100–150 children given brachytherapy for the treatment of rhabdomyosarcoma and NRSTS have been reported. The techniques have included low-dose rate applications, high-dose rate applications, and pulse applications. Although the local control rate is excellent, it is clear from the retrospective reviews that careful patient selection is essential for successful outcomes. In general, brachytherapy seems to be most appropriate for patients who have NRSTS and microscopic small-volume residual disease at an accessible site and who have responded well to chemotherapy, external beam RT, and surgery. The American Brachytherapy Society's recommendations for brachytherapy for soft tissue sarcomas offer general guidelines as to the appropriate dosage. When brachytherapy

alone is used, 45–50 Gy is administered over 4–6 days. For patients in whom low-dose rate brachytherapy is used in combination with EBRT (generally 40–50 Gy), a 15- to 25-Gy boost is given. There are few clinical data to invoke in selecting dosages for fractionated high-dose rate brachytherapy. When high-dose rate therapy is used as the sole local control in modality, a dosage of 2.5–3 Gy twice daily, to a total dosage of 30–36 Gy, may be considered (182,183). If high-dose rate brachytherapy is used as a boost to EBRT, then the linear quadratic model can be used to devise a fractionated scheme that generates the equivalent to a low-dose rate brachytherapy dosage of 15–25 Gy (182,184).

What are we to conclude, on the basis of these NRSTS studies, concerning the role of brachytherapy in pediatric patients? Brachytherapy should be considered as an option in treating children. It has the ability to deliver a highly localized dose while sparing normal tissue (Fig. 12.11). However, in children brachytherapy poses problems of inpatient management: Can the child provide for his or her own feeding, bodily care, and immediate needs while radioactive? If not, will there be an unacceptable exposure to nursing personnel or to the parents during the implant? Several solutions have been proposed. One is to use a remote

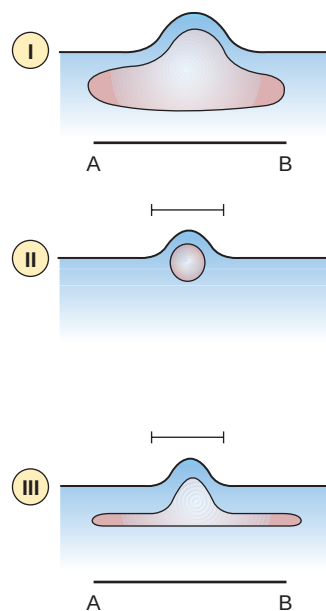


Figure 12.11 The volume selection for pediatric brachytherapy for NRSTS is highly nuanced. In many cases the patient has been treated with induction chemotherapy or EBRT. Often one cannot be sure whether a partial response of gross tumor implies a complete response of all or part of the initial occult disease volume. Consider the following hypothetical example. (i) An NRSTS is shown near an epithelial surface. The bulky tumor's left-to-right dimension is noted by line AB. Let us assume that the tumor is treated with induction cytotoxic therapy and that it regresses. (ii) The left-to-right dimension, demarcated in relation to line AB, has shrunk. If the brachytherapy volume is denoted by the bracketed area, then the irradiated volume will be adequate. (iii) On the other hand, assume that the tumor regressed significantly but that the total left-to-right dimension did not change. If the brachytherapy volume is addressed only to the readily palpable or visible tumor, as shown by the bracketed area, then a large portion of the tumor will be missed.

afterloading brachytherapy machine. If a high-dose rate remote afterloader is used, the duration of the radiation exposure is short and personnel exposure is minimized. The drawback is that the dose rate is so high that some of the normal tissue-sparing benefits of brachytherapy may be lost. To address this latter concern, some physicians pulse or fractionate the brachytherapy (i.e., use multiple exposures). As an alternative, one can use a remote afterloader with conventional activity sources. In this way, the duration of the implant is no different than with conventional afterloading. However, the sources can be withdrawn whenever nursing personnel or a parent enters the room for a planned feeding, wound care, bathing the child, and so on. A third way to deal with the particular problems of brachytherapy in a child is to use iodine-125 instead of iridium-192. The treatment energy for iodine-125 is 28 keV, compared with 380 keV for iridium-192. The lower energy of iodine-125 reduces exposure to clinical staff and family, allows more efficacious shielding with lead drapes, and reduces exposure to normal tissue at a distance from the implant. The iodine-125 may be embedded in suture material or absorbable mesh (186).

Intraoperative radiation therapy (IORT) has been described for the treatment of NRSTS (189). There are two general forms: intraoperative electron beam therapy (IO-ERT) and intraoperative high-dose rate brachytherapy (IO-HDRBT). There are three techniques for administering IO-ERT. Historically, patients underwent surgery in the operating room and then were transported, using specialized sterile techniques, from the operating room to the radiation oncology department. The linear accelerator suite was draped and prepared as a temporary operating room.

The accelerator was “docked” to a cone used to demarcate the area that the physicians wanted to irradiate. A single large fraction of electrons was administered. Normal tissue was spared by retraction and shielding. A second technique involved placing a linear accelerator in the operating room as a dedicated IO-ERT device. Of course, this necessitated reinforcing the weight-bearing capacity of the floor of the operating room, particularly if it was located in an upper floor of the hospital. The accelerator was only used for its electron-generating capabilities, so the purchase of a conventional linear accelerator with photon and electron capabilities wasted the photon capabilities of the machine. This problem was addressed by the third technique for IO-ERT: the development of an electron-only dedicated linear accelerator for placement in the operating room. Such devices are now available and can be moved from operating room to operating room. Because they generate only electrons, shielding needs for the walls, floor, and ceiling of the operating room are minimal.

Some authorities view IO-HDRBT as an alternative to IO-ERT or an adjunct to it. Intraoperative electrons often cannot treat inaccessible or highly contoured sites such as the base of the skull, the pelvic side wall, the deep pelvic area, or angled areas in the abdomen or thorax. The IO-HDRBT device uses flexible applicators and catheters to treat almost any surface. Retraction and shielding are used to spare critical normal structures. A single high-activity iridium-192 source is used, and one can customize the dose distribution. However, one is constrained by the penetration attendant to iridium-192. There is very limited clinical experience with the use of IORT to treat childhood NRSTS. In small series of highly selected patients, excellent local control rates have been achieved. The generally recommended dosage, if 40–50 Gy of EBRT is used, is an IORT boost of 10–15 Gy (181–184).

Hyperthermia

Hyperthermia has been demonstrated to be an effective radiosensitizer in a variety of clinical situations. Cells that are hypoxic, in S phase, or low pH are particularly sensitive to heating, the converse of conventional radiation. It is not surprising that hyperthermia plus radiation has been evaluated for the preoperative treatment of NRSTS and the primary treatment of inoperable tumors. Uno et al. (190) from Tokyo treated eight patients with NRSTS with external beam irradiation, doxorubicin infusion, and radiofrequency hyperthermia. Five of the eight patients had a gross recurrent tumor after surgical excisions; there were two complete responses and three partial responses. Five of the eight had no local tumor progression until death or last follow-up.

A trial of preoperative RT plus hyperthermia for NRSTS in adults at Duke University Medical Center was opened in 1984. Forty-four patients with deep nonmetastatic high-grade NRSTS received 50 Gy of RT and microwave hyperthermia. Negative surgical margins were obtained in 40 patients. The local control rate was 98%, the 3-year overall survival 72%, and 3-year disease-free survival 58%. Patients with tumor median PO₂ less than 10 mm Hg had an 18-month actuarial disease-free survival of 35%, compared with 70% for patients with a median tumor PO₂ of more than 10 mm Hg ($p = 0.01$) (191–193).

RT with hyperthermia and surgery seems capable of achieving high local control rates. To date it has not shown an ability to reduce distant metastases. The modality is largely untested in children.

Neutrons

Radiobiologists and clinical radiotherapists have been intrigued by the therapeutic uses of neutrons (194). High-linear energy transfer neutrons, by virtue of a low oxygen enhancement ratio and lack of cell cycle cytotoxicity preference, are toxic and have been used to treat bulky tumors of various histologies and sites. Data are available from the United States, Europe, and Japan concerning the use of neutrons to treat bulky sarcomas of adults and children. Although definitions of local tumor control vary between reports, the local control rate for neutron treatment of inoperable or residual soft tissue sarcomas is about 50% (195). In a retrospective comparison, Laramore et al. (196) found a higher local control rate of bulky sarcomas with neutrons than with photons and electrons (53% vs. 38%). Between November 1980 and June 1981, 14 patients, presumably adults, were entered in a prospective trial comparing postoperative photons and fast neutrons (15.6 Gy) for NRSTS. Two of the nine patients treated with photons (63 Gy) relapsed locally, as did two of the five patients treated with neutrons. The trial was halted because of unacceptable late tissue damage in the neutron-treated patients. Schwarz has summarized the prior European experience with neutron therapy at 11 centers to treat 1171 sarcoma patients (197). For patients with resectable tumors, no advantage to neutron therapy was evident. For unresectable sarcomas or following a debulking surgery, neutron therapy resulted in a local control rate of 47%. Complications at various centers ranged from 7% to 29%, roughly correlating with treatment volume effects and perhaps with the experience of the particular center. There has been little published experience on neutron therapy for soft tissue sarcomas since the mid-1990s; however, with the theoretical advantages of proton RT and its evolving clinical experience related to the Bragg peak depth dose characteristic, there is a growing investigation of heavy charged particle radiations that have the

combined elements of high LET, Bragg peak, and elimination of an exit beam beyond the targeted tumor.

RESULTS

When NRSTS in children is localized and amenable to definitive surgical excision or limited excision plus RT, the survival probability is 60–90%. The 5-year event-free survivals in the retrospective reviews from St. Jude Children's Research Hospital are group I, 83%; group II, 65%; group IV, ~9%; groups I and II and less than 5 cm, 92%; groups I and II and more than 5 cm, 55% (6,38). In the Mayo Clinic series the 10-year event-free survival was 76%. A worse prognosis is associated with high stage, high grade, and tumor size greater than 5 cm (46). The 5-year disease-free survival for children with NRSTS of the head and neck in the M. D. Anderson Hospital series was 75% (34). For patients with stages I–III NRSTS treated on SIOP trial MMT84, the 5-year survival rate was 73%; it was 80% for trial MMT89 (146,147). A multivariate analysis of predictive factors for local tumor recurrence in the Royal Marsden series of NRSTS (adults and children) showed significant worsening of the risk for local recurrence with retroperitoneal versus lower limb tumors, high versus low grade, and inadequate surgical margins. Metastases were predicted by tumor size more than 5 cm, high grade, local recurrence, or the presence of involved lymph nodes (104). In POG Study 8653/8654 the 5-year overall survival for IRS groups I–II NRSTS was 82% and event-free survival was 71%; for IRS groups III–IV disease the overall survival was 26% and event-free survival was 19% (12). A retrospective review from the Rambam Medical Center, which includes desmoid tumors in the series, showed 5-year overall survival of 72% for IRS group, 75% for group II, 90% for group III, and 40% for group IV (45). A retrospective review of synovial sarcoma treatment in children and adolescents treated with surgery, chemotherapy, and RT found that progression-free survival was associated with IRS group (I, 79%; II, 82%; III, 38%; IV, 0%), maximum tumor diameter (less than 5 cm, 82%; more than 5 cm, 56%), and histology (monophasic, 86%; biphasic, 54%) (57). A small series of childhood angiosarcomas had a characteristically poor event-free (29%) and overall (22%) survival (63). For fibrosarcomas, because of the difference in behavior between the congenital or infantile and adult types, survival is a function of age (younger than 2 years, 79%; older than 2 years, 51%) (64,198).

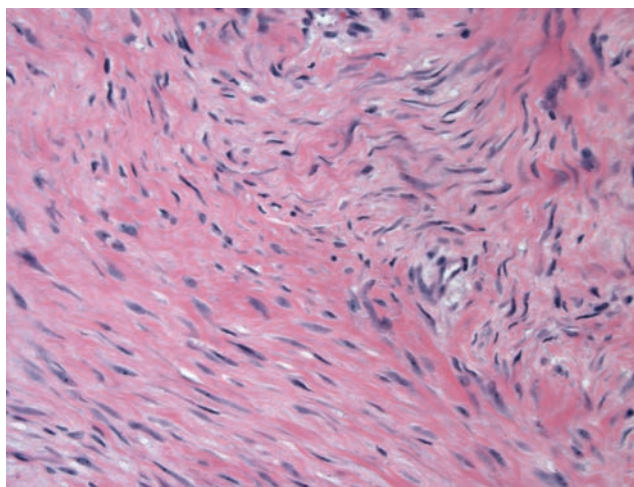
Locally advanced (group III) NRSTSs continue to be challenging problems. Preoperative chemotherapy and RT may convert a subset of these patients to having resectable tumors, which improves local control and has some prospects for cure. The small series from St. Jude Children's Research Hospital showed a 33% 5-year disease-free survival with this strategy (88). More encouragingly, within the POG 9553 protocol of ifosfamide and doxorubicin followed by EBRT to 54 or 64 Gy, depending on age, 25 patients with group III tumors had a 60% 3-year disease-free survival (13). Fifteen of these patients had synovial cell sarcoma, thought by some investigators to be more sensitive to chemotherapy.

Unresectable or metastatic disease carries a dismal prognosis. Unresectable NRSTSs are rarely cured by RT with chemotherapy, and the local control rate is also poor (128). The 5-year survival rate for children with stage IV NRSTS treated on SIOP trials MMT84 and MMT89 was 15% (146,147). In a St. Jude Children's Research Hospital review of metastatic NRSTS, the 2-year progression-free survival was 15% (6,89) (4,81).

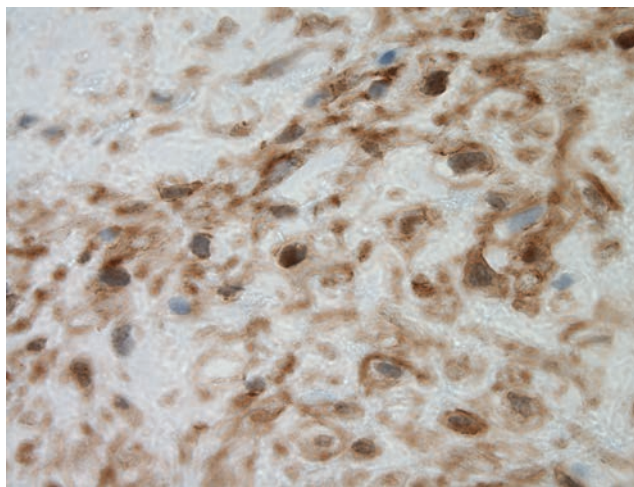
DESMOID TUMORS

There are a variety of childhood mesenchymal tumors of fibroblastic and myofibroblastic derivation that are generally regarded as benign in the sense that these tumors have no potential for metastasis. The group includes infantile myofibromatosis, digital fibromatosis, fibromatosis colli, and desmoid tumors (199). The term desmoid derives from the Attic Greek word δέσμη or *desmē* meaning “package, bundle,” and in medicine has come to refer to ligamentous or tendinous (3). In addition to the term *desmoid tumor* (which dates back to an 1847 surgical treatise), these lesions are called extra-abdominal desmoid, well-differentiated nonmetastasizing fibrosarcoma, aggressive fibromatosis, and grade 1 fibrosarcoma (desmoid) (72,200). The usual presenting complaint is a deep-seated, firm mass arising in muscles or soft tissues (72,199–201). These lesions tend to extend along fascial planes. Histologically, spindle cells with an abundant collagenous background form interlacing bundles and infiltrate surrounding tissue. Mitoses are rare (Fig. 12.12) (50,201–203).

Occurring with an estimated incidence of two to four cases per million persons per year, desmoid tumors have relative peaks in incidence between 6 and 15 years of age and between puberty and 40 years of age in women. Risk factors include high estrogen



A



B

Figure 12.12 Desmoid tumor in a child. Note both H&E (A) and immunostaining (B) for beta-catenin, in which nuclear staining is characteristic for this disease.

states (like pregnancy) and prior surgical trauma (204). A small fraction of desmoid tumors are associated with the Gardner syndrome. As such there is an associated, inherited mutation in the *adenomatous polyposis coli* (APC) tumor suppressor gene (204).

Desmoid tumors almost never metastasize. The goal of treatment is to obtain local control. Desmoid tumors can occur in a wide variety of locations. For this reason, the degree of resectability is quite variable. Tumors in an accessible site, not adjacent to vital structures, are more amenable to gross total excision than those adjacent to major nerves or vessels. In general, about two thirds of desmoids can undergo gross total excision. The problem of the extent of excision leads us to the first of several controversies in the management of pediatric desmoid tumors.

What is to be done in the child who has undergone an excision but in whom there are positive margins of resection? Several papers from the Massachusetts General Hospital (MGH) argue that such patients ought to be closely observed. In a 2001 review, Suit and Spiro (201) wrote:

Patients with primary desmoid tumors who have had grossly complete resection, but whose surgical margins are positive on pathological examination are exposed to a risk of no local regrowth of at least some 30–40%. This high local control results in margin-positive patients and the fact that salvage treatment of patients who failed locally is usually successful warrant a policy of placing such patients on observation. This policy has been followed at the MGH for approximately 25 years. To date there have been no regrets and a worthwhile number of patients have not been exposed to the risk of radiation-induced damage to normal tissues, including tumor induction. In contrast, margin-positive resection of recurrent desmoid tumors is an unequivocal indication for additional treatment.

In contrast to this argument, one can turn to a recent review by Nuytens (203) of 22 articles concerning the treatment of desmoid tumors. Table 12.10, derived from this review article, shows that the local control rate for patients with positive margins treated with surgery alone is approximately half that of patients treated with surgery and radiation therapy. Data of this sort may be used to argue for the routine use of postoperative irradiation in patients with positive margins.

If one weighs the conflicting data on this point, several issues ought to be considered:

- The long-term ill effects of radiation therapy in children with desmoid tumors can be considerable. Therefore, it would be best to minimize the use of radiation wherever possible.
- Although postoperative irradiation in patients with positive margins reduces the risk of local relapse, most patients with local relapse after surgery alone can be cured by additional surgery and radiation therapy.
- Therefore, it would be reasonable to adopt a policy of watchful waiting in accessible sites, amenable to close follow-up. A significant number of these patients might be locally controlled with surgery alone, even with positive margins. For those who relapse, one could use surgery and radiation therapy to obtain local control.

The probability of local control with surgery alone is highly debatable, and a wide range of local control rates are reported (50,72,199,200,205–207). A consensus view is that local control in patients with free margins is obtained in about 70% of cases. Several types of patients are at particularly high risk for local recurrence and progression. These include those with unresectable lesions, those who have undergone resection and gross tumor has been left behind, those who have undergone resection with large areas of clearly positive histologic tumor margins, and those who have already suffered one or more local recurrences after primary surgical therapy. With the exception of patients with microscopic positive margins, the remainder should be considered for RT (Fig. 12.13).

Several retrospective series, combining pediatric and adult patients, have demonstrated that fractionated external beam irradiation or external beam plus brachytherapy can locally control approximately 75% of desmoid tumors (Tables 12.10 and

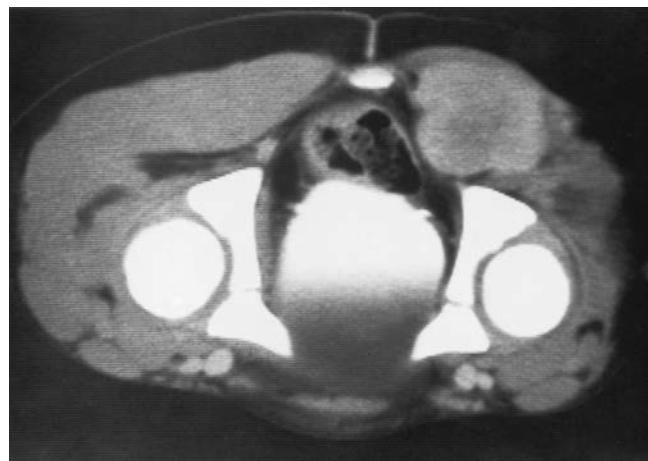


Figure 12.13 A right buttock desmoid tumor was diagnosed in a 6-year-old boy. The lesion was excised in 1979, 1980, 1982, and 1983 and recurred each time. Postoperative irradiation (49.6 Gy) was given after a re-excision of gross disease. Angled photon fields were used to minimize rectal dosage. The tumor slowly regressed, and local control has been maintained up to the time of this writing (2009). There is partial atrophy of the right buttock musculature, the bones of the right hemipelvis are smaller than those of the left hemipelvis, and the patient walks with a marked limp. Diabetes mellitus was diagnosed in 1994. In 2002, 19 years after RT, the thin, atrophied tissues gave way and a deep, infected ulcer developed in the right buttock. Plastic surgery with rotation of vascularized flaps was needed for wound closure.

Table 12.10
Local Control of Desmoid Tumors With Three Forms of Therapy

	Surgery Alone	Surgery and Radiotherapy	Radiotherapy Alone
Free margins	72%	94% ^a	78%
Positive margins	41%	75% ^a	
Unknown margins	56%		54%

^a $p < 0.005$ vs. surgery alone.

Modified from Nuytens J, Rust PF, Thomas Jr CR, et al. Surgery versus radiotherapy for patients with aggressive fibromatosis or desmoid tumors: a comparative review of 22 articles. *Cancer* 2000;88:1517–1523.

Table 12.11

Local Control Rates in Combined Pediatric and Adult Series of Radiotherapy with or without Surgery for the Management of Desmoid Tumors

Institution	Year of the most recent update of the series	Number of patients	Dosage (Gy)	Disease status	Local control
Harvard Joint Center (202)	1981	9	30–68.6	8 gross disease	87%
University of California San Francisco (44)	1983	19	40.8–61.2	1 postoperative	100%
Netherlands Cancer Institute (211)	1986	21	60	13 gross disease	69%
				6 microscopic	67%
				11 status after subtotal resection	91%
				8 status after gross total resection	87%
Westminster Hospital (126)	1988	38	27–63	2 gross disease	100%
Institut Curie (212)	1988	16	45–65	29 postoperative	76%
				9 gross disease	67%
				3 postoperative for microscopic disease	100%
				4 postoperative for macroscopic disease	75%
				9 radical radiotherapy for extensive disease	67%
Memorial Sloan–Kettering (213)	1991	38	¹⁹² Ir brachytherapy (20–60.55 Gy) and often supplemental external beam radiotherapy		
Duke (200)	1993	16	49.6–56.2	15 gross disease	93%
				1 postoperative	
Groningen University Hospital (214)	1995	17	50–60	14 resection with post-operative treatment	93%
				2 gross disease	100%
				1 re-excision with brachytherapy	100%
Memorial Sloan–Kettering (215), pediatric patients only	1995	11	30–50	2 of 11 were treated preoperatively	64%
Mayo Clinic (216)	1996	13	50.4–64.8	Operation and radiation therapy	100%
				2 wide resection	75%
				4 marginal resection	75%
				4 intralesional resection	33%
				3 radiation therapy only	
Massachusetts General Hospital (199,201)	1997	58	22–70.9	15 radiation therapy alone	92%
				41 radiation therapy and surgery	79% primary tumors, 67% recurrent tumors
University of California at Los Angeles (233)	1997	11	49.6–70	11 postoperative	78%
St. Jude Cancer Research Hospital (209), pediatric cases only	2000	13	32–60	13 gross disease	15%
				(1 combined EBRT + brachytherapy)	
University of Washington (234)	2001	35	54 (median)	14 gross disease	73%
				21 postoperative	
				5 treated with intraoperative boost (extra 10 Gy)	
University of Florida (210,217,232)	2002	72	35–70	30 treated at initial diagnosis	98%
				24 treated at recurrence	75%
				(43 received hyperfractionated RT)	
University of Heidelberg (235)	2002	28	36–60	2 gross disease	73%
				26 operative	
Yonsei University, Seoul, Korea (236)	2003	24	39.6–59.4	11 gross disease	100%
				15 postoperative	87%
Princess Margaret Hosp., Toronto, CA (237)	2003	58	50	15 postoperative	87%
				58 preoperative	81%
Instituto Nazionale Tumori, Milan (238)	2003	40	45–65	40 postoperative	75%
University of Münster, Germany (239)	2005	345	36–65	204 gross disease	81.4%
				141 postoperative	79.6%
M. D. Anderson Hospital (208,240,241)	2008	115	50–75	41 gross disease	68%
			44–66	65 postoperative	79%
			50–50.4	7 preoperative	78%
St. Vincent's Hospital, Melbourne, Australia (242)	2009	34	50.4 (median)	17 gross disease	93%
				17 postoperative	84%

Table derived from a concept originally in Acker JC, Bossen EH, Halperin EC. The management of desmoid tumors. *Int J Radiat Oncol Biol. Phys.* 1993;26:851–858; updated and modified by the authors of this chapter.

12.11). Complete or partial resolution may take 2–3 years after completion of a course of treatment (200,208). For some patients, “local control” means cessation of growth rather than tumor regression. The long-term ill effects of radiation therapy for the treatment of desmoid tumors can include fibrosis in the treated area, paresthesias that are most often associated with growth of tumor into a nerve, limb edema, fracture associated with surgical stripping of the ostium or curettage, skin ulcers, cellulitis, and the induction of second malignant neoplasms (Fig. 12.13) (203,209,210).

This risk of late effects raises the question of whether one should be particularly cautious in using radiation therapy in children with desmoid tumors. A recent report by Merchant et al. (209) from St. Jude Children’s Research Hospital argued that desmoid tumors in pediatric patients are particularly locally aggressive and often occur after radiation therapy. This adverse biologic behavior, in conjunction with the associated ill effects of radiation, argues against the use of radiation therapy in desmoid tumors. The study by Merchant et al. contains data from only 13 patients collected over a 36-year period. The desmoid tumors arose from a particularly unusual set of locations, such as the paraspinal region in five cases and the nasopharynx and pterygoid fossa in two cases. A wide variety of treatments were used, including surgery and chemotherapy, in addition to radiation therapy. Enzinger and Shiraki (205) and Walther et al. (218) also reported a high risk of failure in adolescents.

On the other hand, as shown in Table 12.11, a large number of patients have been treated successfully with radiation therapy. Most series are a mixture of adults and children. However, they do not report that desmoid tumors in children are more aggressive. Therefore, it seems reasonable to use radiation therapy to treat desmoid tumors in children, albeit with the cautions about positive margins raised earlier in this section.

Desmoids can widely infiltrate. When external beam is used, treatment portals should be generous. Marginal relapses account for a very large number of the relapses after external beam radiation therapy (203,210,213,217,219). MRI studies of desmoids often show an infiltrative margin. At surgery, microscopic tumor has been found to extend beyond the volume defined by MRI (11). All available evidence from the physical examination, surgical report, CT, and MRI should be integrated to determine the tumor volume. Generous margins (about 5 cm) should then be used around this volume. Daily fractions of 1.8–2 Gy are used. There may be a higher local recurrence rate when dosages less than 50 Gy are used. In 1984, Kiel and Suit (199) suggested that dosages greater than 60 Gy may be associated with a greater incidence of local control and have treated some patients with 70 Gy, often using photons and protons. Schulz-Ertner et al. (219) found no benefit of administering more than 50 Gy rather than less than 50 Gy on univariate analysis. Zlotecki et al. (210) found no benefit of hyperfractionated irradiation over standard fractionation. Almost all patients received 50–56 Gy. However, Ballo et al. (220) reported a significant difference in local control between dosages less than 50 Gy and dosages more than 50 Gy. They also found greater irradiation-associated morbidity in patients who received dosages less than 56 Gy. Neutron boosts have also been used (208). Evidence indicates that a total dosage of 50–55 Gy is appropriate and that higher dosages may increase the risk of complications without commensurate gain in local tumor control (200,207,208). Brachytherapy has been reported as a treatment for desmoids, either alone or with external beam therapy, by one institution (213). Because of concerns about the assessment of

tumor margins and their coverage, we believe that the role of brachytherapy is limited in children with desmoids.

In young children with desmoids, radiation’s effects on growing bone, the risk for subsequent soft tissue fibrosis, and the potential for secondary malignancy may prompt consideration of alternative therapies. A large range of drugs are available for managing desmoid tumor. There have been some efforts to use cytotoxic chemotherapy, mostly employed to treat recurrent tumor after surgery and radiation. For instance, a series of six children with fibromatosis were treated with VAC (vincristine, actinomycin D, and cyclophosphamide) with five having long-term control, although three subjects also received high-dose RT (221). The POG recently published a prospective phase II trial of vinblastine and methotrexate showing a response rate of 31% (222). Of a total of 27 patients, 16 had recurrent desmoid tumor and 11 had untreated disease not amenable to either surgery or irradiation. There have been other anecdotal reports of the use of gemcitabine, liposome-encapsulated doxorubicin, and temozolomide.

Other medical treatments are evolving. Several reports on the pathophysiology of desmoid tumors show expression of platelet-derived growth factor receptor (223,224), estrogen receptor (225,226), somatostatin receptors (227), and cyclooxygenase-2 (228). In turn, this has provided a rationale for the reported use of various “targeted therapies” either alone or in combinations. This has included imatinib mesylate (223,224), tamoxifen or other estrogen antagonists (225,226,229), octreotide radiolabeled with Y-90 (227), and nonsteroidal anti-inflammatory drugs (229–231). An ongoing COG study is formally evaluating high-dose tamoxifen and sulindac in pediatric patients with recurrent or untreated fibromatosis where surgery or RT is not feasible. Finally, there have been anecdotal reports of responses to other agents including colchicine and interferons.

SELECTED REFERENCES

The full list of References for this chapter can be found online at the book’s website. Listed here are References particularly recommended for further reading.

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Wilms Tumor

John A. Kalapurakal and Edward C. Halperin

HISTORY

The first description of a Wilms tumor was from Thomas F. Rance (1) in his 1814 report “Case of Fungus Haematodes in Kidnies.” In 1828, Dr Ebenezer Gairdner (2), Fellow of the Royal College of Physicians, Edinburgh, published the second case. The patient was a 3-year-old girl named Agnes B. Agnes B. died of a left renal tumor that weighed 5 pounds, 3 ounces. In 1879, renowned physician William Osler (3) described two cases of “myosarcoma of the kidney,” one of

which had tumor extension into the right heart and pulmonary artery. Max Wilms (1867–1918), who was trained in pathology, internal medicine, and surgery, thoroughly reviewed the pertinent literature and added seven new patients in his 1899 monograph *Die Mischgeschwulste*. In addition to renal tumors, Wilms described the histologically “mixed tumors” of the ovary, testicle, head and neck, bladder, and other organs (4). It was because of Wilms exceptional monograph that his name became connected with this childhood tumor (Fig. 13.1) (5).

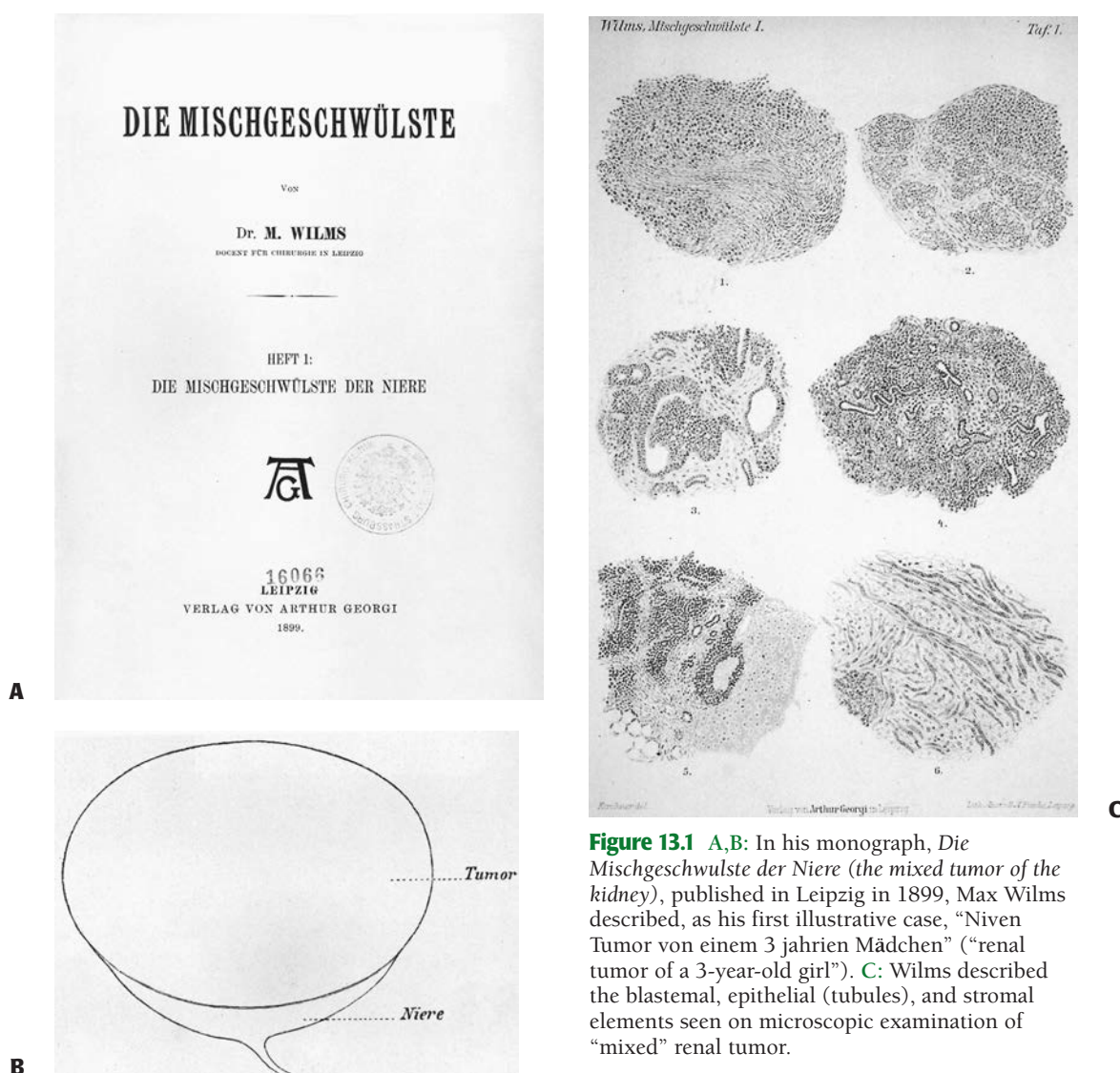


Figure 13.1 A,B: In his monograph, *Die Mischgeschwulste der Niere* (the mixed tumor of the kidney), published in Leipzig in 1899, Max Wilms described, as his first illustrative case, “Niven Tumor von einem 3 jährigen Mädchen” (“renal tumor of a 3-year-old girl”). C: Wilms described the blastemal, epithelial (tubules), and stromal elements seen on microscopic examination of “mixed” renal tumor.

By the mid-20th century, radiation oncologists had developed a large body of clinical experience with Wilms tumor and began formulating opinions about the role of radiotherapy in the management of the tumor. Ralston Paterson (6), distinguished radiation oncologist of the Christie Hospital and Holt Radium Institute of Manchester, England, wrote in his 1948 textbook:

We feel that the most promising policy's to start treatment by radiotherapy and not by surgery. X-ray therapy is used and consists of abdominal x-ray baths to cover the entire tumor and any possible intra-abdominal extension. An interval of 6 weeks to 3 months is then allowed in which the tumor mass entirely disappears. ... Two opposing fields, anterior and posterior ... cover the whole abdomen including the liver. ... The essential point in the treatment of Wilms tumor is to remember that even enormous tumors can be made operable and that radiation followed by nephrectomy can undoubtedly obtain cure in some cases.

Dean and Guttman (7) expressed the predominant viewpoint of US radiation oncologists when they wrote in their 1950 textbook:

The successful treatment of a Wilms tumor depends upon the complete removal or complete devitalization of the primary growth before metastasis occurs. No type of treatment given singly or combined with other forms of treatment has proved successful after metastasis has become established. Ladd, working at the Children's Hospital of Boston, has obtained by far the best end results by operating on these infants as soon as possible. We also recommend prompt removal ... [When preoperative therapy is necessary] ... to shrink a Wilms tumor and thereby facilitate its operable removal, external roentgen therapy is the treatment of choice. Usually, however, after five or six exposures, the tumors become significantly smaller and sometimes at the end of 2 weeks it is no longer palpable. ... Following radiation infarction seems to be more widespread.

Dean and Guttman's views were reinforced by Jacox and Cahill's (8) review of the management of Wilms tumor. They wrote:

At present we believe that nephrectomy should be performed as soon as the diagnosis of Wilms tumor is made, irrespective of the size of the mass. In general, preoperative irradiation is not favored, because we believe that waiting needlessly jeopardizes the patient's chances of survival. Ladd and White and their confreres at the Boston Children's Hospital have made a serious study of the removal of these tumors by the transperitoneal route, with a minimum of handling either for diagnosis or on the operating table, with ligation of the renal vessels and pedicle before displacement of the tumor. The result has been a much higher proportion free from recurrence that has formerly been reported.

What we can see, in this brief historical review of the origins of radiotherapy for Wilms tumor, is the divide between US radiation oncologists and their European colleagues. The European literature favored preoperative treatment, and the US literature favored postoperative radiation therapy. We also see the acknowledgment that wide treatment volumes to cover the entire tumor bed are necessary. We will address these themes in more detail later in this chapter.

EPIDEMIOLOGY

Wilms tumor (nephroblastoma) is an embryonic kidney tumor. It is the most common abdominal tumor in children and represents 6% of childhood cancer. The incidence rate in white children younger than 15 years is 8.1 new cases per million population (9). There are approximately 470–500 new cases in the United States per year (10,11). Wilms tumor is bilateral at presentation in 4–8% of cases (12–14).

The median age at diagnosis is 41.5 months for boys with unilateral tumors and 46.9 months for girls with unilateral tumors. For bilateral tumors, the median age at presentation is 29.5 months for boys and 32.6 months for girls (11). More than 75% of patients present before 5 years of age. The male-to-female ratio is 0.92 for unilateral tumors and 0.6 for bilateral tumors (11). The incidence rate is approximately three times higher for blacks in the United States and Africa than for East Asians. Rates for the white populations in Europe and North America are intermediate between those of blacks and East Asians. Children tend to present with more advanced disease in less developed nations (11–14).

MOLECULAR BIOLOGY

In Chapter 5, we discussed the Knudson “two-hit” hypothesis of the origins of retinoblastoma. After vetting his hypothesis for retinoblastoma, Knudson proposed a similar model for Wilms tumor in 1972 (15,16). Like retinoblastoma, Wilms tumor may be unilateral or bilateral. The 4–8% occurrence of bilateral disease, appearing at an earlier age than unilateral disease and associated with a greater frequency of other hereditary anomalies, supports the concept of a specific predisposing constitutional chromosomal deletion. It should be noted that fewer familial and bilateral cases of Wilms tumor than retinoblastoma were available for analysis because of the lower incidence of familial Wilms tumor and the poor disease survival at that time (15–17).

Wilms tumor is associated with congenital anomalies in 10–13% of cases (16–19). Aniridia is present in 1% of children with Wilms tumor; hemihypertrophy is noted in 2–3% (19–21). Other genitourinary malformations are identified in 5% of cases, primarily cryptorchidism, hypospadias, double collecting system, or fused kidney (21,22). It seemed reasonable to look for candidate Wilms tumor genes in association with these congenital anomalies.

The next major clue to the molecular genetics of Wilms tumor was found from the syndrome of Wilms tumor with aniridia, genitourinary malformations, and mental retardation (WAGR syndrome). Karyotypic analysis of children with WAGR syndrome showed a deletion on the short arm of chromosome 11, band 13 (11p13). This deletion encompasses the aniridia gene *PAX6* and the Wilms tumor suppressor gene *WT1*. *WT1* is a developmentally regulated transcription factor of the zinc finger family. However, analysis of sporadic Wilms tumors shows evidence of *WT1* mutation in only 5–10% of cases. Therefore, although *WT1* appears to be a tumor suppressor gene, it accounts for a minority of Wilms tumors (19–24).

Wilms tumor also occurs with greater frequency in the Beckwith–Wiedemann syndrome (BWS) (25,26). This familial condition variably includes macrosomia or hemihypertrophy, macroglossia, omphalocele, abdominal organomegaly, and ear pits or creases. The genetic locus of this syndrome is also on

the short arm of chromosome 11 (11p15). The putative second Wilms tumor suppressor gene, located at this site, is called *WT2*. *WT2*(1P15) has effects on *IGF2*, the H19 tumor suppressor gene, and the P57 cell cycle regulator (25–28).

In addition to the tumor suppressor genes associated with Wilms tumor, there is evidence of genetic loci that may be related to more malignant or aggressive Wilms tumors. In a study of patients from National Wilms Tumor Studies (NWTs) 3 and 4, loss of chromosomal material (called loss of heterozygosity [LOH]) on the long arm of chromosome 16 (16q) and short arm of chromosome 1p was associated with inferior outcomes (27,28). In NWTs-5, 2021 children were prospectively evaluated for the poor prognostic significance of tumor-specific LOH for chromosomes 1p or 16q. In clear cell sarcoma of the kidney (CCSK) and rhabdoid tumor (RTK), LOH for 1p and 16q were rarely observed. The results for favorable histology (FH) Wilms tumor are shown in Table 13.1A and B. The incidence of LOH at 1p and 16q was 11.3% and 17.4%, respectively. LOH at either 1p or 16q was only associated with higher risk of relapse for low-stage (stage I/II) patients in comparison to stage III/IV. It was postulated that two-drug chemotherapy was insufficient to overcome the effect of loss of the putative tumor suppressor genes located within these chromosomal regions. Conversely, the more intensive treatment with three drugs did overcome the effect of this loss in stage III/IV patients. The relative risk of relapse and death in low- and high-stage patients was significantly elevated in those patients with LOH at both loci (29). The Children's Oncology Group (COG) is presently using LOH status at 1p and 16q in addition to tumor stage and histology in stratifying patients according to risk of relapse. Children with low- and high-stage tumors with LOH at both 1p and 16q will have more intensified therapy compared to NWTs-5.

In 2007, a previously unknown gene on the X chromosome *WTX* was found to be inactivated in approximately one third of tumors. Tumors with mutations in *WTX* lack *WT1* mutations and both genes share a restricted temporal and spatial expression pattern in normal renal precursors. The data suggest that *WTX* is a Wilms tumor suppressor gene with an important role in normal kidney development. *WTX* is frequently altered in sporadic tumors by a single somatic event that affects both sexes equally. The one-hit inactivation of a

tumor suppressor gene is a departure from the biallelic Knudson model (30). Other known abnormalities in Wilms tumor include activating mutations in the β -catenin gene (*CTNNB1*) on chromosome 3p22, which often coincide with *WT1* mutations (31).

Another interesting study showed constitutional 11p15 abnormalities in genomic lymphocyte DNA from 3% of patients with nonsyndromic sporadic Wilms tumors, including 12% of bilateral cases. No such abnormalities were detected in control subjects. Such findings may be helpful in assessing the risk of contralateral Wilms tumor development and for targeted surveillance of at-risk family members (32).

In an effort to identify specific biologic markers associated with relapse in FH Wilms tumor, the COG conducted a study to determine the feasibility and potential clinical utility of classifiers of relapse based on global gene expression analysis. There were no significant genetic markers for relapse in stages I and II tumors. However, for stage III tumors the classifiers developed using 50 genes were associated with relapse with a sensitivity of 47% and specificity of 70%. This compares with a sensitivity of 8% and specificity of 96% for LOH of both 1p and 16q in stages III and IV FH Wilms tumor. Analysis of specific genes revealed apoptosis, *IGF-1* signaling, Wnt/ β -catenin pathway, 1q gain, and epigenetic modification to be mechanisms important in relapse. Two additional potential therapeutic targets identified in this study were FRAP/MTOR and CD40. All these pathways are potential targets for future therapies (33).

PATHOLOGY

The childhood kidney tumor pathology classification systems are those of the NWTs (Table 13.2) and the International Society of Pediatric Oncology (SIOP) study (Table 13.3) and COG (Table 13.4).

Mesoblastic Nephroma

Mesoblastic nephroma is the most common renal tumor encountered in the first month of life. Its median age at presentation is 3 months. It is distinguished from Wilms tumor by its usually benign behavior, a preponderance of mesenchymal derivatives, and a lack of the malignant epithelial components

Table 13.1

Analysis for the Joint Effect of LOH at 1p and 16q for (A) Stage I/II and (B) Stage III/IV Favorable Histology Patients (29)

LOH Status	No. of Patients	No. of Relapses	4-Year RFS	RR/ p-Value	No. of Deaths	4-Year Overall Survival	RR/ p-Value
(A) Stage I/II favorable histology patients							
Neither	750	60	91.2	—	14	98.4	—
1p only	60	11	80.4	2.19/0.02	4	91.2	4.03/0.02
16q only	114	19	82.5	1.91/0.01	3	98.1	1.40/0.60
Both	46	11	74.9	2.88/0.001	4	90.5	4.25/0.01
(B) Stage III/IV favorable histology patients							
Neither	500	82	83.0	—	38	91.9	—
1p only	56	6	89.0	0.69/0.37	2	97.6	0.52/0.36
16q only	100	15	85.3	0.89/0.67	7	92.0	0.88/0.76
Both	30	9	65.9	2.41/0.01	5	77.5	2.66/0.04

Table 13.2		
Classification of Pediatric Renal Tumors		
	International Society of Pediatric Oncology	National Wilms Tumor Study
I.	Low risk	
	Cystic partially differentiated Wilms tumor	Mesoblastic nephroma
	Mesoblastic nephroma	
	Wilms tumor with fibroadenomatous structures	
	Highly differentiated epithelial Wilms tumor	
II.	Intermediate risk	Favorable histology
	Nonanaplastic	Wilms tumor
	Wilms tumor with its variants (excluding low-risk types)	
III.	High risk	
	Anaplastic Wilms tumor	Anaplastic
		Focal
		Diffuse
	Clear cell sarcoma	Clear cell sarcoma
	Rhabdoid tumor	Rhabdoid tumor

Modified from Schmidt D, Beckwith JB. Histopathology of childhood renal tumor. *Hematol Oncol Clin North Am.* 1995;9:1179–1200, with permission.

seen in Wilms. The tumor consists of spindle-shaped cells in interlacing bundles adjacent to renal parenchyma where there are foci of cystic or dysplastic tubules. The treatment of choice is nephrectomy. Local recurrence is unusual. Nonetheless,

Table 13.3	
Revised International Society of Pediatric Oncology Working Classification of Renal Tumors of Childhood (2001) for Pretreated Cases	
Low-risk tumors	
Mesoblastic nephroma	
Cystic partially differentiated nephroblastoma	
Completely necrotic nephroblastoma	
Intermediate-risk tumors	
Nephroblastoma, epithelial type	
Nephroblastoma, stromal type	
Nephroblastoma, mixed type	
Nephroblastoma, regressive type	
Nephroblastoma, focal anaplasia	
High-risk tumors	
Nephroblastoma, blastemal type	
Nephroblastoma, diffuse anaplasia	
Clear cell sarcoma of the kidney	
Rhabdoid tumor of the kidney	

From Vujanic GM, Sandstedt B, Harms D, et al. Revised International Society of Paediatric Oncology (SIOP) working classification of renal tumors of childhood. *Med Pediatr Oncol.* 2002;38:79–82, with permission.

Table 13.4	
Children's Oncology Group Classification of Renal Tumors	
Nephroblastic tumors	Nephroblastoma
	Favorable histology
	Anaplasia (diffuse, focal)
	Nephrogenic rests and nephroblastomatosis
	Cystic nephroma and cystic partially differentiated nephroblastoma
	Metanephric tumors
	Metanephric adenoma
	Metanephric adenofibroma
	Metanephric stromal tumor
	Cellular, classic, mixed
Mesoblastic nephroma	
Clear cell sarcoma	
Rhabdoid tumor	
Renal epithelioid tumors of childhood	
Angiolipoma	
Ossifying renal tumor of infancy	

adequate margins of resection should be obtained, although recurrence even after operative rupture or positive margins at resection is rare. Distant metastases are also rare. The actuarial 2-year survival rate is excellent at 98% (34–37).

Nodular Renal Blastemas and Nephrogenic Rests

A spectrum of “pre–Wilms tumor” entities has been described. Nodular renal blastemas are small but visible sub-capsular nodules composed of benign embryonic rests. Nephrogenic rests may be limited to the periphery of the renal cortex (perilobar) or randomly distributed throughout the renal lobe (intralobar). Multifocal or diffuse nephrogenic rests are called nephroblastomatosis.

Wilms Tumor

Wilms tumor is a triphasic embryonal neoplasm, which includes blastemal, epithelial (tubules), and stromal elements. Each element may exhibit a variety of patterns of aggregation or lines of differentiation (Fig. 13.2A–C) (35–37). The proportion of the three components varies from tumor to tumor. If one of the components comprises more than two thirds of the tumor sample, the pattern is designated according to the predominant component. The mixed type is most common (41% of Wilms tumor), followed closely by the clinically more aggressive blastemal predominant (39%), the more indolent epithelial predominant (18%), and the stromal predominant (1%), which behaves like the mixed type (35–37).

The gross pathologic features of Wilms tumor include its general occurrence as a single unilateral tumor, although multicentric growth and bilateral disease can occur. The tumor is typically solid, lobulated, and not calcified. However, soft and cystic areas may be encountered.

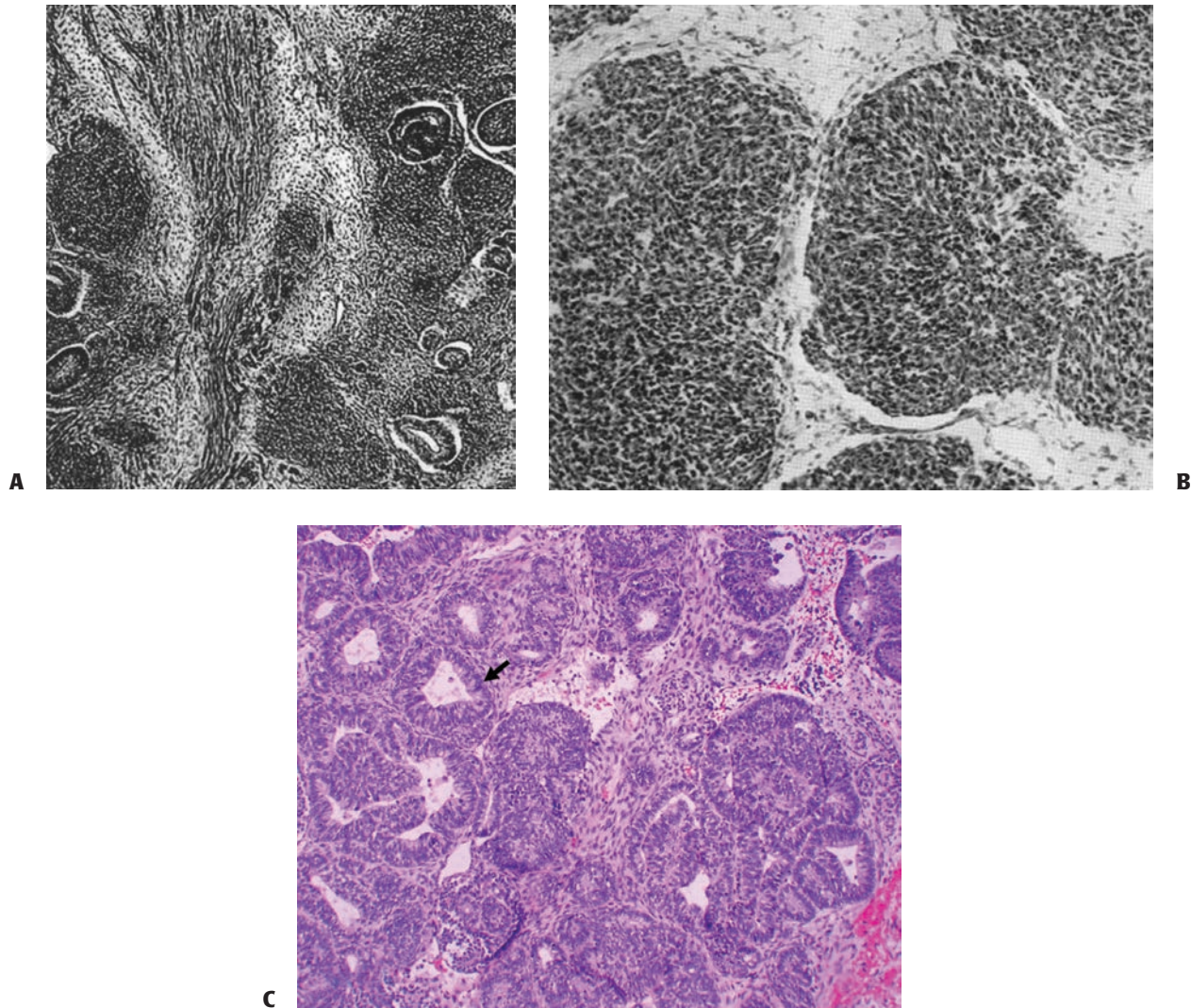


Figure 13.2 A,B: James B. Ewing, renowned for the four editions of his book *Pathology of Neoplasia* (Philadelphia, PA: WB Saunders; 1942) and his identification for the tumor now called Ewing sarcoma, also provided excellent histologic descriptions of Wilms tumor. These slides, from Ewing's book, show the topography of Wilms embryonal tumor of the kidney with (A) epithelial tubules lining in masses of spindle and polyhedral cells and (B) the small round cells of the embryonal tumor infiltrating adjacent tissue. C: Favorable histology triphasic Wilms tumor with predominantly epithelial (tubular) differentiation (arrow).

Histopathologic studies in the NWTs identified factors that correlate with prognosis. In the first NWTs, 88% of cases were categorized as FH, defined as having typical histologic features of Wilms tumor without anaplastic or sarcomatous components (38). The frequency of this pattern was upheld in the third NWTs, with 89% of cases categorized as FH on central pathology review (39).

Three entities traditionally have been grouped under the general term unfavorable histology (UH) in the NWTs: anaplastic Wilms tumor, CCSK, and RTK (36). The latter two are no longer considered to be variants of Wilms tumor but are distinct entities (35).

Anaplasia is defined as the significant enlargement of nuclei in the stromal, epithelial, or blastemal cell lines to at least three times the diameter of adjacent nuclei of the same cell type; hyperchromatism of these enlarged nuclei; and multiple mitotic figures. DNA indices greater than 1.5 are associated with anaplastic histology (Fig. 13.3A and B) (35,37,40,41). Anaplasia was noted in 4% of all NWTs-3 entries and in 5%

of patients in the SIOP studies (35,37,40,41). Anaplastic tumors are extremely rare in infants, are uncommon before 2 years of age, and make up about 10% of Wilms tumors diagnosed after 5 years of age (37). Anaplasia appears to be associated with greater resistance to chemotherapy rather than greater aggressiveness of Wilms tumor. The 4-year survival rate in NWTs-3 for patients with anaplastic histology was 82% but was lower in earlier studies (38–41).

Anaplastic Wilms tumor may be focal or diffuse. When this distinction was originally drawn, the term *diffuse anaplasia* was applied to tumors with anaplastic nuclear changes in more than 10% of 400 microscopic fields. *Focal anaplasia* was applied to the remainder of anaplastic tumors. Using this distinction, focal anaplasia was associated with a more favorable outcome than diffuse anaplasia in the first NWTs, but this difference did not obtain statistical significance and was not confirmed in the second and third NWTs trials (42).

The original distinction between focal and diffuse anaplasia did not consider distribution of tumor throughout

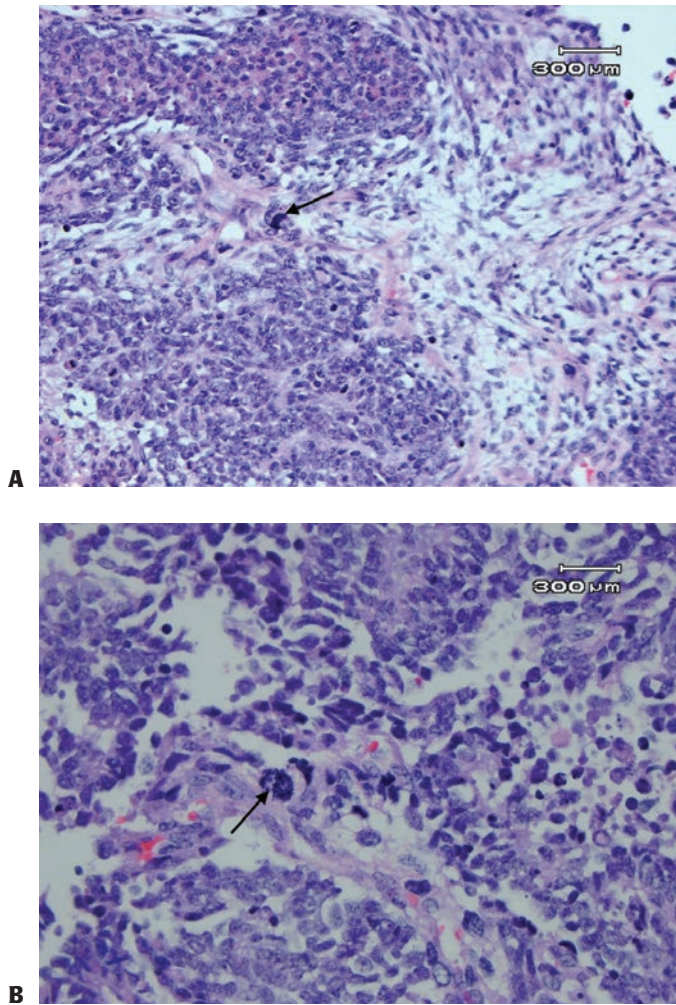


Figure 13.3 Anaplastic Wilms tumor with a large dark hyperchromatic nucleus (arrow) (A) and multipolar mitosis (arrow) (B).

the kidney, which might affect the likelihood of complete resection. In a recently revised definition, *focal anaplasia* refers to anaplasia that is sharply localized in the primary tumor, without significant nuclear or mitotic atypia in the remainder of the lesion. Diffuse anaplasia is either nonlocalized anaplasia, localized anaplasia with severe nuclear unrest elsewhere in the tumor, anaplasia outside the tumor capsule or in metastases, or anaplasia found in a random biopsy taken from the tumor.

Using the new criteria, and on review of patients in NWT-3 and NWT-4, patients with focal anaplasia had a 4-year survival rate statistically significantly higher than that of patients with diffuse anaplasia (97% vs. 50%). This difference did not exist for stage I tumors (100% survival for focal or diffuse) but did exist for stages II (90% vs. 55%), III (100% vs. 45%), and IV (100% vs. 4%) (37,42).

Patients with anaplastic histology Wilms tumor were treated in prospective single-arm studies in NWT-5. Patients with stage I anaplastic tumors were treated with vincristine and dactinomycin for 18 weeks without radiation therapy. Patients with stages II–IV diffuse anaplastic histology were treated with regimen “I” chemotherapy that consisted of vincristine, doxorubicin, cyclophosphamide, and etoposide for 24 weeks plus flank/abdominal radiation therapy. Among

2596 patients with Wilms tumor enrolled onto NWT-5, 281 (10.8%) had anaplastic histology. The 4-year event-free and overall survival rates for stage I anaplastic histology tumors were 70% and 83%, respectively. The 4-year event-free and overall survival rates in stages II, III, and IV diffuse anaplastic tumors after immediate nephrectomy were 83% and 82%, 65% and 67%, and 33% and 33%, respectively. These results form the basis for the COG study with augmentation of therapy for stages I, III, and IV anaplastic tumors (43).

Rhabdoid Tumor of the Kidney

RTK is a highly malignant tumor characterized by uniform cellular infiltrates initially interpreted as rhabdomyoblastic or sarcomatous elements. The tumor is unrelated to rhabdomyosarcoma or Wilms tumor and may be of neural crest origin (35–37). Rhabdoid cells are characterized by eosinophilic cytoplasm that contains hyaline globular inclusions. On electron microscopy, these inclusions are found to be intermediate filaments; most contain vimentin and cytokeratin. The nuclei are large, round, and vesicular, often containing a centrally placed eosinophilic nucleolus (Fig. 13.4) (37).

Most RTK of the kidney are diagnosed in the first 2 years of life. RTK have also been reported as primary extrarenal lesions; there is a known association between RTK and primary central nervous system neoplasms (37). Children with RTK have responded poorly to the therapies of the NWT-5. The 4-year relapse-free survival rate for patients treated with vincristine, actinomycin D, and adriamycin on NWT-3 was 23%, and the 4-year overall survival rate was 25% (39,44).

Clear Cell Sarcoma of the Kidney

CCSK is a primitive mesenchymal neoplasm that makes up 4% of childhood renal tumors. The cell of origin is unknown. The lesion is distinguished by cells with poorly stained cytoplasm. The cell boundaries are indistinct, and cytoplasmic vacuolation may be prominent. The classic histologic pattern has a characteristic arborizing network of thin-walled capillary blood vessels that separates groups of cells (Fig. 13.5A and B) (37,45). In NWT-3, 23% of children with CCSK developed bone metastases, compared with 0.3% of all other

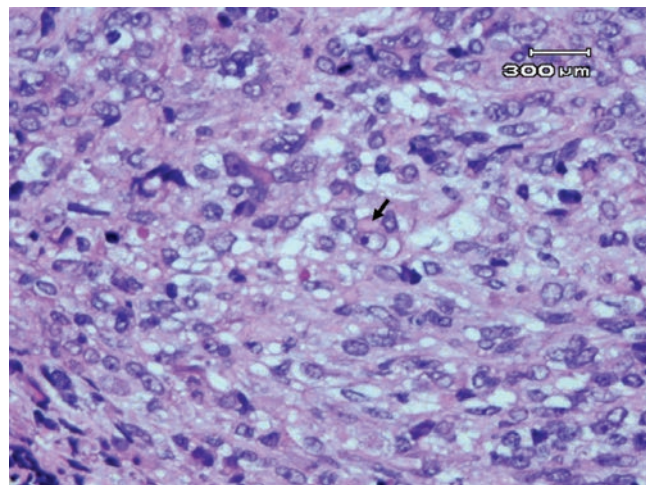


Figure 13.4 Rhabdoid tumor (RTK) with tumor cells with large eccentric vesicular nuclei, prominent nucleoli, and cytoplasmic inclusions (arrow).

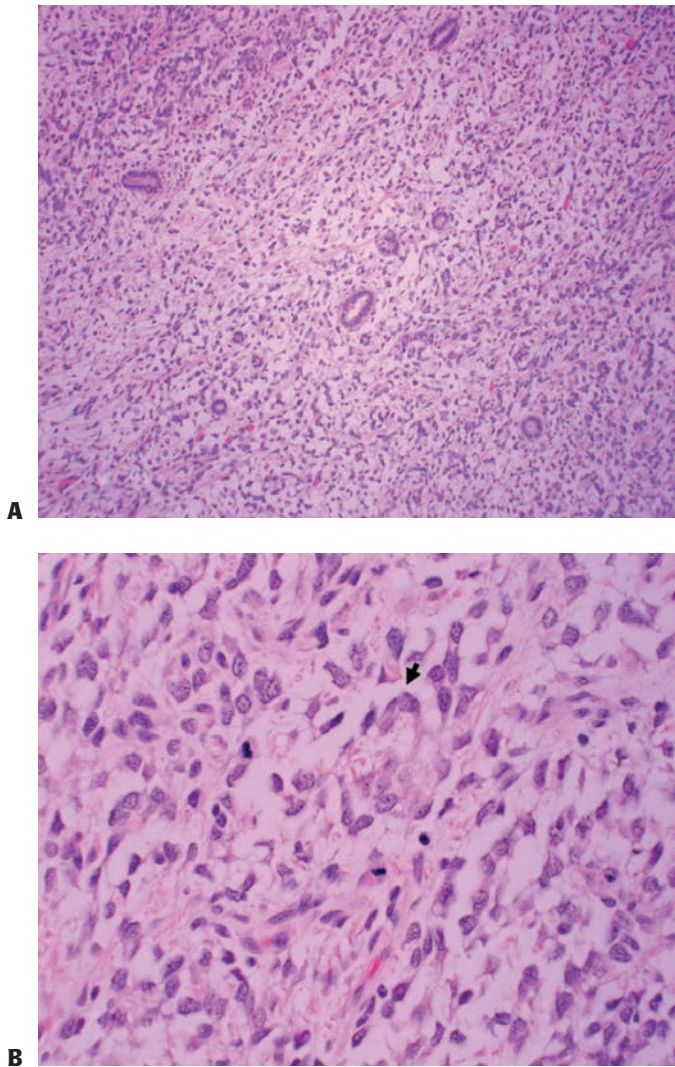


Figure 13.5 Clear cell sarcoma (CCSK) with tumor cells composed of uniform clear cytoplasm surrounding entrapped renal tubules: (A) low power, (B) high power showing prominent vacuolated cytoplasm (arrow).

children entered in the study. Response of CCSK to therapy was poor until adriamycin and local irradiation were added to the treatment program. The 4-year relapse-free survival rate for patients with stages I–IV CCSK treated with vincristine, adriamycin, and actinomycin D on NWTS-3 was 71% (39).

A total of 86 patients with CCSK were registered in NWTS-4. This study was designed to compare the efficacy and toxicity of a new schedule of administration of dactinomycin and doxorubicin. There was no significant difference between those patients initially randomized to standard and pulse-intensive (PI) chemotherapy with vincristine, dactinomycin, and doxorubicin. The 8-year relapse-free and overall survival rates were 72% and 87% for PI and 70% and 84% for standard chemotherapy, respectively. The second randomization was to short-duration (no further chemotherapy) and long-duration (additional 9 months) chemotherapy. Again, there was no significant difference in survival between the two arms. The 8-year relapse-free and overall survival rates were 61% and 86% for the short-duration chemotherapy and 88% and 88% for the long-duration chemotherapy, respectively.

Even though the relapse-free survival rates were not significantly different ($p = 0.08$) the long-duration arm resulted in a higher relapse-free survival rate. The overall survival rate in NWTS-4 (83%) was significantly higher than in NWTS-3 (67%) (46).

CLINICAL PRESENTATION AND WORKUP

As we have already noted, several clinical syndromes are risk factors for the development of Wilms tumor. These include aniridia, BWS (exomphalos, macroglossia, and gigantism), and hemihypertrophia. If somatic changes of these kinds are known to exist, then routine screening in an attempt to make the early diagnosis of Wilms tumor is appropriate (47). A physical examination and periodic ultrasound are indicated. It is interesting to note that in Germany, 10% of patients with Wilms tumor are diagnosed at infant and childhood screening examinations, conducted for known predisposing syndromes, and at routine well-baby examinations (47).

The majority of children with Wilms tumor are diagnosed in response to a medical complaint causing a visit to the doctor; the clinical presentation usually is an abdominal mass (83%), fever (23%), or hematuria (21%). Abdominal pain (37%) may be the result of local distention, spontaneous intralesional hemorrhage, or peritoneal rupture. In one major series, abdominal pain correlated with poorer 5-year survival (48). Less common presenting signs and symptoms include hypertension, varicocele, hernia, enlarged testicle, congestive heart failure, hypoglycemia, Cushing syndrome, hydrocephalus, pleural effusion, and an acute abdomen (49).

The presence and character of the abdominal pain, the previous medical history, and the family history are important aspects of the medical interview. Physical examination is of value in assessing abdominal status and identifying associated congenital anomalies.

The optimum diagnostic imaging workup for Wilms tumor is a matter of controversy. Evaluation of disease extent classically included intravenous pyelogram (IVP) and chest radiograph. Current imaging protocols largely replace the IVP with abdominal ultrasound. Ultrasound usually allows determination of the origin of a childhood abdominal mass, identifies a contralateral kidney, and demonstrates the presence or absence of tumor extension into the renal vein or inferior vena cava (50).

When an abdominal mass is identified or suspected, abdominal computed tomography (CT) is used to assess the volume of tumor involvement in one or both kidneys, renal function, retroperitoneal lymph nodes, and invasion of the collecting system or renal vein; evaluate the margin between tumor, kidney, and surrounding structures; assess hepatic metastasis (although many children thought to have invasion of the liver from a right-sided Wilms tumor are found at surgery to have hepatic compression rather than invasion); and demonstrate lesions in the opposite kidney, which may represent either bilateral Wilms tumor or nephrogenic rests (Fig. 13.6) (50). The evaluation of the contralateral kidney has become a matter of discussion in the surgical literature. Some authorities believe that preoperative CT and magnetic resonance imaging (MRI) can be used to rule in or rule out



Figure 13.6 A 5-year-old girl presented with intermittent sharp abdominal pain, nausea, vomiting, weight loss, and hematuria. Abdominal computed tomography showed a 7.9- to 12.5-cm mass at the left renal region, beginning immediately subdiaphragmatically and extending to just below the aortic bifurcation. There was a calcified rim superiorly and a heterogeneous parenchymal enhancement. Left renal vein invasion and inferior vena cava thrombosis were observed. On exploratory laparotomy, tumor was palpated in the inferior vena cava. The tumor was resected, with some tumor spillage from a weak point on Gerota fascia. Tumor thrombus was removed from the inferior vena cava. Pathology showed a favorable histology Wilms tumor, 13.5 cm in greatest diameter, invading through the renal capsule to the inked surgical margin. Rupture of the renal capsule was identified. Tumor was present at the renal vein margin of the tumor thrombosis with focal invasion of the vein wall. No lymph nodes were involved. For pathologic stage III Wilms tumor, favorable histology, the child was treated with chemotherapy and flank irradiation. There was no evidence of persistent or recurrent tumor 3 years after diagnosis.

bilateral Wilms tumor. Others believe that imaging is useful but not definitive and that a surgical exploration of the contralateral kidney remains essential during the surgical approach to the primary tumor (17,47).

Plain chest radiographs should be obtained to determine whether pulmonary metastases are present. Some centers recommend thoracic CT to detect pulmonary metastasis that might be missed on chest radiograph. CT-positive, chest radiograph-negative lung metastases do occur (50). There has been much uncertainty regarding appropriate therapy for pulmonary disease documented only by CT in the presence of normal plain chest films (51). Radionuclide bone scan is indicated in CCSK and renal RTK. Bone scan and skeletal survey are complementary in CCSK. If only one technique is used, metastases may be missed (38,52). Cranial CT is of value in RTK and, perhaps, in Wilms tumor with overt pulmonary involvement at diagnosis.

STAGING

A staging system for Wilms tumor was first published by Cassady et al. (53,54) in 1973, building on prognostic factors identified in a review from Garcia et al. (55). The Cassady system remains useful for determining whether young children with early stage disease may be appropriate for therapy with surgery alone. For tumor confined to the kidney and com-

pletely excised in children younger than 2 years of age at diagnosis and with tumors that weigh less than 550 g, the prognosis is excellent. Such patients may be treated appropriately with surgery alone and are considered to have stage I disease (54–56). The absence of an inflammatory pseudocapsule, renal sinus invasion, capsular invasion, and intrarenal vessel invasion in such patients are additional factors that mitigate against the risk of relapse when treated with nephrectomy alone (50).

The NWTS proposed initial staging criteria to prospectively address tumor-related factors. The first two NWTS studies were based on a system of surgically identified groups (38).

Beginning with the third NWTS trial in 1979, a new staging system was adopted. Specific disease-related parameters noted to be prognostically significant in analyses of NWTS-1 and NWTS-2 led to modifications of the system and the change from groups to stages. A closed or open biopsy permitted categorization as stage II (rather than group III), assuming subsequent total tumor removal. Local spill of tumor during surgery was downstaged from group III to stage II, reflecting data indicating that such cases had excellent tumor control even with limited irradiation and chemotherapy in NWTS-1 and NWTS-2 (57). Also, the NWTS-3 staging system upstages all previous group II cases with lymph node metastasis to stage III, even when all visible disease has been completely resected. The adverse impact of lymph node involvement, both on abdominal recurrence and on ultimate relapse-free survival, has been documented (13,22,38,58).

For NWTS-5, the most significant change was the distinction between stages I and II. Criteria for stage I was refined to accommodate an important subset of patients who were being managed by nephrectomy alone. Before NWTS-5, the distinction between stages I and II in the renal sinus was established by the hilar plane, which was an imaginary plane connecting the most medial aspects of the upper and lower poles of the kidney. This criterion was difficult to apply because of tumor distortion, and thus the hilar plane criterion has been replaced with renal sinus vascular or lymphatic invasion. This definition includes not only the involvement of vessels within the hilar soft tissue, but of vessels located in the radial extensions of the renal sinus into the renal parenchyma (59,60).

The COG staging guidelines for Wilms tumor are shown in Table 13.5. These guidelines are essentially similar to NWTS-5 except for the fact that children with tumor spillage are upstaged from stage II to stage III because of the higher risk for relapse with two-drug chemotherapy alone (61).

In the SIOP Wilms tumor trial 1, investigators compared preoperative radiotherapy with primary surgery. The staging system used in this trial is shown in Table 13.6. SIOP subsequently began using NWTS grouping and staging, with the proviso that the NWTS systems were not specifically designed for the preoperative therapy often used by SIOP (62–71). For this reason, outcomes between NWTS and SIOP studies should not be compared stage-for-stage. In addition, SIOP uses a “stage II, node negative” and “stage II, node positive” distinction and therefore includes some NWTS stage III tumors in the stage II infradiaphragmatic SIOP stage.

Table 13.5
Children's Oncology Group Staging of Wilms Tumor

Stage I	Tumor limited to kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection. <i>Note:</i> For a tumor to qualify for certain therapeutic protocols as Stage I, regional lymph nodes must be examined microscopically.
Stage II	The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond kidney, as is evidenced by any one of the following criteria: There is regional extension of the tumor (i.e., penetration of the renal capsule, or extensive invasion of the soft tissue of the renal sinus, as discussed below). Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor. <i>Note:</i> Rupture or spillage confined to the flank, including biopsy of the tumor, is no longer included in Stage II and is now included in Stage III.
Stage III	Residual nonhematogenous tumor present following surgery, and confined to abdomen. Any one of the following may occur: Lymph nodes within the abdomen or pelvis are involved by tumor. (Lymph node involvement in the thorax or other extra-abdominal sites is a criterion for Stage IV.) The tumor has penetrated through the peritoneal surface. Tumor implants are found on the peritoneal surface. Gross or microscopic tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination). The tumor is not completely resectable because of local infiltration into vital structures. Tumor spillage occurring either before or during surgery. The tumor was biopsied (whether tru-cut, open, or fine needle aspiration) before removal. Tumor is removed in greater than one piece (e.g., tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen).
Stage IV	Hematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdominopelvic region are present. (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present.)
Stage V	Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease.

NWTS, SIOP, AND THE MANAGEMENT OF WILMS TUMOR

The NWTS, SIOP, and the United Kingdom Children's Cancer Study Group (UKCCSG) have compiled a large body of information concerning the clinical management of Wilms tumor. The most widely quoted studies are those of NWTS and SIOP.

The NWTS and SIOP Strategies

The SIOP studies began with the presumption that treatment with radiation therapy or chemotherapy before surgery would

render a Wilms tumor less vulnerable to intraoperative rupture and surgery-related tumor seeding. Downstaging the tumor was also hoped to reduce treatment-related morbidity by reducing the total amount of treatment (62–64). In accordance with this philosophy, the initial strategy of SIOP was to evaluate the roles of radiotherapy and chemotherapy before definitive surgery based on clinical diagnosis. Subsequently, treatment was assigned according to the extent of disease found at surgery. One disadvantage is the risk of misdiagnosis and mistreatment (i.e., treating a tumor other than Wilms tumor or treating benign disease). In SIOP 9, the error rate (i.e., the proportion of patients who were found not to have Wilms tumor) was 6%. In addition, the SIOP approach runs the risk of obscuring important prognostic clues in individual patients (64). Lymph node involvement and histologic subtype may be affected by preoperative therapy. A particular drawback of preoperative therapy is that one may miss diffuse anaplasia. Because prognosis and subsequent therapy are influenced by histology and lymph node involvement, the SIOP approach may render therapy less precise by interfering with histology obtained at the time of definitive surgery. Supporting this contention was a review of data from two SIOP studies indicating that necrotic changes were more frequently seen in patients pretreated with radiotherapy than in those pretreated with chemotherapy. However, an analysis of

Table 13.6
Staging System Used in SIOP Wilms Tumor Trial 1

Stage I	The tumor is limited to the kidney and is completely excised
Stage II	The tumor extends outside the kidney but is completely excised
Stage III	Incomplete excision of the tumor but without hematogenous metastatic spread
Stage IV	Hematogenous metastases are present
Stage V	Bilateral renal tumors

posttreatment histology in these two SIOP studies and in 83 patients who underwent prenephrectomy chemotherapy in NWTs-3 showed no evidence that prenephrectomy therapy altered the detection of anaplastic histology (62–64). It appears that the SIOP presurgical therapy approach does not influence histology.

The NWTs strategy is to forgo preoperative therapy in order to obtain the maximum amount of information concerning prognostic factors and tailor therapy accordingly. Therefore, the local extent of the primary tumor, degree of anaplasia, presence of unusual histology, and presence or absence of lymph node involvement are assessed in the absence of the confounding influence of preoperative chemotherapy or radiotherapy in order to select therapy. The benefits of the NWTs approach are the generation of a large body of information about prognostic clues, the avoidance of misdiagnosis, and the customization of therapy.

The National Wilms Tumor Studies

NWTs-1 (1969–1974) asked several important treatment questions: Is postoperative radiotherapy necessary in group I disease? Is single-agent chemotherapy with either vincristine or actinomycin D equivalent to combining these drugs for group II and III disease? Is preoperative vincristine of value in group IV disease? The study is shown schematically in Figure 13.7, and the results are summarized in Table 13.7 (38). Radiotherapy dosages were age adjusted (birth to 18 months of age, 18–24 Gy; 18–30 months, 24–30 Gy; 31–40 months, 30–35 Gy; 41 months or older, 35–40 Gy). Radiotherapy appeared to be unnecessary in group I babies; combined drug therapy was superior in groups II and III; and preoperative vincristine was not helpful in group IV. Patients older than 2 years with group I tumors showed an advantage with irradiation. However, patients with group II tumors receiving actinomycin D with vincristine seemed to do as well as

Table 13.7

NWTs-1 Results

Group and Therapy	n	4-Year Relapse-Free Survival (%)	4-Year Survival (%)
Stage I. Age <2 years	38	89	94
A. Radiotherapy	38	89	94
B. No radiotherapy	41	88	90
Stage I. Age ≥2 years			
A. Radiotherapy	42	76	98
B. No radiotherapy	42	57	81
Stages II. and III.			
A. AMD	63	56*	71*
B. VCR	44	57*	71*
C. AMD and VCR	63	79	84
Stage IV.			
A. Immediate surgery	13		83* ^d
B. Preoperative VCR	13		29* ^d

* $p \leq 0.02$.

^d2-year survival.

AMD, actinomycin D; VCR, vincristine.

From Refs. 38,57,72, and 75 with permission.

those with group I disease. It was postulated that postoperative vincristine with actinomycin D could substitute for postoperative radiotherapy with actinomycin D (38,72). This study demonstrated the significance of the UH versus FH distinction, with a 2-year relapse-free survival rate of 29% for UH and 89% for FH (72,73). Large tumor size, lymph node involvement, and age older than 2 years were confirmed as poor prognostic factors. No radiation dose–response relationship

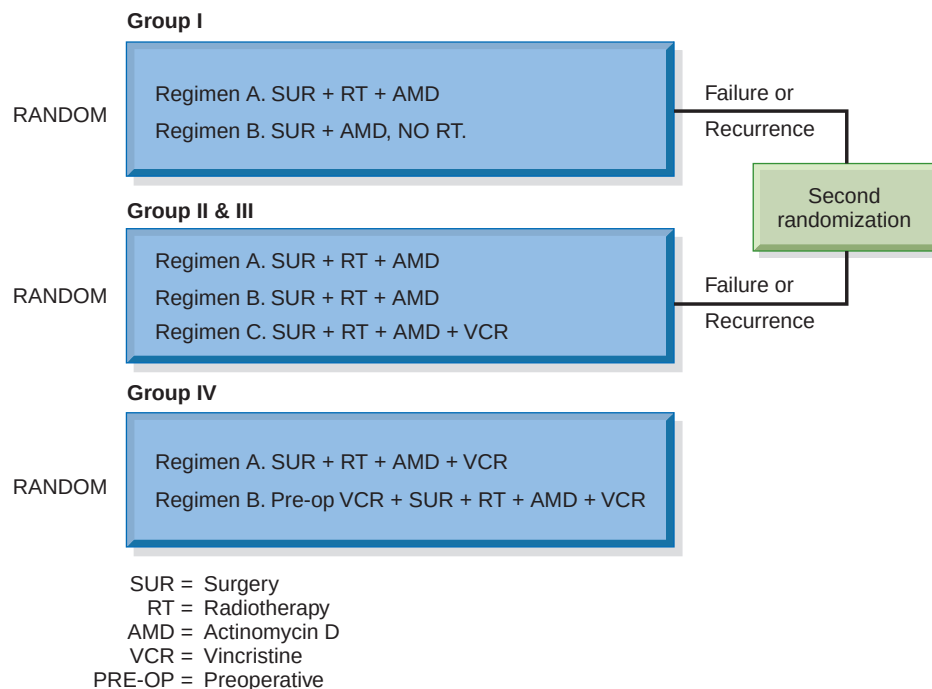


Figure 13.7 The design of NWTs-1. (From D’Angio GJ. *National Wilms’ Tumor Study*. Seattle, WA: NWTs Data and Statistical Center; 1991 [Informational Bulletin #19], with permission.)

was discerned in the 10- to 40-Gy range, delays of up to 10 days in initiating postoperative irradiation appeared acceptable, and whole-abdomen irradiation was not found to be necessary for tumor spills confined to the flank or for prior tumor biopsy (17,41,57). In these patients, limited radiotherapy fields sufficed.

NWTS-2 (1974–1979) explored three major questions: Can vincristine and actinomycin D substitute for radiotherapy in older children with group I disease? Are adjuvant vincristine and actinomycin D for protracted periods helpful in group I? Is the addition of adriamycin to actinomycin D and vincristine of value in groups II to IV? The study is shown schematically in Figure 13.8 (74). Flank irradiation was given in groups II–IV disease according to the same age-dependent scale as NWTS-1. Whole-abdomen irradiation was reserved for diffuse peritoneal seeding. Lung metastases were initially treated with 14 Gy of whole-lung irradiation (WLI), but when a 10% incidence of pneumonitis occurred, the dosage was scaled back to 12 Gy. Study results are summarized in Table 13.8. About 85% of the patients were FH and 15% UH. Two-year survival rates were 54% for UH, 90% for FH, 54% for lymph node positive, and 82% for lymph node negative. Excellent survival rates appeared to be achievable without irradiation in group I, and adriamycin added considerable benefit in groups II–III FH and some benefit in groups II–III UH and group IV. The 2-year relapse-free survival rate for all NWTS-2 patients was 88% for group I, 78% for group II, 70% for group III, and 49% for group IV (17,74–76).

NWTS-3 (1979–1985) incorporated two major changes in treatment planning: Patients were stratified by stages rather than by groups and the distinction between FH and UH was incorporated into the treatment algorithm (Fig. 13.9). Although data from NWTS-1 and NWTS-2 were analyzed by histology, histology was not used to stratify treatment (38,50,74).

Table 13.8
NWTS-2 Results

Group and Therapy	n	3-Year Relapse- Free Survival (%)	3-Year Survival (%)
Stage I			
E. 6 months, ADR, VCR	88	89	97
F. 15 months, ADR, VCR	91	84	92
Stages II and III FH			
C. VCR, AMD	121	70*	82
D. VCR, AMD, ADR	11	88	92
Stages II and III UH			
C. VCR, AMD	16	35	38
D. VCR, AMD, ADR	19	42	78
Stage IV			
C. VCR, AMD	22	43*	44
D. VCR, AMD, ADR	27	60*	60
Lymph node status			
Negative or not examined	383	82 ^a	
Positive	84	54	

* $p \leq 0.05$.

^a2-year survival.

ADR, adriamycin; VCR, vincristine; FH, favorable histology; AMD, actinomycin D; UH, unfavorable histology.

From Refs. 74 and 75 with permission.

NWTS-3 considered five major questions: Can the duration of chemotherapy be shortened for stage I FH? Can radiotherapy be eliminated for stage II FH? What is the minimum effective radiotherapy dosage for stage III FH? Is cardiotoxic

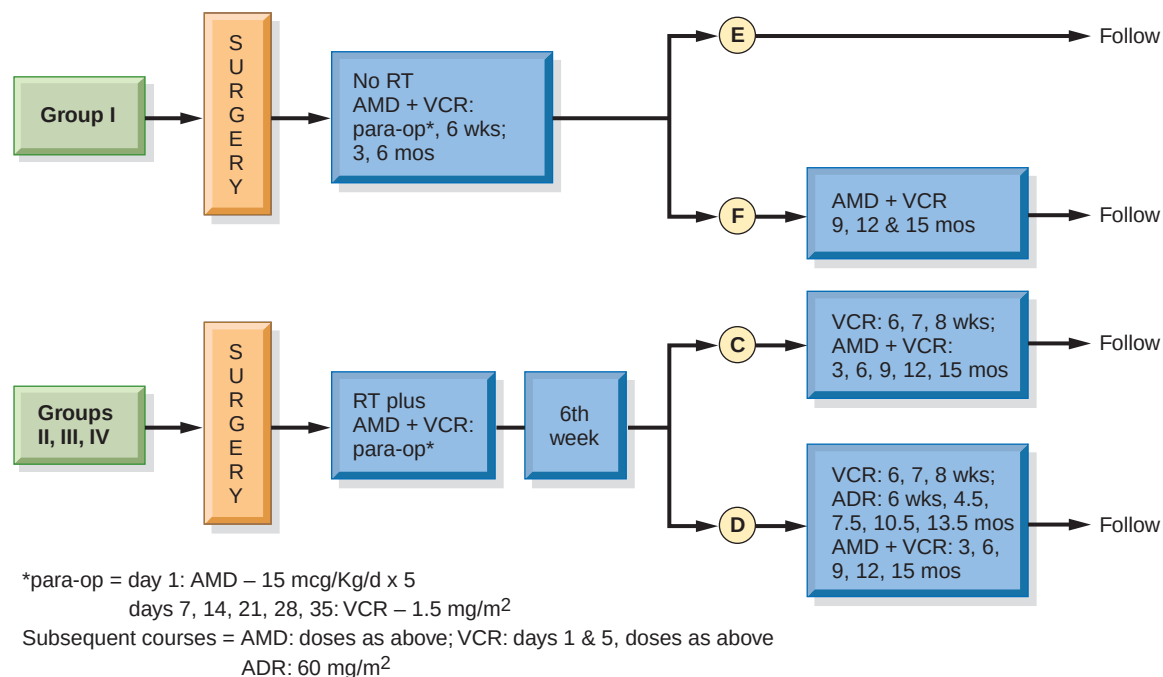
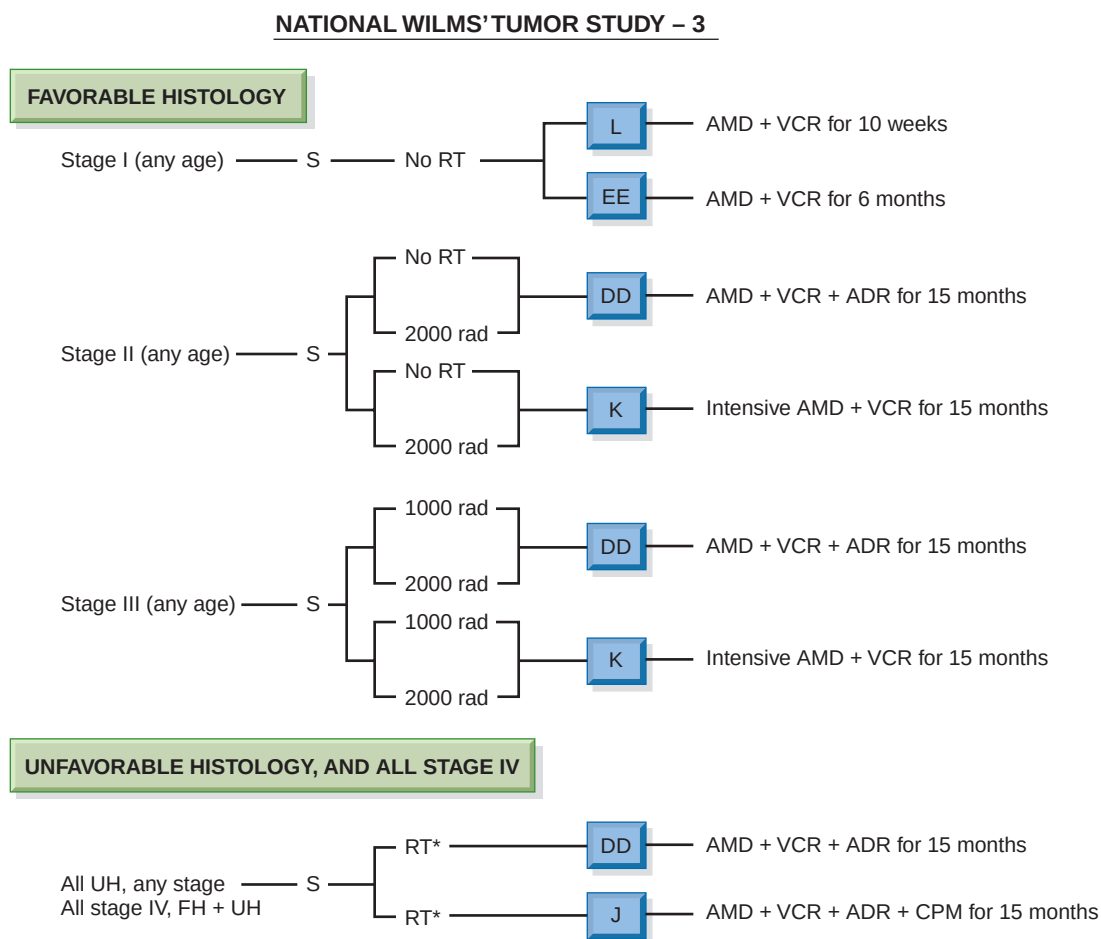


Figure 13.8 The design of NWTS-2. (From D'Angio GJ, Tefft M, Breslow N, et al. Radiation therapy of Wilms' tumor: results according to dose, field, post-operative timing and histology. *Int J Radiat Oncol Biol Phys.* 1978;4:769–780, with permission.)



*All FH Stage IV receive 2000 rad flank RT and RT to other sites as in NWT-2
All UH, all stages receive age-adjusted flank RT and to other sites as in NWT-2

Figure 13.9 The design of NWT-3. (From D'Angio GJ, Evans A, Breslow N, et al. The treatment of Wilms' tumor: results of the Second National Wilms' Tumor Study. *Cancer*. 1981;47:2302–2311, with permission.)

adriamycin clearly beneficial and therefore necessary in stages II and III FH? Will the addition of cyclophosphamide improve survival in stages I–III UH and in stage IV FH and UH?

NWT-3 results are summarized in Tables 13.9 and 13.10. Short-course therapy appeared equivalent to long-course therapy in stage I FH. Patients in this group can be treated successfully with a 10-week program of vincristine and actinomycin D without irradiation and can achieve a 4-year relapse-free survival rate of 89% and overall survival rate of 96%. Elimination of radiotherapy was acceptable in stage II FH. The 4-year relapse-free and overall survival rates for the patients not receiving irradiation were 87% and 91%, respectively. In stage III FH, 10 Gy was equivalent to 20 Gy. There was no statistically significant difference in frequency of intra-abdominal relapse between 10 and 20 Gy, although the trend favored the use of adriamycin or irradiation (intra-abdominal relapse for vincristine, actinomycin D, and 10 Gy, 7 out of 61, or 11%; vincristine, actinomycin D, and 20 Gy, 3 out of 68, or 4%; vincristine, actinomycin D, adriamycin, and 10 Gy, 3 out of 70, or 4%). In an analysis of patients with stage III, local relapse with doxorubicin occurred in 4 out of 134 patients, whereas without doxorubicin, it occurred in 11 out of 141 patients, suggesting that chemotherapy played a

role in establishing local control. The addition of adriamycin was not clearly beneficial in stage II but seemed to be of benefit in stage III FH. Cyclophosphamide did not benefit stage IV FH. The 4-year survival rate for stage IV FH treated with vincristine, actinomycin D, adriamycin, and abdominal and lung irradiation was 81%. The use of cyclophosphamide seemed to help patients with focal anaplasia. Patients with CCSK did well, whereas those with RTK continued to do poorly (17,22,39,50).

NWT-4 (1986–1994) addressed issues of minimization of therapy (and, presumably, therapy-related toxicity) and customization of therapy by stage and histology. The trial was the first study of a pediatric population to evaluate the economic impact of two different treatment approaches, one of which entailed fewer clinic visits. By the end of NWT-3 it had been shown that 62% of patients with Wilms tumor (stages I–II, FH) needed neither irradiation nor adriamycin. The study was designed to compare the relapse-free and overall survival rates of patients with stages I and II FH and stage I anaplastic tumors treated with conventional actinomycin D and vincristine and with pulsed, intensive actinomycin D and vincristine. Stages III and IV FH and stages I–IV CCSK were treated with conventional actinomycin D, vincristine, and

Table 13.9**NWTS-3 Results**

Group and Therapy	n	4-Year Relapse-Free Survival (%)	4-Year Survival (%)
Stage I FH			
L. 10 weeks ADR, VCR	306	89	96
EE. 6 months ADR, VCR	301	92	97
Stage II FH			
DD. No radiotherapy; AMD, VCR, ADR	70	88	94
DD2. 20 Gy; AMD, VCR, ADR	71	87	90
K. No radiotherapy; AMD, VCR	67	87	91
K2. 20 Gy; AMD, VCR	70	90	95
Stage III FH			
DD1. 10 Gy; AMD, VCR, ADR	68	82	91
DD2. 20 Gy; AMD, VCR, ADR	66	86	87
K1. 10 Gy; AMD, VCR	71	71	85
K2. 20 Gy; AMD, VCR	70	77	85
Stage IV FH ^a			
DD. AMD, VCR, ADR	64	72	78
J. AMD, VCR, ADR, CPM	56	78	87
Stages I–III UH ^a			
DD. AMD, VCR, ADR	69	67	68
J. AMD, VCR, ADR, CPM	61	62	68
Stage IV UH ^a			
DD. AMD, VCR, ADR	12	58	58
J. AMD, VCR, ADR, CPM	17	53	52
Anaplastic ^a			
DD. AMD, VCR, ADR	31	1:80	
II–IV	37	1:78	
II–IV	38*		
J. AMD, VCR, ADR, CPM	17	1:100	
II–IV	83	1:100	
II–IV	82*		
CCSK ^a			
DD. AMD, VCR, ADR	25	71	75
J. AMD, VCR, ADR, CPM	25	60	76
Rhabdoid ^a			
DD. AMD, VCR, ADR	13	23	25
J. AMD, VCR, ADR, CPM	18	27	26

* $p \leq 0.05$.^aRadiotherapy also given; not a randomized radiotherapy question.

FH, favorable histology; ADR, adriamycin; VCR, vincristine; AMD, actinomycin D; CPM, cyclophosphamide; UH, unfavorable histology.

From Refs. 39,44,76 with permission.

Table 13.10**NWTS-3 Relapse Rates**

Stage and Dosage	Flank Relapse (8 years) (%)	Beyond Flank (%)
0 Gy	3.2	
<15 Gy	1.6	
>15 Gy	0	
Stage II: 0 Gy	12.8	4.6
Stage II: 20 Gy	0	4
Stages III–IV		
10–20 Gy		3.5–11.8
10 Gy		0–1.8
20 Gy		0

From Refs. 39,44,76.

adriamycin, compared with pulsed, intensive actinomycin D, vincristine, and adriamycin; all patients received radiotherapy (for FH, 10.8 Gy to the abdomen; 12 Gy WLI where appropriate; for stages II–IV anaplastic tumors, a sliding scale of radiation dosage was used, as in NWTS-1). Stages II–IV anaplastic Wilms tumors were treated with appropriate irradiation followed by actinomycin D, vincristine, and adriamycin, compared with these three drugs plus cyclophosphamide. Stages II–IV FH and stages I–IV CCSK were treated with 26 or 54 weeks of chemotherapy (Fig. 13.10).

The results of NWTS-4 are shown in Table 13.11. There was no difference in the low-risk or high-risk patients for standard or PI therapy. When one breaks down the results based on histology, stage, standard or PI therapy, and, for the more advanced patients, short or long course of therapy, there are, once again, no significant differences between the various

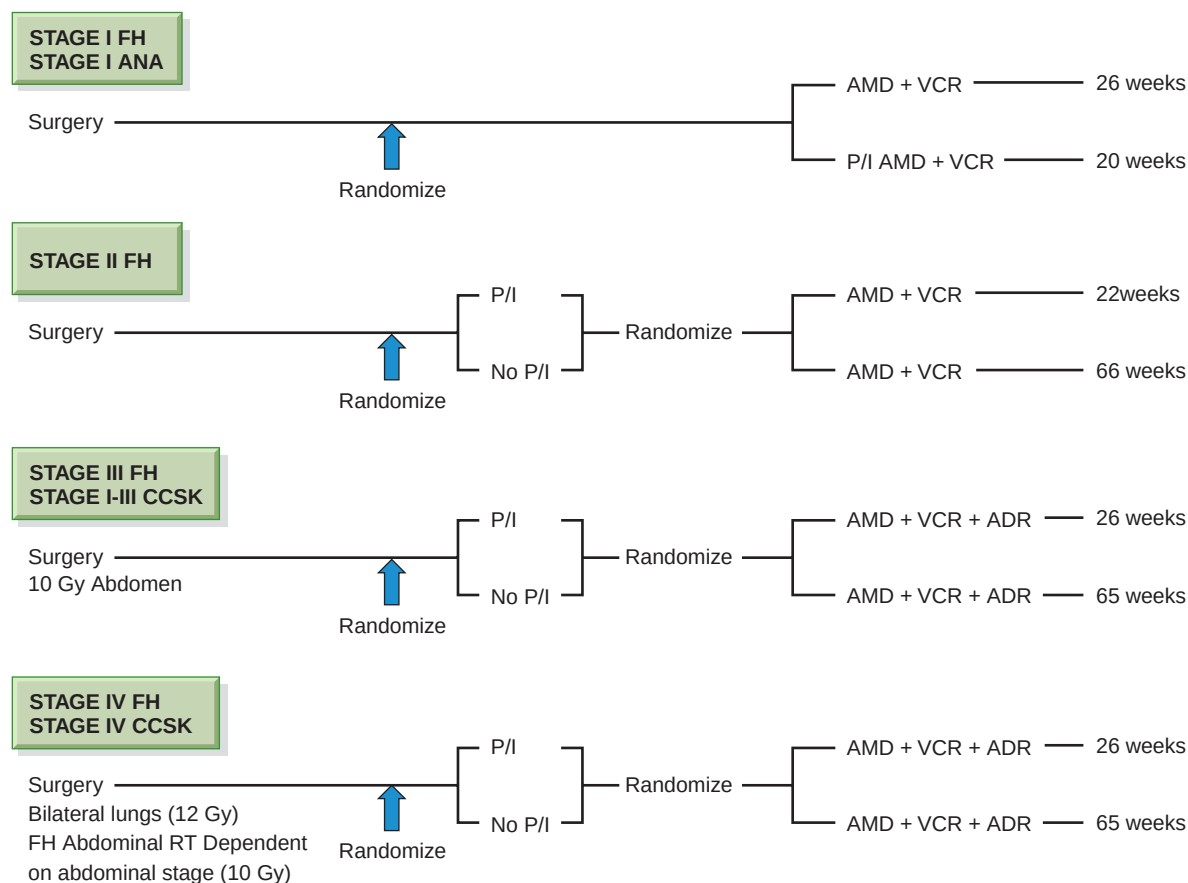


Figure 13.10 NWTS-4 simplified schema. Stage IV anaplastic tumors continued the randomization of NWTS-3. (From Thomas PRM. Wilms' tumor: changing role of radiation therapy. *Semin Radiat Oncol.* 1997;7:204–211, with permission.)

treatment groups (77,78). Comparing the results from NWTS-4 with those of the UKCCSG Wilms Tumor Study 2, reported contemporaneously, we see surprisingly similar results (Table 13.12) (79). The risk of local recurrence of patients enrolled in NWTS-4 is shown in Table 13.13.

The NWTS evaluated the frequency with which spilled tumor cells of FH produce intra-abdominal disease recurrence. Flank irradiation but not doxorubicin reduced abdominal relapse rates. The odds ratio for the risk of recurrence relative to no radiation was 0.35 for 10 Gy and 0.08 for 20 Gy. Tumor spillage resulted in higher relapse and significantly lower survival among stage II patients. For stage II patients (NWTS-4), the 8-year event rates, with and without spillage, respectively, were 79% and 87% for relapse-free survival ($p = 0.07$), and 90% and 95% for overall survival ($p = 0.04$) (61).

The evidence from NWTS-4 is that PI initial chemotherapy is as effective as a longer program. Shorter-course subsequent chemotherapy appears as effective as a longer program. Overall survival rates are excellent, and few patients are irradiated (77,78).

The long-term data from NWTS-3 and NWTS-4 show no significant effects for doxorubicin in stage II FH patients; however, for stage III patients, the relapse-free and overall survival rates were 84% and 89% with and 74% and 83% without doxorubicin, respectively. For stage III patients, the use of doxorubicin results in a significant reduction in local and general recurrence without any improvement in overall survival (80).

NWTS-5 (1995–2001) treated stage I favorable and anaplastic histology and stage II FH with 18 weeks of actinomycin D and vincristine. Stage I FH in children younger than 24 months of age and with tumor weight less than 550 g was treated with surgery alone. Stages III–IV FH and stages II–IV focal anaplastic tumors were treated with 24 weeks of actinomycin D, vincristine, adriamycin, and local irradiation and WLI as appropriate. Stages II–IV diffuse anaplastic sarcoma and stages I–IV CCSK were treated with cyclophosphamide, vincristine, adriamycin, and etoposide along with local irradiation and WLI as appropriate. Stages I–IV RTK was treated with carboplatin, etoposide, cyclophosphamide, and radiotherapy. The radiotherapy guidelines in NWTS-5 were similar to those used in NWTS-4 except for anaplastic tumors where a dose of 10.8 Gy was recommended as compared to an age-adjusted schedule used in NWTS 1–4. As a major objective, NWTS-5 sought to evaluate the importance of LOH for chromosome 1p and 16q markers for prognosis. These results have been detailed earlier in the chapter (Table 13.1) (29).

The outcome of 57 patients with FH tumors and peritoneal implants at the time of nephrectomy in NWTS-4 and NWTS-5 were analyzed. Stage III tumors were seen in 74%, and 26% had stage IV tumors. All children received multimodality therapy with three-drug chemotherapy and irradiation. Forty-seven patients (82%) received whole-abdominal radiation therapy and the radiation dose was

Table 13.11**NWTS-4 Results**

4-Year Relapse-Free Survival (%)			
Low Risk		High Risk	
STD	PI	STD	PI
88	84	89	90
Stage and Treatment		Relapse-Free Survival	
Stage I			
FH-STD		93	
FH-PI		95	
Ana-STD		93	
Ana-PI		88	
Stage II			
FH-STD + Short		82	
FH-STD + Long		88	
FH-PI + Short		86	
FH-PI + Long		89	
Stage III			
FH-STD + Short		94	
FH-STD + Long		91	
FH-PI + Short		92	
FH-PI + Long		90	
Stage IV			
FH-STD + Short		82	
FH-STD + Long		93	
FH-PI + Short		83	
FH-PI + Long		78	

STD, standard; PI, pulse intense; FH, favorable histology; ANA, anaplastic; Short, short therapy course; Long, long therapy course; From Refs. 77 and 78.

Table 13.12**Comparing Results: NWTS-4 and UK Children's Cancer Study Group Wilms Tumor Study 2**

Stage and Histology	Relapse-Free Survival/ Event-Free Survival ^a %	Survival ^b %
Stage I FH	89/87	96/94
Stage II FH	88/82	91/91
Stage III FH	91/82	/84
Stage IV FH	~80/70	80/75

^aThe number to the left of the slash is the NWTS-4 relapse-free survival. The number to the right of the slash is the UKCCSG Wilms Tumor Study 2 event-free survival.

^bThe number to the left of the slash is the NWTS-4 survival. The number to the right of the slash is the UKCCSG Wilms Tumor Study 2 survival.

FH, favorable histology.

From Refs. 77–79.

Table 13.13**Risk of Local Recurrence in NWTS-4**

	Relative Risk
Stage	
I	1
II	2.1
III	3.2
Histology	
Favorable histology	1
Diffuse anaplasia	4.7
Clear cell sarcoma of the kidney	2.8
RTK (with other sarcoma)	3.1
Invasion of adjacent organs	
No	1
Yes	1.8
Spillage (local and diffuse)	
No	1
Yes	3.7
Biopsy, spillage, preoperative rupture, and tumor cut across	
No	1
Yes	2.5
Age (months)	
0–23	1
24–47	0.9
48+	2.6
Removal	
Complete	1
Incomplete	2.7
Margin	
—	1
+	2
Nodes	
Negative	1
Hilar	1.1
Aortic	3
None examined	2.6

RTK, rhabdoid tumor of the kidney.

From Shamberger RC, Guthrie KA, Ritchey ML, et al. Surgery-related factors and local recurrence of Wilms' Tumor Study 4. *Ann Surg.* 1999;229:292–297.

10.5 Gy in 50 patients. The overall abdominal and systemic tumor control rates were 97% and 93%, respectively. The detection of peritoneal implants was not associated with inferior survival after this therapy. The 5-year relapse-free survival rates with and without peritoneal implants were 90% and 83%, respectively (81).

Children's Oncology Group Studies

The COG is the successor of the NWTS. The COG risk-group classification for treatment assignment in the new generation of Wilms tumor protocols is shown in Table 13.14. This classification, will in addition to tumor stage, also consider patient's age, tumor weight, presence or absence of LOH at 1p and 16q, and response to chemotherapy in children with FH tumors and lung metastases. The main objectives of the first generation of COG protocols are listed below. The COG

Table 13.14
COG Risk-Stratification Schema for Renal Tumor Protocols

Age (years)	Tumor Weight (g)	Stage	LOH	Histology	Rapid Response	Final Risk Group	Treatment Study
<2	<550	I	Any	FH	N/A	Very Low	AREN0532
Any	≥550	I	None	FH	N/A	Low	None
≥2	Any	I	None	FH	N/A	Low	None
Any	Any	II	None	FH	N/A	Low	None
≥2	Any	I	Yes	FH	N/A	Standard	AREN0532
Any	≥550	I	Yes	FH	N/A	Standard	AREN0532
Any	Any	II	Yes	FH	N/A	Standard	AREN0532
Any	Any	III	None	FH	Any	Standard	AREN0532
Any	Any	III	Yes	FH	Any	Higher	AREN0533
Any	Any	IV	Yes	FH	Any	Higher	AREN0533
Any	Any	IV	None	FH	Yes	Standard	AREN0533
Any	Any	IV	None	FH	No	Higher	AREN0533
Any	Any	V	Any	FH	Any	Bilateral	AREN0534
Any	Any	I–IV	N/A	FA	N/A	High	AREN0321
Any	Any	I–IV	N/A	DA	N/A	High	AREN0321
Any	Any	I–IV	N/A	CCSK	N/A	High	AREN0321
Any	Any	I–IV	N/A	MRT	N/A	High	AREN0321

radiation therapy (Table 13.15) and chemotherapy regimens are outlined in Table 13.16.

AREN03B2

This is a renal tumors classification, biology, and banking study. The objectives are as follows:

1. To classify patients with renal tumors by histologic categorization, surgicopathologic stage, presence of metastases, age at diagnosis, tumor weight, and LOH for chromosomes 1p and 16q, to thereby define eligibility for a series of therapeutic studies
2. To maintain a biologic samples bank to make specimens available to scientists to evaluate additional potential biologic prognostic variables and for the conduct of other research by scientists
3. To monitor outcome for those patients who are not eligible for a subsequent therapeutic study including patients initially classified as low risk, defined as those with favorable histology Wilms tumor stage I (>2 years old or tumor weight >550 g) or stage II whose final risk classification is low risk and whose tumors do not have LOH at 1p and 16q
4. To describe the sensitivity and specificity of abdominal CT by comparison with surgical and pathologic findings for identification of local tumor spread beyond the renal capsule to adjacent muscle and organs, lymph node involvement at the renal hilum and in the retroperitoneum, preoperative tumor rupture, and metastases to the liver.
5. To compare the sensitivity and specificity of preoperative abdominal CT and MRI for the identification and differentiation of nephrogenic rests and Wilms tumor in children with multiple renal lesions.
6. To correlate the method of conception (natural vs. assisted reproductive technology) with the development of Wilms tumor.
7. To evaluate the frequency of *INI1* mutations in renal and extrarenal malignant RTK.

AREN0321

This is a study for the treatment of children with high-risk renal tumors. The primary objectives are as follows:

1. To evaluate whether a regimen of cyclophosphamide/carboplatin/etoposide alternating with vincristine/doxorubicin/cyclophosphamide improves the event-free and overall survival of patients with diffuse anaplastic Wilms tumor
2. To evaluate in a stage II “window” study, the antitumor activity of a combination of vincristine and protracted-schedule irinotecan against metastatic diffuse anaplastic Wilms tumor
3. To evaluate whether a regimen of cyclophosphamide/carboplatin/etoposide alternating with vincristine/doxorubicin/cyclophosphamide improves the event-free and overall survival of patients with malignant RTK
4. To evaluate in a stage II “window” study, the antitumor activity of a combination of vincristine and protracted-schedule irinotecan against metastatic or unresectable RTK
5. To maintain the excellent event-free survival of patients with stage I CCSK without the use of abdominal irradiation.

AREN0532

This is a study for the treatment of children with very low and standard risk FH Wilms tumor. The objectives are as follows:

1. To demonstrate that very low risk patients treated by nephrectomy and observation alone will have a 4-year event-free survival rate of ≥85% and 4-year overall survival rate of ≥95%
2. To document continued excellent outcome (4-year event-free and overall survival rates of ≥85% and ≥95%) for patients with stage III FH Wilms tumor without LOH of 1p and 16q treated with vincristine, dactinomycin, doxorubicin, and radiotherapy (regimen DD4A)

Table 13.15

COG Radiation Therapy Guidelines

Treatment Site	Clinical Presentation	Dose
Flank irradiation Patients with residual tumor will receive supplemental irradiation with 10.8 Gy	Stage III FH Stage I–III focal anaplasia (FA) Stage I–II diffuse anaplasia (DA) Stage I*–III CCSK	10.8Gy *Stage I CCSK patients will not receive flank irradiation if complete staging, lymph node sampling, and central pathologic review are performed
	Recurrent Wilms tumor	
	Age 0–12 months	12.6–18 Gy
	Age >12 months	21.6 Gy
	Stage III DA	19.8 Gy
	Stage I–III rhabdoid tumor (RTK)	(10.8 Gy for patients ≤12 months)
Whole-abdomen irradiation (WAI) Patients with residual tumor will receive supplemental irradiation with 10.5 Gy	Stage III FH, FA, DA ^a , CCSK, RTK ^a , recurrent WT (a) Cytology-positive ascites (b) Any preoperative tumor rupture (c) Diffuse surgical spillage (d) Peritoneal seeding	10.5 Gy 21 Gy
	Abdominal stage III FH, FA, DA (>12 months age), CCSK, RTK (>12 months age)	
	Recurrent WT with diffuse unresectable peritoneal implants	
Metachronous Wilms tumor	Negative surgical margins	No RT
	Microscopically involved margins or nodes	10.8 Gy
	Diffuse spillage or abdominal involvement	Follow WAI guidelines
	Microscopically involved margins after partial nephrectomy	14.4 Gy
	Gross residual disease after partial resection or biopsy	21.6 Gy
Whole-lung irradiation (WLI) Patients with favorable histology tumors whose lung metastases are <i>not</i> in complete remission after three-drug chemotherapy on central radiology review at week 6 will receive WLI. All unfavorable histology patients with lung metastases will receive WLI	Lung metastases	10.5 Gy; age <12 months 12 Gy; age ≥12 months
Whole-brain irradiation	Brain metastases	21.6 Gy + 10.8 Gy boost; age <16 years 30.6 Gy; age ≥16 years
Liver irradiation	Focal metastases	19.8 Gy
Patients with residual tumor will receive supplemental irradiation with 5.4–10.8 Gy	Diffuse metastases	19.8 Gy
Bone irradiation	Bone metastases	25.2 Gy; age <16 years 30.6 Gy; age ≥16 years
Lymph node irradiation	Resected LN metastases	10.8 Gy
	Unresected LN metastases	19.8 Gy

^aPatients aged ≤12 months with stage III DA/RTK will receive 10.5 Gy and patients aged >12 months will receive 10.5 Gy WAI and flank boost of 9 Gy.

Table 13.16
Chemotherapy Regimens

Drug	Days	Week
Regimens EE4A		
Vincristine	1	0–10, 12, 15, 18
Dactinomycin	1	0, 3, 6, 9, 12, 15, 18
Regimen DD4A ^a		
Vincristine	1	0–10, 12, 15, 18, 21, 24
Dactinomycin	1	0, 6, 12, 18, 24
Doxorubicin	1	3, 9, 15, 21
Regimen M ^b		
Cyclophosphamide/MESNA	1–5	7, 10, 19, 25
Etoposide	1–5	7, 10, 19, 25
Vincristine	1	8, 9, 11, 12, 13, 16, 22, 28, 31
Dactinomycin	1	13, 16, 22, 28, 31
Doxorubicin	1	13, 16, 22, 28, 31
Regimen I ^c		
Vincristine	1	1–3, 5–7, 8–9, 11–14, 19, 25
Doxorubicin	1	7, 13, 19, 25
Cyclophosphamide/MESNA	1–3	1, 7, 13, 19, 25
	1–5	4, 10, 16, 22
Etoposide	1–5	4, 10, 16, 22
Regimen UH1		
Vincristine	1	1–3, 10–15, 22–24, 28–30
Doxorubicin	1 and 2	1, 10, 13, 22, 28
Cyclophosphamide/MESNA	1	1, 10, 13, 22, 28
Carboplatin	1	4, 7, 16, 19, 25
Etoposide	1–5	4, 7, 16, 19, 25
Cyclophosphamide/MESNA	1–5	4, 7, 16, 19, 25

^aThe dose of dactinomycin at week 6 and dose of doxorubicin at week 3 should be reduced by 50% if whole-lung or whole-abdomen radiation has been given.

^bThe dose of dactinomycin and doxorubicin will be reduced by 50% if administered during or within 6 weeks of completing whole-lung or whole-abdomen radiation. The full dose of these agents may be administered if it coincides with the start of radiation.

^cThe dose of doxorubicin at week 7 should be reduced by 50% if whole-lung or whole-abdomen radiation has been given.

3. To improve the current 4-year event-free survival for patients with FH Wilms tumor with LOH of 1p and 16q by adding doxorubicin but not radiotherapy to the standard dactinomycin and vincristine regimen
4. To determine whether omission of adjuvant therapy increases the incidence of renal failure in the very low risk patients that have metachronous relapse
5. To monitor the outcomes for very low and standard risk subsets of FH Wilms tumors for correlation with biologic data generated from the study of the tissues collected from these cases.

AREN0533

This is a study for the treatment of newly diagnosed higher-risk FH Wilms tumors. The objectives are as follows:

1. To demonstrate that patients with stage IV FH Wilms tumor with pulmonary metastases only, who have complete resolution of the pulmonary lesions after 6 weeks of regimen DD4A chemotherapy (vincristine, dactinomycin, and doxorubicin) called rapid complete responders (RCR), will have at least an 85% 4-year event-free survival after therapy with additional chemotherapy (regimen DD4A) and without WLI
2. To demonstrate that stage IV FH patients who do not have resolution of pulmonary metastases by week 6, called slow

incomplete responders (SIR), will have a 4-year event-free survival rate of 85% with the addition of cyclophosphamide and etoposide to a modified regimen DD4A (regimen M) and WLI

3. To improve the 4-year event-free survival rate to 75% for patients with stage III or IV FH Wilms tumor with LOH for chromosomes 1p and 16q
4. To determine the relationship between the burden of pulmonary metastatic disease and outcome in stage IV FH patients.

AREN0534

This is a study for the treatment for patients with bilateral, multicentric, or bilaterally predisposed unilateral Wilms tumor. The objectives are as follows:

1. To improve the 4-year event-free survival rate to 73% for patients with bilateral Wilms tumor
2. To prevent complete removal of at least one kidney in 50% of patients with bilateral Wilms tumor (BWT) by using prenephrectomy three-drug chemotherapy induction with vincristine, dactinomycin, and doxorubicin
3. To evaluate the efficacy of chemotherapy in preserving renal units in children with diffuse hyperplastic perilobar nephrogenic rests (DHPLNR) and preventing Wilms tumor development

Table 13.17

Results of the Treatment of New Cases of Historically Confirmed Wilms Tumor, with More Than 2 Years of Follow-Up, As Reported by Schweisguth and Bamberger of the Institut Gustave Roussy in 1963

Treatment	n	Alive Without Metastases (%)	Alive With Metastases Treated (%)	Dead (%)
No nephrectomy	4	0	0	100
Nephrectomy done	3	0	0	100
XRT and nephrectomy	15	27	0	73
Nephrectomy and XRT	24	33	0	67
XRT, nephrectomy, and XRT	50	40	4	56
Laparotomy, XRT, nephrectomy, and XRT	2	0	0	100
	98	33	2	65

Derived from Schweisguth O, Bamberger J. Le nephroblastome de l'enfant. *Ann Chir Infant Paris*. 1963;4:335–354. Translation from French courtesy of Dr Gustavo Montana.

Table 13.18

SIOP 1 Wilms Tumor Treatment Protocol

Randomization	S	Stage	Postoperative Treatment	Maintenance	Months
RT (20 Gy)	N	I	A	No treatment	0
Randomize		II	RT (15 Gy) + A	Randomize	
		III ^a	RT (15 Gy) + A		
		I	RT (20 Gy) + A		
		II	RT (30 Gy) + A		
Nephrectomy		III ^a	RT (30 Gy) + A	A (6 courses)	16

^aRT whole abdomen: dosage to kidney 12 Gy; dosage to liver 30 Gy. S, surgery; RT, radiation therapy; N, radical nephrectomy; A, actinomycin D. From Refs. 62–65 and with additional material supplied by Professor F Oldenburger.

- To facilitate partial nephrectomy in lieu of nephrectomy in 25% of children with unilateral tumors and aniridia, BWS, hemihypertrophy, or other overgrowth syndromes by using pre-nephrectomy two-drug chemotherapy induction with vincristine and dactinomycin
- To have 75% of children with BWT undergo definitive surgical treatment by 12 weeks after initiation of chemotherapy.

SIOP Wilms Tumor Studies

A classic study by Schweisguth and Bamberger (82), published in 1963, suggested that about one third of patients with Wilms tumor could be cured by preoperative radiotherapy and nephrectomy (Table 13.17). The SIOP studies built on this experience.

SIOP Study 1 (1971–1974) (Tables 13.18 and 13.19) registered 397 patients from 42 participating centers. In patients older than 1 year and younger than 15 years at diagnosis, the randomized trial was designed to ascertain whether preoperative plus postoperative primary tumor site irradiation is superior to postoperative irradiation only and whether a single postoperative course of actinomycin D is equal to multiple courses. To answer the first question, 73 children were randomized to receive 20 Gy before surgery, and 64 children underwent immediate surgery. SIOP stage I patients randomized to undergo preoperative irradiation received no additional irradiation, and stages II and III patients were given an additional 15 Gy. Children who were randomized to the postoperative irradiation arm received 20 Gy for stage I and were given 30 Gy

for stages II and III, with provision for additional boosts for bulky stage III. Three of 72 evaluable patients who received preoperative radiotherapy had tumor rupture during surgery (4%), whereas 20 of 60 patients who received no preoperative irradiation suffered from tumor rupture (33%, $p = 0.001$). The 5-year recurrence-free survival rate was 51% for those without tumor rupture and 27% for those with rupture ($p = 0.01$), with no difference in 8-year overall survival rate (66% vs. 61%) between the two groups (8). In the randomization between one and seven courses and actinomycin D (15 mg/kg/day $\times$ 5 days), there was no survival difference (62–65).

SIOP trial 2 (1974–1976) (Tables 13.20 and 13.21) was a nonrandomized study comparing patients receiving 20 Gy of

Table 13.19

SIOP 1 Results

Randomization	Outcome
(A) Radiotherapy, surgery, and radiotherapy	4% ruptures 31% stage I
(B) Surgery and radiotherapy	32% ruptures 14% stage I
Actinomycin D, 1 course	n.s.
Actinomycin D, 6 courses	

(A) vs. (B), $p = 0.001$.

From Refs. 62–65 and with additional material supplied by Professor F Oldenburger.

Table 13.20

SIOP 2 Wilms Tumor Treatment Protocol

First Treatment	Stage	Postoperative Treatment	Maintenance
Preoperative	I	AV	1 or 5 courses A
RT 20 Gy + S (average tumors)	II–III	AV + RT (15 Gy)	for 6 or 15 months
A + S (small tumors)	I	AV	1 or 5 courses A
	II–III	AV + RT (30 Gy)	for 6 or 15 months

RT, radiation therapy; S, nephrectomy; A, actinomycin D; V, vincristine.
From Refs. 64–65 and with additional material supplied by Professor F. Oldenburger.

Table 13.21

SIOP 2 Results

V added to A Postoperatively	9 months vs. 15 months	Disease-Free	Survival and Survival Equal
Preoperative RT	Ruptures	5%	$p = 0.0025$
Surgery (e.g., small tumors)	Ruptures	20%	

V, vincristine; A, actinomycin D; RT, radiation therapy.
From Refs. 62–65 and with additional material supplied by Professor F. Oldenburger.

Table 13.22

SIOP 5 Wilms Tumor Treatment Protocol

Preoperative Treatment	S	Stage	Postoperative Treatment	Maintenance	Weeks
VA (4 weeks)	S	I	AV	AV (5 courses)	43
Randomization		II/III	AV + RT (30 Gy)		
RT (20 Gy) + A	S	I	AV + RT (15 Gy)	AV (5 courses)	45
		II/III	AV + RT (15 Gy)		

S, nephrectomy; V, vincristine; A, actinomycin D; RT, radiation therapy.
From Refs. 62–65 and with additional material supplied by Professor F. Oldenburger.

irradiation and 5 days of actinomycin D before surgery with children treated with primary surgery. Tumor rupture occurred in 5% of the preoperatively treated patients and in 20% of the other patients ($p = 0.0025$) (62–64). The main reason for not giving preoperative therapy was small tumor size. Survival rate was only 61% in patients with larger tumors who received preoperative and postoperative irradiation. SIOP trials 1 and 2 demonstrated that presurgical treatment with radiotherapy reduced the number of tumor ruptures. This, in turn, reduced the need for whole-abdomen irradiation and its attendant ill effects in young children (62–64).

SIOP trial 5 (1977–1980) was designed to ascertain whether preoperative actinomycin D (two 3-day courses, 15 mg/kg) and vincristine (four weekly injections, 1.5 mg/m²) were equally effective preoperative therapy when compared with the previously used program of 20 Gy plus actinomycin D (Table 13.22). After surgery, the preoperatively irradiated patients were given an additional 15 Gy for NWTs group II or III disease, whereas those treated preoperatively only with chemotherapy received 30 Gy for group II or III disease. All patients received postoperative maintenance vincristine and actinomycin (Table 13.23). An analysis of the 172 randomized

patients showed no significant difference in the reduction in tumor size, incidence of tumor rupture, stage distribution, mean weight of the tumor specimen, or 3-year recurrence-free survival (89% for preoperative chemotherapy alone vs. 83% for chemotherapy plus radiotherapy). Major histologic changes such as necrosis were significantly less common after preoperative chemotherapy than after preoperative chemoradiotherapy (Tables 13.23 and 13.24) (62–65,83).

Table 13.23

SIOP 5 Results

	Relapse-Free Survival (%)	Survival (%)
Chemotherapy first	77	84
Radiotherapy first	67	83
Overall	71	86

From Refs. 62–65 and with additional material supplied by Professor F. Oldenburger

Table 13.24
Effect of Preoperative Treatment: SIOP Trial 5

Effect	Chemotherapy	Chemotherapy and Radiotherapy	p-Value
Major clinical reduction in tumor size (%)	84	88	n.s.
Mean weight of the specimen (g)	519	473	n.s.
Tumor rupture (%)	9	6	n.s.
Stage (% of cases)			
I	43	52	n.s.
II	36	32	n.s.
III	21	16	n.s.
Major change in pathologic pattern (% of cases)	17	53	<0.001
3-year recurrence-free survival (%)			
Stage I	43	52	
Stage II	36	32	
Stage III	21	16	
Overall 3-year survival (%)	89	83	n.s.

From Refs. 62–66 and with additional material supplied by Professor F. Oldenburger.

SIOP trial 6 (1980–1987) adopted the prenephrectomy chemotherapy used in SIOP trial 5. All patients received actinomycin D and vincristine. Patients who had stage I disease at the time of surgery were randomized to receive postoperative vincristine and actinomycin D for 17 or 38 weeks. All lymph node–negative stage II patients received 38 weeks of vincristine and actinomycin D and were randomized to receive or not receive 20 Gy of involved-field irradiation. Stage II node-positive patients and stage III patients were randomized to receive vincristine, actinomycin D with intensified vincristine, or the two drugs with doxorubicin (Table 13.25). The stage distribution for the 396 SIOP trial 6 patients was stage I (56%), stage II node negative (27%), and stage II node positive and stage III (17%). Tumor rupture was found in 6% of cases (62–66,83).

In the radiotherapy randomization for stage II node-negative patients in SIOP trial 6, there were eight relapses among 50 nonirradiated patients. Of these eight, seven had subdiaphragmatic regrowths of tumor, and in six the tumor bed was the site of first relapse. This was in contrast to only one local recurrence of the 58 patients given postoperative

irradiation. However, 12 of the 58 children developed lung metastases. Three of the 50 nonirradiated patients died, and 5 of the 58 irradiated patients died of disseminated Wilms tumor. The overall survival rate of the two groups at 4 years was not different: 90% of the nonirradiated patients and 85% of the irradiated patients (Table 13.26) (62–66,83).

SIOP trial 9 (1987–1993) had, as its primary question, the appropriate duration of prenephrectomy chemotherapy. One half of the patients with disease confined to the abdomen received 4 weeks of actinomycin D and vincristine, and one half received 8 weeks. After nephrectomy, patients with multicystic, tubular, and nephroblastoma with fibroadenomatous-like structures received no additional therapy. Patients with UH received actinomycin D, epidoxorubicin, vincristine, ifosfamide, and generally, irradiation. Patients with FH tumors received the following postoperative treatments along with local irradiation (15 Gy to the tumor bed with an optional boost to residual disease up to 30 Gy): stage I, actinomycin D and vincristine; stage II node negative, actinomycin D, vincristine, and epidoxorubicin; and stage II node positive and

Table 13.25
SIOP 6 Wilms Tumor Treatment Protocol

Preoperative Treatment	S	Stage	Postoperative Treatment	Maintenance	Weeks
	S	I	AV	AV (2 courses)	17
				↑ Randomization ↓	
AV × 4 weeks	S	II N0	RT (20 Gy) + AV	AV (5 courses)	38
			↑ Randomization ↓		
	S	II N1	AV	AV (5 courses)	38
			IntVCR + RT (30 Gy)	AV (5 courses)	40
			↑ Randomization ↓		
		III	AdriaAV + RT (30 Gy) (6 courses)	AV (5 courses)	38

S, radical nephrectomy; A, actinomycin D; V, vincristine; RT, radiation therapy; IntVCR, intensified vincristine (two extra injections during maintenance courses); Adria, adriamycin.

From Refs. 62–66

Table 13.26**SIOP 6 results**

Stage	2-Year Disease-Free Survival (%)	5-Year Survival (%)	p-Value
All stages	80	84	
Stage I (trial)	82	89	
Short arm	92	95	n.s.
Long arm	88	92	
Stage II N0	76	86	
Radiotherapy	72	78	n.s.
No radiotherapy	88	85	
Stage II N1–III	61	75	
Intensive vincristine	49	74	
Adriamycin	77	80	
Favorable histology	97	97	
Unfavorable histology		58	

From Refs. 62–66.

stage III, actinomycin D, vincristine, and epidoxorubicin. Infants younger than 6 months underwent upfront nephrectomy. Children with a preoperative diagnosis of stage IV disease received actinomycin D, vincristine, and epidoxorubicin. This was followed by nephrectomy and possible metastasectomy. Those rendered free of disease continued on actinomycin D, vincristine, and epidoxorubicin. Those with persistent metastatic disease received ifosfamide, vincristine, and actinomycin D and irradiation (Tables 13.27–13.29). The study's results show that the duration of prenephrectomy chemotherapy did not influence the stage distribution at the time of surgery. There was also no difference in toxicity between the 4-week and 8-week chemotherapy arms (62–67). Among patients receiving 4 weeks compared to 8 weeks of preoperative chemotherapy, there was no difference in the frequency of stage I tumors (64% vs. 62%), tumor rupture (1% vs. 3%), and 5-year overall survival (92% vs. 87%). Thus, 4 weeks of preoperative chemotherapy was established as the standard duration of induction chemotherapy in SIOP protocols (67).

Table 13.27**SIOP 9 Wilms Tumor Treatment Protocol**

Preoperative Treatment	Eligible for Randomization	N	Stage	Histology	Postoperative Treatment	Weeks
AV 4 weeks	AV 4 weeks		I	FH	None	0
	↑ Yes → Randomize	S	I	ST	AV × 3	18
	↓ No further preoperative treatment		I	UH	AV × 3	18
	No	S	II N0	ST	AVE × 5	27
			II N1	ST	AVE × 5 + RT 15 Gy ^a	27
			III	ST	AVE × 5 + RT 15 Gy ^a	27
			II–III	UH	DEVI × 5 + RT 30 Gy ^b	36

N, radical nephrectomy; A, actinomycin; V, vincristine; FH, favorable histology; S, surgery; ST, standard; UH, unfavorable histology; E, anthracycline; RT, radiation therapy; D, actinomycin D; I, ifosfamide.

^aStages II N1/III standard histology: RT 15 Gy ± boost 10–15 Gy.

^bUnfavorable histology: RT 30 Gy ± boost 5–10 Gy.

From Refs. 62–65,67–69.

Table 13.28**SIOP 9: Stage IV Protocol**

Preoperative Chemotherapy	N ± R	Response of Metastases	Abdomen Stage	RT Lung/Boost (Gy)	RT Abdomen/Boost (Gy)	Postoperative Chemotherapy	Weeks
AVE 6 weeks	N ± R	M–	I	0	0	A*VE	32
			II N1	0	15/15	A*VE	32
			III	0	15/15	A*VE	32
		M+	I	0	0	A*VI	25
			II N1	17.5/5–10	15/15	A*VI	25
			III	17.5/5–10	15/15	A*VI	25

N, nephrectomy; R, metastasectomy; RT, radiation therapy; A, actinomycin D 0.5 mg/m² IV; V, vincristine 1.5 mg/m² IV; E, epirubicin 50 mg/m² IV; A*, actinomycin D 0.9 mg/m² IV; M, metastases; M–, complete response or completely resected; M+, not a complete response or incompletely resected or multiple inoperable metastases; I, ifosfamide 3000 mg/m² IV.

From Refs. 62–65,67,68.

Table 13.29**SIOP 6 Results**

	2-Year Event-Free Survival (%)	5-Year Survival (%)
Tumor rupture, 4 weeks	84	92
Tumor rupture, 8 weeks	83	87
Tumor volume regression >50%	88	93
Tumor volume regression, <50%	82	89
Stage I, favorable histology	100	100
Stage I, standard and anaplastic	86	93
Stage II N0, standard	82	87
Stage II N1, III	77	89
Unfavorable histology	64	79
Entire pre-eligible population		
Stage I–III nonanaplastic	86	92
Stage I, anaplastic	75	92
Randomized patients	84	90
Pre-eligible, nonrandomized patients	81	88

From Refs. 62–65,67,68.

In SIOP 9, approximately 10% of patients had completely necrotic tumors with no viable tumor after induction chemotherapy. The 5-year event-free survival rate among these patients was 98% and the only death was due to veno-occlusive disease. It was proposed that such patients be considered for reduction in therapy after nephrectomy (68).

SIOP trial 93-01 (1993–2000): Patients were classified into three histologic groups as shown in Table 13.3. Because the available results show no difference between 4-week and 8-week preoperative chemotherapy, 4 weeks has been adopted as the standard. Patients with stage I low-grade histology received no additional therapy. Patients with stage I intermediate- or high-grade tumors were randomized to a 4-week

Table 13.30**SIOP 93-01 Wilms Tumor Treatment: Postoperative Treatment Strategies for Unilateral Wilms Tumor**

Stage	Postoperative	Maintenance
I, low risk	None	None
I, intermediate risk	AV (4 weeks)	AV for 2 courses, 18 weeks ↑ Randomization ↓ No further treatment
II N0, anaplasia	AVE	AVE for 27 weeks
II N1 and III	AVE + RT	AVE for 27 weeks
High risk (I–III)	E/I/Vp/C + RT ^a	E/I/Vp/C for 34 weeks

A, actinomycin; V, vincristine; E, epirubicin 50 mg/m² IV; RT, radiation therapy; I, ifosfamide 3 g/m² IV; Vp, etoposide 100 mg/m² IV; C, carboplatin 600 mg/m² IV.

^aStage I high risk, no abdominal RT.

From Refs. 62–64,69–71.

postoperative program of vincristine and actinomycin D or a 6-week program. All stage II and III patients with intermediate-grade tumors received therapy as in SIOP trial 9. Stage II and III high-grade tumors were treated with ifosfamide, etoposide, and carboplatin (Table 13.28). The survival results are excellent (Tables 13.30–13.33) (62–65,69). In SIOP 93-01, 410 patients with stage I intermediate-risk and anaplastic Wilms tumor after 4 weeks of chemotherapy were randomized postoperatively to no further therapy or two additional cycles of chemotherapy. There was no difference in 2-year event-free survival between the no further therapy group (91%) compared to those who received additional chemotherapy (89%) (69). Among 1090 patients in SIOP 93-01, 5% had tumor progression during preoperative chemotherapy in SIOP 93-01. These tumors were generally smaller at diagnosis, more often stage III after surgery and associated with higher grade histology. They had significantly poorer event-free and overall survival compared to those who responded to chemotherapy (70). A pathologic review of stage II tumors in SIOP 93-01

Table 13.31**SIOP 93-01 Stage IV Protocol**

Preoperative Chemotherapy	N ± R	Response of Metastases	Abdominal Stage	RT Lung (Gy)	RT Abdomen (Gy)	Postoperative Chemotherapy	Weeks
AVE 6 weeks	N ± R	M–	I	0	0	AVE	27
		M–	II N1	0	15/10	AVE	27
		M–	III	0	15/10	AVE	27
		M+ at week 11 evaluation	I	15/5–10	0	Vp/C/I/E	34
			II+	15/5–10	15/10	Vp/C/I/E	34
			III	15/5–10	15/10	Vp/C/I/E	34
			High risk II/III	15/5–10	25	Vp/C/I/E	34

N, nephrectomy; R, metastasectomy; RT, radiation therapy; A, actinomycin; V, vincristine; E, epirubicin 50 mg/m² IV; M, metastases; M–, complete response or completely resected; M+, not a complete response or incompletely resected or multiple inoperable metastases; Vp, etoposide 100 mg/m² IV; C, carboplatin 600 mg/m² IV; I, ifosfamide 3 g/m² IV.

From References 62–64,69–71.

Table 13.32
SIOP 93-01 Results

Stage	Disease-Free Survival (%)		Survival (%)	
	2-Year	5-Year	2-Year	5-Year
Stage I				
VCR and actinomycin	91	88	98	97
No further treatment	89	87	98	95
Stage II	88	88		
Stage III	78	75		

From Refs. 62–64,69–71 and with additional material generously supplied by Professor F. Oldenburger.

Table 13.33
SIOP 93-01 Results

Risk Group	4-Year Event-Free Survival (%)
Low	100
Intermediate	~89
High	~65
Tumor volume	4-year event-free survival (%)
≤500 mL	89
>500 mL	72, $p = 0.0095$
Subtype	Survival (%)
Focal anaplasia	~90
Blastemal predominant	~75
Diffuse anaplasia	~59

From Refs. 62–64,69–71 and with additional material generously supplied by Professor F. Oldenburger.

revealed that there was a significantly higher survival among patients who were stage II due to nonviable tumor in the renal sinus or perirenal fat compared to those with viable tumor in these sites (100% vs. 91%). It was proposed that the definition of stage II be revised (71).

A summary of SIOP trials 1, 2, 5, 6, 9, and 93-01 shows that 4 weeks of prenephrectomy chemotherapy, without irradiation, results in 56% of patients having stage I disease at

Table 13.35
SIOP 2001 Stage IV Postoperative Treatment

Metastases absent or completely resected, intermediate risk		
Act, Vcr, Dox (27 weeks)	Local stage I–II	No RT
	Local stage III	Abdominal RT week 2–5
Multiple inoperable metastases or incompletely resected metastases		
VP16, Carbo, Cyclo, Dox (34 weeks)	Local stage I–II	No abdominal RT
	Local stage III RT	Abdominal RT week 1–4

Act, actinomycin; Vcr, vincristine; Dox, doxorubicin; RT, radiation therapy; VP16, etoposide; Carbo, carboplatin; Cyclo, cyclophosphamide.

From Refs. 62–67 and with additional material generously supplied by Professor F. Oldenburger.

surgery. In most cases, these patients go on to receive postoperative chemotherapy and have a survival rate of more than 90%. Stage II node-positive and stage III patients have approximately a 61% relapse-free survival and a 75% overall survival (62–65). A diminishing number of patients have received radiotherapy in the sequential SIOP trials. The estimated percentages of patients who received irradiation are as follows: SIOP 1, 90%; SIOP 2, 90%; SIOP 5, 72%; SIOP 6, 34%; SIOP 9, 24% (65). If one excludes patients with metastases, then only about 16% of SIOP patients receive irradiation (83,84).

The latest SIOP protocol 2001 treatment and radiation therapy guidelines are summarized in Tables 13.34–13.37.

SELECTION OF THERAPY

Surgery

If one follows the NWTS philosophy, 90–95% of intra-abdominal tumors are resectable at diagnosis, and surgery is the initial definitive treatment. Operative approaches have included a vertical incision or a thoracoabdominal exposure. The current preferred approach is a wide transverse abdominal incision and total resection generally is achievable with a transperitoneal approach (85). The surgeon should try and accomplish the safe and complete removal of the tumor. A thorough exploration of the abdominal cavity should be performed and the liver and regional lymph nodes should be examined for evidence of tumor spread. The presence or

Table 13.34
SIOP 2001 Postoperative Treatment Strategies for Localized Tumors

Risk Level	Stage I	Stage II	Stage III
Low risk	No further treatment	AV-2 (27 weeks)	AV-2
Intermediate risk	AV-1 (4 weeks)	Randomize to either: Dox + AVD or Dox – AV-2	Randomize to either: RT + Dox + AVD (27 weeks) or RT + Dox – AV-2
High risk	AVD (27 weeks)	High risk + RT (34 weeks)	High risk + RT

AV-1 is a 4-week program; AV-2 is a 27-week program; A, actinomycin; V, vincristine; D, adriamycin; RT, radiation therapy; Dox, doxorubicin.

From Refs. 62–67 and with additional material generously supplied by Professor F. Oldenburger.

Table 13.36
SIOP 2001 Indications for Radiotherapy

Flank RT:
Stage III, intermediate risk
Stage II, high risk, except blastemal type
Stage III, high risk
Stage IV: abdominal stage III, intermediate-risk abdominal stage II–III high risk
Whole-abdomen RT: in all risk groups
Stage III, diffuse spillage, peritoneal metastases
Pulmonary RT: if pulmonary metastases at diagnosis:
Persistent metastases at week 9 after chemotherapy or surgery
High-risk primary tumor, independent of pulmonary metastases
Secondary metastases

RT, radiation therapy.

From *Nephroblastoma Clinical Protocol SIOP 2001*.

International Society of Pediatric Oncology, Zurich, 2001.

absence of lymph node metastases is of major importance in determining treatment and relapse-free survival. Lymph node sampling is necessary for accurate staging. After the abdominal exploration is completed, radical nephrectomy is performed. The tumor should be handled carefully throughout the procedure in order to avoid tumor spillage, as this complication results in a significant increase in local abdominal relapse. The incidence of operative rupture or spill ranges from 15% to 30% (38,58,61–67). Most cases of operative spill are focal (limited to the operative site) rather than diffuse (contamination of the peritoneal cavity) (64). The risk of abdominal relapse and mortality has been significantly greater after surgical spill (38,61,62,86,87). In cases with marginally operable tumors or with large areas of central necrosis, preoperative radiotherapy or chemotherapy may be preferable to attempted resection with spill. As noted earlier in this chapter, the SIOP philosophy, using preoperative chemotherapy, has significantly reduced the risk of operative spill and tumor rupture.

Surgical staging is important in determining treatment and prognosis. Palpation and visual assessment of the opposite kidney and liver are routine, although, as noted earlier in this chapter, some surgeons believe that preoperative imaging

studies, particularly MRI, can exclude contralateral kidney involvement with tumor. The prognostic importance of lymph node involvement has been established (Table 13.8) (73,88,89).

Surgery can be a cause of morbidity in children with Wilms tumor. A review of NWTs-4 patients undergoing primary nephrectomy found an 11% incidence of surgical complications (90). The most common complications of nephrectomy are hemorrhage and small bowel obstruction. The risk factors associated with increased surgical complications were higher local tumor stage, incorrect preoperative diagnosis, intravascular extension, and en bloc resection of other visceral organs. Heroic attempts to excise en bloc all or parts of adjacent organs to which the tumor appears to be adherent are not warranted, because such procedures are associated with an increased risk of surgical complications (90,91). Wilms tumors are generally very large and their gross appearance at the time of surgery can be misleading in interpreting tumor extent or operability. These tumors often compress and adhere to adjacent structures and in the majority of cases pathologic evidence of organ invasion is not present (91).

In NWTs-3, surgeons encountered renal vein involvement in 10% of patients. Extension into the inferior vena cava and atrium occurs in up to 5% more. En bloc removal of the kidney and renal vein tumor thrombus are possible in most children, and separate removal is possible in others. In some cases, the thrombus is “milked” from the inferior vena cava to the renal vein before removal. With meticulous surgery, renal vein involvement does not adversely affect prognosis (92).

Inoperability results primarily from large tumor size with direct involvement of the liver or retroperitoneal structures. Some surgeons recommend preoperative chemotherapy to improve the chance of resectability. Those who subscribe to the viewpoints of the SIOP studies will be predisposed to using preoperative chemotherapy without a biopsy. For those who feel uncomfortable with a diagnosis made by physical findings and diagnostic imaging, percutaneous biopsy is indicated, and tumor resection is planned after response to preoperative chemotherapy (90). A needle biopsy may entail general anesthesia or heavy sedation with local anesthesia. Ultrasound or contrast-enhanced CT scans may be used to localize the biopsy site. A proper biopsy must provide an adequate, representative specimen (36,75). Tumor subcapsular bleeding is a possible biopsy-related complication. For this reason, some clinicians prefer a posterior approach for the biopsy so that bleeding is more locally confined and less likely to spill into the abdominal cavity.

In the 1930s, nephrectomy alone achieved cure in 15–30% of children (85). Recent experience with the management of highly selected small intrarenal primary Wilms tumor suggests that one can identify a group of patients at extremely low risk of systemic micrometastasis potentially treatable with surgery alone. In a pilot study at Children's Hospital in Boston, eight patients younger than 2 years with unilateral, nonmetastatic, small (less than 550 g total tumor and kidney specimen weight) FH tumors (stage I) underwent nephrectomy with no additional therapy. With mean follow-up of 5 years, all eight children are alive. Seven are continuously disease free; one developed a metachronous bilateral tumor and was treated successfully (53,54). In NWTs-5, 75 children younger than 2 years and with stage I FH tumors weighing less than 550 g were enrolled in a prospective study and treated with nephrectomy only. Eleven patients relapsed,

Table 13.37
SIOP 2001 Radiation Therapy Dosage (Total Dose/Dose per Fraction)

Hemiflank:
Intermediate risk: 14.1/1.8 Gy $\pm$ boost: 10.8/1.8 Gy
High risk, II and III: 25.2/1.8 Gy
Whole abdomen: 14.4 Gy up to a maximum of 21 Gy
Dosage/fraction 1.25–1.5 Gy
Children, <1 year: 10–12 Gy total
Lungs: 15.0/1.5 Gy, boost 5–10 Gy
Brain: 25.5/1.5 Gy, boost 4.5 Gy
Liver: 20.0/1.5 Gy

From *Nephroblastoma Clinical Protocol SIOP 2001*.

International Society of Pediatric Oncology, Zurich, 2001.

among them five had recurrent disease in lung, three in the operative bed, and three in the contralateral kidney. The 2-year disease-free and overall survival rates were 87% and 106%, respectively (93).

Surgical techniques in children with Wilms tumor can impact both the tumor stage and risk of local recurrence. In a surgical quality assessment (QA) review from the NWTs-5, among 1305 patients who underwent nephrectomy, 117 (9%) did not have lymph node sampling and tumor spillage occurred in 253 patients (19%). A total of 30 patients were deemed to have had unnecessary biopsies either preoperatively or intraoperatively leading to local tumor spillage. This report and an earlier one from NWTs-4 have clearly demonstrated that the absence of a lymph node biopsy and tumor spillage were both associated with a higher rate of abdominal relapse (87,94). A surgical QA program is presently in place in the COG to educate surgeons regarding the value of lymph node sampling and avoidance of procedures that result in tumor spillage.

Radiation Therapy

In 1950, Gross and Neuhauser of Boston Children's Hospital reported that 10 of 31 (32%) patients treated for Wilms tumor from 1931 to 1939 appeared to be cured of their tumors, compared with 18 of 38 (47%) cured when treated between 1940 and 1947. The authors suspected that the difference resulted from the radiotherapy administered to 36 of the 38 patients in the later period. It was customary to irradiate children in the immediate postoperative period (i.e., shortly after they left the operating room). Dosages of 200 R/day were given to a total dosage of 4000–5000 R (95).

At present approximately 70–75% of children with Wilms tumor are treated without radiation therapy. The number rises to 80–85% if metastatic disease is excluded. The NWTs and SIOP trials that have led to this restricted use of radiation therapy are described earlier in this chapter. When irradiation is used, it is successful in limiting the frequency of abdominal relapse to 0–4% of children with FH tumors (76).

Chemotherapy

In 1966, Sidney Farber reported improved results in the treatment of recurrent and metastatic Wilms tumor. His series included 16 patients with recurrent disease and 15 with metastatic disease at diagnosis. Patients were treated primarily with actinomycin D and, to a limited degree, vincristine. The 2-year survival rate was 58% (96).

The addition of effective chemotherapy has substantially improved the overall results in Wilms tumor in the past two decades. The NWTs and SIOP studies that have substantially established the indications for chemotherapy are discussed earlier in this chapter.

RADIOTHERAPEUTIC MANAGEMENT

The current guidelines for external beam radiation therapy in COG protocols are summarized in Table 13.15. Indications for radiation therapy in the current SIOP 2001 trial are summarized in Tables 13.34–13.37.

The timing of postoperative irradiation is important. Delayed initiation of treatment beyond 10 days after surgery has been related to higher risk of abdominal recurrence in several, but not all, studies (38,39,57,74–76). Most relapses

related to delayed start of therapy have been in patients with UH. A recent analysis (NWTs-3 and NWTs-4) looked at the influence of delay of radiation therapy on outcome in Wilms tumor in patients with stages II–IV FH tumors. The mean delay in radiotherapy was 10.9 days from surgery, and the median was 9 days; 59% of children were treated 8–12 days postoperatively. For children who were treated 0–9 days postoperatively and those treated at least 10 days postoperatively, there was no difference in the rate of flank or abdominal recurrence. In NWTs-1 and NWTs-2, 80% of children were treated with radiotherapy during week 1, whereas in NWTs-3 and NWTs-4, 24% of children were treated in week 1 but 66% were treated with radiotherapy in week 2 (97). NWTs-5 recommended that postoperative irradiation begins no later than the ninth postoperative day. In the COG protocols, it is recommended that radiation therapy be initiated by day 9 if possible, but no later than day 14 after nephrectomy.

Volume

The irradiation volumes for the flank, whole-abdomen, and whole-lung fields are identical in NWTs, SIOP, and COG protocols.

Local-regional irradiation treatment fields include the tumor bed, importantly differentiated from the renal bed to include the entire preoperative tumor extent in the abdomen. The tumor bed is defined as the outline of the kidney and any associated tumor. The tumor volume is established by careful review of the surgical findings, IVP, CT, ultrasound, or MRI. The superior margin of the field is placed at the upper pole of the kidney, with an additional 1-cm margin in a child with a lower pole neoplasm, and the inferior portal margin encompasses the lower margin of the tumor with a 1-cm margin. The field should extend to the dome of the diaphragm only in patients in whom the tumor is known to have extended that far superiorly. A variable proportion of the liver is necessarily included to adequately encompass the initial tumor extent for right-sided lesions. Medially, the target volume should encompass the entire width of the vertebral bodies, with adequate contralateral extension to include the entire para-aortic lymph node chain but exclude the remaining kidney. The choice of the medial margin reflects the importance of lymph node radiation therapy. In addition, homogeneous irradiation of the vertebral bodies avoids one mechanism of late scoliosis by equally affecting growth on each side of the vertebral body. Laterally, the treatment field tangentially includes the abdominal wall. Parallel-opposed anterior and posterior fields are used (Fig. 13.11).

For patients with preoperative intraperitoneal tumor rupture, intraoperative rupture with diffuse dissemination of tumor, diffuse peritoneal implants, or massive abdominal disease, irradiation must address the entire abdominal cavity. The target volume includes all of the peritoneal surfaces, defined superiorly by the diaphragms and inferiorly through the lower pelvic region, generally at the bottom of the obturator foramen. The acetabulum and femoral heads are blocked (Fig. 13.12). Attempts to limit irradiation by blocking the contralateral pelvic region of the peritoneal cavity have been associated with abdominal recurrence when abdominal irradiation was appropriate (98).

WLI must be administered carefully to encompass both apices and the posterior inferior extent of the lungs. The average field extends above the clavicles and approximately down to T12-L1. The shoulders are excluded from the field

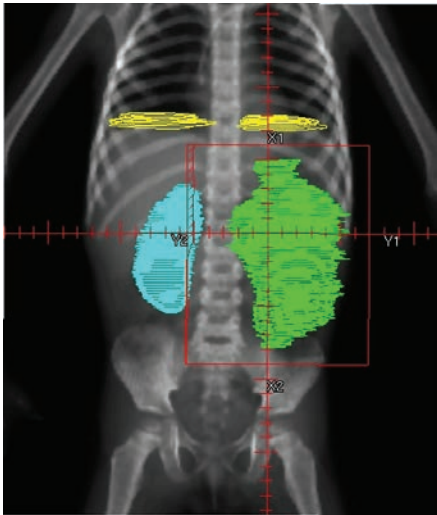


Figure 13.11 Flank radiation therapy field for a left-sided Wilms tumor. The gross tumor volume (GTV) based on preoperative CT scan is shown in green. The right kidney (blue) and the diaphragm (yellow) are also shown.

by blocks. Care should be taken not to irradiate the uninvolved kidney in the whole-lung field (Fig. 13.13).

When clinical situations call for WLI plus flank irradiation as in abdominal stage III patients with lung metastases, it is preferred that patients be treated with one large field, reducing off the flank at 10.5 Gy and then continue with WLI to 12 Gy. If these fields are treated separately, field matching with appropriate gaps and feathering are important in avoiding excessive liver irradiation in right-sided disease and avoiding irradiation of the remaining kidney in left-sided tumors.

Dosage for Abdominal Disease

As stated earlier, the first two NWTs trials incorporated an age-dependent scale of dosages ranging from 18 to 40 Gy and

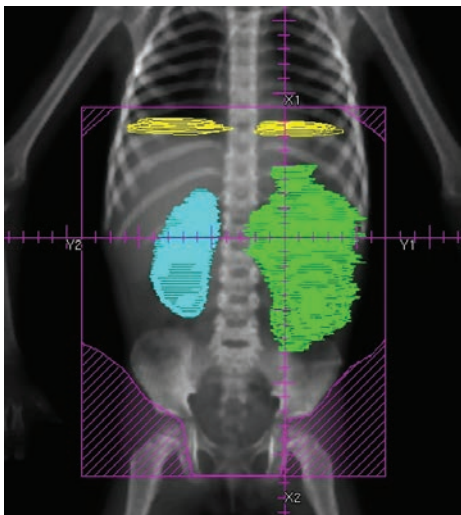


Figure 13.12 Whole-abdomen radiation therapy field for a left-sided Wilms tumor (green). The field encompasses the entire peritoneal cavity extending from the dome of the diaphragm to the pelvic floor. The right kidney (blue) and diaphragm (yellow) are also shown.

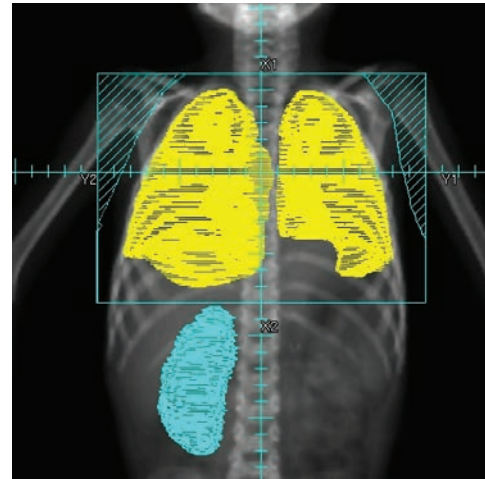


Figure 13.13 Whole-lung radiation therapy field for stage IV Wilms tumor after left radical nephrectomy. The total lung volumes (yellow) and right kidney (blue) are shown.

the results showed no apparent dose–response relationship, with equal frequency of abdominal recurrence at dosage levels of 18–20 Gy, 20–24 Gy, and 24–40 Gy (38,74). The NWTs-3 trial has established that doses of 10 Gy are adequate with three-drug chemotherapy and this has been adopted in subsequent NWTs and COG protocols (39). In patients with residual disease (>3 cm), a boost (10.8 Gy) dose may be given for a cumulative tumor dose of 21.6 Gy. In recent SIOP trials, local-regional radiation therapy is given to patients who, after preoperative chemotherapy and nephrectomy, are found to have stage II high-risk tumors or stage III. These categories comprise approximately no more than 25% of patients. The dosage to the tumor bed is 14.4–25.2 Gy, with an optional boost to localized areas of tumor as needed (Tables 13.34–13.40 (65)).

Bilateral Wilms Tumor

Stage V or bilateral Wilms tumor is found in 4–8% of patients (10,11,40). The 2-, 5-, and 10-year survival rates are 83%, 73%, and 70%, respectively (10,40,100). The majority of bilateral cases present with simultaneous or synchronous involvement in both kidneys. UH is found in 10%, and discordant histology (i.e., UH on one side and FH on the other) is found in some patients (10). UH, older age at diagnosis, and the most advanced stage of the individual tumors are the most important prognostic factors (10,40,100).

Table 13.38
Long-Term Complications of Renal Function

Dosage (Gy)	Impaired Creatinine Clearance (%)
<12	19
12–24	32
>24	73

From Egeler RM, Wolff JE, Anderson RA, et al. Long-term complications and post-treatment follow-up of patients with Wilms' tumor. *Semin Urol Oncol*. 1999;17:55–61.

Table 13.39
Long-Term Complications of Cardiac Function (99)

Treatment	Congestive Heart Failure at 15 Years (%)
Doxorubicin	1.7
No whole-lung irradiation	1.0
Whole-lung irradiation	5.4

The goal of therapy is cure with preservation of renal function. Radical nephrectomy should almost never be performed as part of the initial surgical procedure. Rather, the initial operation defines the extent of tumor in each kidney, obtains bilateral biopsies to histologically confirm the diagnosis, and biopsies suspicious lymph nodes. Subsequently, the child should be treated with chemotherapy tailored to the worst histology (favorable or unfavorable) and the stage of the primary tumors (i.e., more aggressive chemotherapy if one of the tumors is intra-abdominal stage III, less aggressive if both tumors are stage I). After this initial chemotherapy, the child is returned to the operating room for second-look surgery. If the tumor can be removed with preservation of renal function, it should. If surgery successfully removes the tumors and there is no gross or pathologic evidence of persistent or residual disease, chemotherapy is continued appropriate to the surgical stage. If there is gross or microscopic residual intra-abdominal tumor after second-look surgery, the patient is switched to alternative chemotherapy. If abnormalities persist in the kidneys on repeat imaging, a third operation may be attempted to finally excise the tumors (10,40,100–103). In NWTs-2 and NWTs-3, complete excision of all gross disease was possible in only 38% of patients following one or more operations. Among them the 34 patients who received only dactinomycin and vincristine had a 100% 3-year survival. They found no statistical difference in outcome between patients undergoing an initial definitive surgery (complete or partial nephrectomy) or biopsy alone at diagnosis (10). In NWTs-4, complete removal of all gross tumor was successful in 118 of 134 (88%) kidneys following renal parenchymal sparing surgery (either partial nephrectomy or enucleation), but local recurrence of tumor occurred in 8% of the remaining kidneys (100,101). Despite these results, the outcomes of children with BWT are not as good as for children with unilateral tumors at diagnosis. In the SIOP protocols, the 10-year overall

survival for synchronous bilateral Wilms tumors treated with preoperative chemotherapy/radiation was 69% (103). Unpublished NWTs-3 and -4 data showed a 10-year relapse-free and overall survival rates of only 65% and 78%, respectively. This was significantly inferior to outcomes for stages I–IV unilateral FH tumors with a relapse-free survival and overall survival rates of 86% and 92%, respectively. Among 158 patients in NWTs-5 with bilateral disease, the 4-year relapse-free and overall survival rates were only 61% and 80%, respectively. The factors that could have contributed to the poor outcomes were: understaging and/or undertreatment, delay in local disease control with definitive surgical resection, and increased incidence of anaplasia. The size of these tumors often precludes access to the hilar area and great vessels to examine lymph nodes. Failure to sample lymph nodes too can lead to understaging and an increased risk for abdominal recurrence, presumably due to undertreatment (87). Delayed definitive surgical resection of the tumor is an important cause of poor outcomes in these patients. In NWTs-4, 38 had clinically progressive or nonresponsive disease. Ten of these lacked pathology review. Of the remaining 28 patients, 15 had rhabdomyomatous differentiation, complete necrosis, or stromal differentiation. These patients would not have required prolonged/intensive courses of chemotherapy with delays in definitive surgery. These 38 patients actually received a median of 7 months of chemotherapy prior to definitive surgery with a range of 2–29 months (104). Anaplastic Wilms tumors are present in about 10% of bilateral Wilms tumors and carry the same adverse prognosis as in unilateral tumors. Although there are several advantages to the initial use of percutaneous needle core biopsies, it was inadequate for identifying anaplasia. In a report from the NWTs, anaplasia was identified in zero of seven tumors by core needle biopsy, three of nine tumors by open biopsy, and in seven of nine patients by partial or complete nephrectomy. The mean duration of first chemotherapy in each of these three groups, respectively, was 20, 39, and 36 weeks, respectively. Early incisional biopsy or tumor resection no later than 6–12 weeks after initiation of chemotherapy was recommended in order to identify anaplastic histology and limit the duration of ineffective chemotherapy (105). Future COG protocols like AREN0534 are aiming for earlier biopsies or resection of tumors that are not responding to therapy in the hope of avoiding prolonged ineffective therapies for patients with diffuse anaplasia. The study aims to intensify chemotherapy upfront (three drugs), require second-look surgery at 6 weeks, definitive surgery at

Table 13.40
Pregnancy Outcome

Flank Dosage	Early or Threatened Labor	Malposition of Fetus	Gestation <36 weeks	Birth weight >2500 g
0	13%	3%	82%	11%
0.01–15 Gy	8%	8%	74%	16%
15.01–25 Gy	19%	3%	79%	13%
25.01–35 Gy	23%	19%	68%	26%
>35 Gy	29%	14%	68%	24%
p	0.03	0.007	0.0005	0.017

From Green DM, Peabody EM, Nan B, et al. Pregnancy outcome after treatment for Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol*. 2002;20:2506–2513.

12 weeks, and recommend chemotherapy based on histologic response after definitive surgery.

Some centers have advocated parenchymal sparing procedures in unilateral Wilms tumors to reduce the risk of renal insufficiency. However, the overall incidence of renal failure following treatment in unilateral tumors is only 0.25% (106). There are certain groups of children at higher risk for renal failure. Breslow et al. (107) reported a 38% risk of renal failure at a median of 14 years after diagnosis among certain subgroups like patients with WAGR and Denys-Drash syndromes. Other groups of children that could benefit from renal parenchymal sparing surgery are those at increased risk for development of metachronous Wilms tumor such as those with aniridia, and a number of overgrowth syndromes, for example, BWS and idiopathic hemihypertrophy (108,109).

Radiation therapy in stage V Wilms tumor is indicated when definitive surgery has been accomplished and one or both of the primary tumors are found to be stage III FH, stages I–III anaplastic tumors, CCSK, or RTK or when preoperative chemotherapy and one or two surgeries have not achieved successful extirpation of tumor with negative resection margins.

Metastatic Disease

The ability to control overt pulmonary metastasis was the major advance consequent to the addition of actinomycin D to irradiation in the management of Wilms tumor (47,49,50,96). In stage IV patients with pulmonary metastasis at diagnosis, conventional NWTs management begins with nephrectomy, postoperative chemotherapy, abdominal irradiation if appropriate, and WLI. The indications for infra-diaphragmatic irradiation are dictated by the degree of abdominal disease. For patients with pulmonary metastasis by chest radiograph at diagnosis, the addition of lung radiation therapy is standard (13,38,39,74). Although earlier reports documented excellent control at dosage levels of 16–18 Gy, the impressive results in recent series using dosages limited to 12 Gy at 1.5 Gy per fraction approach the control rates for abdominal disease with attenuated dosage levels (13,38,39,74). A boost to local sites of residual pulmonary nodules to cumulative levels of up to 20 Gy is appropriate if permitted by the lung volumes. Stage IV FH with lung metastases had an 80% 4-year survival rate on NWTs-3, whereas survival rate for those with stage IV UH was about 55% (39).

In the new SIOP protocol, stage IV disease is treated with preoperative chemotherapy. Nephrectomy is then performed. Radiation therapy is administered according to SIOP guidelines for intra-abdominal disease (discussed earlier in this chapter). WLI is reserved for those who do not have a complete pulmonary tumor response and are not rendered free of disease by metastasectomy.

Is WLI necessary in stage IV (pulmonary) Wilms tumor? In a UKCCSG study, patients with stage IV FH were spared WLI if they had complete resolution of pulmonary metastases after chemotherapy. Thirty-five of 39 patients were treated without WLI. The 6-year disease-free and overall survival rates were 50% and 65%, respectively (110). These results appear to be somewhat worse than the 4-year survival rate of 82% on NWTs-3, probably because of the inclusion of routine lung irradiation in the NWTs-3 (39). In the second UKCCSG Wilms tumor study (UKW2), the 4-year survival rate in these patients improved to 75%, probably owing to

the greater use of WLI (79). In an SIOP study, 36 patients with stage IV FH received chemotherapy, with abdominal irradiation given for stage III or node-positive stage II. Chemotherapy eradicated lung disease in 27 of 36 patients. Six additional patients were cleared of lung metastases with surgery. Only seven children ultimately received WLI: seven for recurrent tumor, one immediately after nephrectomy for inoperable multiple metastases, and two after complete tumor clearance by chemotherapy. Five-year actuarial disease-free survival rates was 83% (63,84,111). A recent UKCCSG report revealed that children with stage IV lung metastases on chest x-ray had a significantly worse outcome when treated with three drugs alone (doxorubicin dose of 360 mg/m²) without lung irradiation compared to those who received lung irradiation and lower dose of doxorubicin (300 mg/m²). The event-free survival rate was 53% versus 79%. However, there was no significant difference in overall survival (73% vs. 84%) (112).

Two recent reports have suggested that children with FH Wilms tumor and CT-only lung metastases registered on NWTs-4 and NWTs-5 have an inferior relapse-free survival when treated with one-drug or two-drug chemotherapy with or without lung irradiation compared to those who received doxorubicin. There were no additional benefits to lung irradiation when doxorubicin was added to two-drug chemotherapy (113,114). A report from the UKCCSG in patients with stage I tumors and CT-only pulmonary metastases showed a significantly higher pulmonary relapse rate (43%) after single-agent vincristine alone. The pulmonary relapse rate in similarly treated patients without CT lung lesions was 10% (115).

The value of a lung biopsy in patients with lung metastasis is not well established. Among 2498 patients registered on NWTs-5, 252 (10%) had pulmonary metastasis detected by chest x-ray (5%) and CT only in 5%. Among patients with CT-only lesions, 33% underwent a lung biopsy. The positive biopsy rate in patients with isolated and multiple lung lesions was 82% and 69%, respectively. Although this report did not conclusively address the issue regarding value of lung biopsies, it does point out that not all lung lesions on detected by CT only were metastasis. The authors recommended that in suspicious lesions on CT scans, a negative lung biopsy may obviate the need for unnecessary intensification of therapy with doxorubicin and/or WLI (116).

The value of WLI in CT-only but not chest x-ray lesions has also not been resolved. A report from St. Jude Children's Research Hospital suggested that patients with pulmonary metastases detectable only by CT scan have an increased risk of pulmonary recurrence following treatment with chemotherapy only (51). However, a retrospective review of the experience with similar patients treated on NWTs-3 and NWTs-4 did not demonstrate a clear benefit of WLI. The 4-year event-free survival rate was 89% for patients treated with chemotherapy only and 80% for those who received irradiation (117). In COG protocol, AREN0533 chemotherapy response at week 6 will be used to determine whether WLI is delivered or not. Patients who achieve a complete radiologic response to three-drug chemotherapy at week 6 will not receive lung irradiation. All patients with UH tumors will receive WLI regardless of whether they are detected by chest x-ray or CT scan (Table 13.15).

Liver metastases may be treated by hepatic irradiation in addition to chemotherapy. Whole-liver irradiation is sometimes given for diffuse disease, with supplementary boosts to

gross disease (38,39,44). When possible, however, more limited radiotherapy fields are used if the disease is more localized in the liver. In a report from NWTs-4 and -5, the relapse-free survival rate for 96 patients with FH tumors and liver metastases was 76%. Their survival rates were similar to that of patients with lung metastases (76%), liver and lung metastases (70%), and metastases to other sites (64%). Twenty-two patients had a primary liver resection and 13 underwent resection after chemotherapy/irradiation. Eighty-two patients received abdominal radiation (118).

Recurrent Wilms tumor

A large body of evidence from the NWTs, UKCCSG, and SIOP trials has been gathered concerning the important prognostic factors after relapse of Wilms tumor (119–122). The major prognostic factors are: site of recurrence, initial stage of disease, tumor histology, time to relapse from initial therapy, and nature of prior therapy (two drugs vs. three drugs $\pm$ RT). In NWTs-2 and NWTs-3, the 3-year postrelapse survival rate was 57% for initial stage I, 36% for initial stage II and III, and 17% for initial stage IV (120). The survival after relapse of patients with FH is two to four times greater than that of patients with UH (119–122). The 3-year postrelapse survival for patients in NWTs-2 and NWTs-3 who relapsed 0–5 months after diagnosis was 18%, 6–11 months after diagnosis was 30%, and 12 months or more after diagnosis was 41% (120). Patients who relapse after initial therapy that included adriamycin or abdominal irradiation fare worse than those who did not receive such therapy. Presumably this is because the use of adriamycin or radiotherapy is a surrogate marker for initially more advanced disease and because tumor that recurs after such therapy may represent more resistant disease (119–122). In NWTs-3, the 3-year postrelapse survival for patients with recurrent Wilms tumor after initial therapy that included radiation therapy was 15%. Among those treated initially with surgery and chemotherapy only, the 3-year postrelapse survival rate is 77% after retreatment (120). The lung is a common site of recurrence of Wilms tumor. Relapse confined to the lung has a 44% 3-year postrelapse survival. Relapse in the liver portends a worse prognosis with a 4-year survival rate of 14% (120). There are some survivors of solitary metastases to brain or liver (119–123). Patients who had relapsed or progressive disease after initial chemotherapy with vincristine and actinomycin D and no radiation therapy were treated on stratum “B” of the NWTs-5 relapse protocol. The relapse treatment included chemotherapy with regimen “I” with alternating courses of vincristine, doxorubicin, cyclophosphamide and etoposide/cyclophosphamide, surgery, and radiation therapy. The 4-year event-free and overall survival rates were 71% and 81% for all patients, 68% and 81% for those who relapsed in the lung only, and 78% and 83% for those who relapsed in the operative bed with or without lung metastasis (124). Patients who had relapsed or progressive disease after initial chemotherapy including vincristine, actinomycin, and doxorubicin and radiation therapy were treated on stratum “C” of the NWTs-5 relapse protocol. The relapse treatment included alternating courses of drug pairs: cyclophosphamide/etoposide and carboplatin/etoposide, surgery, and radiation therapy. The 4-year event-free and overall survival rates were 42% and 48% for all patients and 49% and 53% for those who relapsed in the lung only (125).

See Table 13.15 for COG radiation therapy guidelines for relapsed Wilms tumor patients.

Renal Tumors in Very Young Children

Renal tumors diagnosed in the first 7 months of life generally have an excellent prognosis though histology is an important factor. A collaborative study by the North American and European Wilms tumor study groups revealed that 7% of 10,430 registered patients were diagnosed with a renal tumor before 213 days of age. The tumor types were Wilms tumor (58%), congenital mesoblastic nephroma (18%), malignant RTK (8%), CCSK (2%), non-Wilms tumor (6%), and unknown histology (9%). Although Wilms tumor is the most common renal tumor in these children, congenital mesoblastic nephroma is a common entity especially in the first 2 months of life. For all patients, the 5-year event-free and overall survival rates were 80% and 86%, respectively. The 5-year overall survival rates for Wilms tumor, CMN, CCSK, and RTK were 93%, 96%, 51%, and 16%, respectively (126).

TOXICITIES

The late effects of treatment of childhood cancer and the causes and frequency of treatment-induced second malignant neoplasms (SMNs) are considered in detail in Chapters 19 and 20. In this section, we will review the late ill effects, including induced neoplasms, particularly associated with the treatment of Wilms tumor.

Hematologic Toxicity

Review of the data from NWTs-3 indicates clinically significant acute hematologic toxicities. Fatal toxicities occur in a small proportion of patients. Depending on the drugs given, severe hematologic toxicity occurs in 6–64% of patients over a 6-week course of treatment. Toxicity and infections account for 15% of the deaths of NWTs children, producing a 1% treatment-related mortality rate (77,78).

Hepatic Effects

Hepatotoxicity from Wilms tumor therapy may be indicated by an increase in transaminases or by hyperbilirubinemia. Veno-occlusive disease consists of the clinical triad of hepatomegaly, ascites, and icterus. In unirradiated NWTs-4 patients, the frequency of hepatic toxicity related to actinomycin D (serum glutamic–oxaloacetic transaminase, serum glutamic–pyruvic transaminase elevations) rose from 2.8% in patients receiving 15 mg/kg of standard divided-dose therapy to 3.7% in those receiving PI 45 mg/kg and 14.3% in those receiving 60 mg/kg PI therapy. These data prompted replacement of the 60-mg/kg treatment with the 45-mg/kg dosage (127). A review of cases accrued via the German Pediatric Oncology Hematology Group to SIOP trial 9 studied 58 patients who received chemotherapy and abdominal irradiation. Eleven of these 58 patients developed signs of hepatotoxicity, four of them with veno-occlusive disease. There was a predominance of children with right-sided tumors in the group with hepatic injury (9 out of 33, 27%, vs. 2 out of 24, 8%) (128). In a report from the NWTs-1 to NWTs-4, a case–control study was conducted to determine relationships among doxorubicin, liver radiation dose, patient gender, and the development of portal hypertension. The 6-year cumulative risk for portal hypertension was 0.7% for right-sided tumors versus 0.1% for those with left-sided tumors ($p = 0.002$). There was a significant association

between minimum and maximum liver dose (>15 Gy) and portal hypertension. Doxorubicin and gender were not significant (129).

Orthopedic Effects

In long-term follow-up studies of Wilms tumor survivors, scoliosis and musculoskeletal abnormalities are more common in irradiated patients than in those not irradiated. This may result from asymmetric irradiation of the vertebral bodies or the paraspinal musculature. Rate et al. (130) identified 31 children with Wilms tumor who received abdominal irradiation between 1970 and 1984 and were followed past skeletal maturity. Ten of the children were irradiated with orthovoltage and 21 with megavoltage. Of the children irradiated with megavoltage, the most common orthopedic abnormalities were lower rib hypoplasia (57%) and mild scoliosis (10–20 degrees) (48%). In the patients irradiated with orthovoltage, lower rib hypoplasia occurred in 50%, mild scoliosis in 40%, severe scoliosis (more than 20 degrees) in 40%, and limb length inequality in 20% (130,131). Scoliosis as a late ill effect of abdominal irradiation for Wilms tumor was confirmed by a report from the University of Helsinki in which 21 of 24 patients (88%) had some degree of scoliosis. Most patients had been irradiated with cobalt-60 (132,133).

Renal Effects

After unilateral nephrectomy in childhood, the remaining kidney generally adjusts its function and size; this is called compensatory hypertrophy of the kidney. One year after nephrectomy for Wilms tumor, the glomerular filtration rate (GFR) and effective renal plasma flow are approximately 90% of normal values for age-matched children with two normal kidneys. Children treated with surgery and chemotherapy also have close to normal values. The addition of radiation to chemotherapy results in a diminished renal function to approximately 73% of normal GFR (Table 13.38) (128,134). In a report from the NWTs, the 20-year cumulative risk of renal failure for children with unilateral tumors without congenital abnormalities, bilateral Wilms tumor, male GU anomalies, Denys-Drash syndrome, and WAGR syndrome was $<1\%$, 5.5%, 10.9%, 62%, and 38%, respectively. It was recommended that patients with aniridia and GU abnormalities be carefully monitored throughout life for signs of nephropathy or renal failure (107).

Cardiac Effects

Cardiac injury in long-term survivors is associated with the use of doxorubicin or the cardiac irradiation that occurs during WLI. The 20-year cumulative frequency of congestive heart failure among patients treated on NWTs-1 to NWTs-4 was 4.4% for patients treated initially with doxorubicin and 17.4% for those treated with doxorubicin for relapse. The relative risk of congestive heart failure was significantly increased in females, cumulative doxorubicin dose, lung irradiation, and left-sided abdominal irradiation (Table 13.39) (99).

Pregnancy Outcome

There is now long-term follow-up on pregnancy outcome in irradiated women who were treated, as children, for Wilms tumor. As Table 13.40 indicates, the risk of early or threat-

ened labor, malposition of the fetus, short gestation, or low birth weight appears directly correlated with the irradiation dosage. The outcome also appears worse for those treated with abdominal–pelvic fields and those treated with higher irradiation dosages (135,136).

Treatment-Induced Neoplasms

Initial reports concerning the risk of SMNs after treatment of Wilms tumor indicated that the cumulative incidence 10 years after diagnosis was 1% (137,138). In an NWTs report, the 15-year cumulative risk of SMN was 1.6% since Wilms tumor diagnosis. The risk of developing a lymphoma or leukemia was 0.4% at 8 years after which no cases occurred. However, the risk of developing a solid tumor continued to rise sharply with time. Approximately 73% of solid tumors arose within a previous irradiated field. Higher abdominal radiation dose, doxorubicin use, and treatment for relapse were the significant factors correlated with the development of second tumors (139). Long-term follow-up indicates that there is a risk of acute myelocytic leukemia in long-term survivors of Wilms tumor. This may be related to the administration of alkylating agents and abdominal irradiation (140). In another NWTs report on the rates and causes of mortality in WT patients, the standardized mortality ratio (SMR) was 24.3 within 5 years of diagnosis, 12.6 for the next 5 years, and >3.0 thereafter. The main cause of mortality within the first 5 years was original disease (91%). However, beyond 5 years the two important causes of mortality were original disease (40%) and late effects of treatment (39%). The three common treatment-related late effects that contributed to mortality were SMNs, congestive heart failure, and end-stage renal disease. The risk of death particularly from treatment-related late effects remained elevated even 20 years after diagnosis (141). In the British Cancer Survivor Study, the cumulative incidence of a second primary neoplasm at 30, 40, and 50 years of age was 2%, 7%, and 12%, respectively. Thirty-five of 39 solid neoplasms that developed in the thoracic, abdominal, or pelvic regions occurred within irradiated tissue. Higher doses of radiation therapy delivered to the abdomen and pelvis was an important reason for the development of secondary tumors (142).

Growth Abnormalities

Abdominal irradiation can also produce significant reduction in sitting height and a more modest decrease in standing height. These effects are more pronounced the younger the

Table 13.41
Predicted Deficit in Height at Age 18 Years After Flank Irradiation at Selected Ages and Dosages

Age at Treatment (years)	Height Deficit (cm) After a Dosage of		
	10 Gy	20 Gy	30 Gy
2	2.4	4.8	7.2
4	1.8	3.5	5.3
6	1.2	2.4	3.6
8	0.8	1.5	2.3

From Hogeboom CJ, Grosser SC, Guthrie KA, et al. Stature loss following treatment for Wilms' tumor. *Med Pediatr Oncol*. 2001;36:295–304.

patient is at the time of radiotherapy (133,136). Long-term analysis of predicted height deficits in children who receive flank radiation for Wilms tumor indicates, as shown in Table 13.41, that the younger a child is at the time of flank irradiation, the greater the predicted height deficit. Furthermore, the higher dosage of irradiation administered, the greater the predicted height deficit. These effects are related to irradiation of the thoracolumbar vertebral bodies. Abnormalities can also ensue from asymmetric irradiation of the paravertebral musculature, which may, over time, lead to a risk of scoliosis.

FUTURE DEVELOPMENTS

In the future, we may begin to assess the risk of local and distant recurrence of Wilms tumor and select appropriate therapy based on a variety of molecular biologic and related markers. These include assessments of the LOH of certain chromosomes. One may also measure vascular density and telomerase activity. The evolving field of proteomics may offer us the opportunity, via initial protein profile and changes in protein profile during the course of therapy, to assess prognosis and therapy. Interstitial PO₂ measurements and noninvasive oxygenation status assessments may prove of value in assessing tumors at risk for local failure and distant metastases. Quantitative positron emission tomography and single-photon emission CT may also be of use.

In the future, we also hope to answer some of the remaining clinical radiotherapy research questions. These include the establishment of the dose–response relationship for the treatment of anaplastic Wilms tumor and the assessment of the appropriate role of radiotherapy for stage II disease after tumor spill and the role of WLI in children with FH tumors. The role of technological advances in radiation therapy such as intensity modulated radiation therapy (IMRT) and proton therapy in primary and recurrent Wilms tumor remains to be defined.

In spite of the tremendous progress that has been made in the management of Wilms tumor, a significant amount of clinical and basic research continues in order to further optimize therapy in this disease. The future risk stratification of Wilms tumors in addition to tumor histology, age, tumor weight, tumor stage, LOH status, and tumor response rate will likely include gene expression profiles. The COG biologic tumor samples bank continues to be an important resource for researchers throughout the world who are exploring novel laboratory research to better understand the biology of tumors with the ultimate hope of finding novel agents for improved and less toxic therapy. Some of the potential targets for future therapies include TP53, EGF-R, TGF- α , NCAM2, IGF1 and 2, N-myc, TrkB, C/EBP β , CRABP2, retinol-binding protein, FRAP/MTOR, CD40, topoisomerase II α , and stathmin 1 (143–148).

It is very important for all physicians involved in the care of children to promote the recruitment of childhood cancer survivors into long-term follow-up programs that are designed to provide education and specific surveillance guidelines for the early detection and prompt management of any potential treatment-induced sequelae. Such measures will go a long way in preventing or ameliorating the negative impacts of such sequelae on their quality of life. The COG long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers are updated annually and are available on the COG website (<http://www.suvivorshipguidelines.org>) (149).

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Liver Tumors in Children

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INTRODUCTION

Childhood primary tumors of the liver are rare. Of these, about two thirds are benign and one third malignant (1). The incidence varies from geographic region to region. According to the Surveillance, Epidemiology and End Results (SEER) data, between 1973 and 1977 and 1993 and 1997, hepatoblastoma rates increased (from 0.6 to 1.2/1,000,000), while hepatocellular carcinoma rates decreased (from 0.45 to 0.29/1,000,000) (2). The most common tumors according to histopathology are hepatoblastoma (HBL), hepatocellular carcinoma (HCC), benign vascular tumor, mesenchymal hamartoma, and sarcoma (Table 14.1) (1). Benign tumors are usually found incidentally as an asymptomatic abdominal mass. Malignant tumors usually present with abdominal distension with or without a palpable abdominal mass. Children with both HBL and HCC may also present with weight loss, fever, and anorexia. Anemia, thrombocytopenia, and leukocytosis are sometimes associated findings.

Complete surgical resection is the standard curative treatment for malignant tumors. Chemotherapy, radiotherapy, and local ablation treatment are adjunctive to surgery or palliative for incurable patients.

Computed tomography (CT) and magnetic resonance imaging (MRI) are the most definitive diagnostic tests and can often help to differentiate benign from malignant tumors preoperatively.

BENIGN TUMORS

Vascular Tumors

The most common benign lesions in children are hemangiomas and hemangioendotheliomas. Hemangiomas are the most common benign liver tumors and usually occur within the first 6 months of life (3). Most hemangiomas are incidentally discovered on imaging studies. Infantile hemangioendothelioma is a subtype of hemangioma that is typically found in infants. A female predilection is noted, with a female-to-male ratio of 4.3:1 to 2:1. Afflicted infants generally present with abdominal distension and cutaneous hemangiomas (10% of cases) that suggest the diagnosis. More than 50% of these infants have high-output cardiac failure at initial presentation (3). Classical triad of hepatomegaly, anemia, and congestive heart failure leads to the suspicion of infantile hemangioendothelioma. Kasabach–Merritt syndrome with consumptive coagulopathy, thrombocytopenia, and hemorrhage is the leading cause of morbidity and mortality seen in infantile hemangioendothelioma (4).

The natural history for hemangiomas is spontaneous regression in the first 2 years of life; however, treatment is required if cardiac failure or platelet consumption occurs. Several treatment options are available, including high-dose corticosteroids (3–5 mg/kg/day), interferon- α (3 million U/m²/kg/day SC), aminocaproic acid, vincristine, and cyclophosphamide, all are associated with potential severe side effects and poor outcome (5). Focal lesions can be treated with complete surgical excision. Selective hepatic artery embolization may not be as successful for multifocal as it is for focal lesions. Operative ligation of the hepatic artery can also be used to decrease shunting through the lesion, with subsequent improvement in cardiac output (6). Radiation therapy is usually avoided because angiosarcomatous degeneration may follow radiation. Rarely, liver transplantation may be indicated for diffuse disease that is unresponsive to steroid and interferon therapy.

Mesenchymal Hamartoma

Infantile mesenchymal hamartomas are rare benign tumors, comprising 6% of liver tumors in children (Table 14.1), and can be considered more of a malformation than true tumors. They tend to be diagnosed before the age of 2 years, more common in the right lobe of the liver. They usually present as an asymptomatic abdominal mass after a period of rapid growth during the first few months of life and cause compression of adjacent tissue but are curable by resection (7). Alpha-fetoprotein (AFP) levels may be variably elevated. CT scan

Table 14.1
Incidence of Primary Hepatic Tumors in Childhood

Tumor	Number of Patients	Percentage
Hepatoblastoma	532	43
Hepatocellular carcinoma	284	23
Benign vascular tumor	166	13
Mesenchymal hamartoma	75	6
Sarcoma	79	6
Adenoma	22	2
Focal nodular hyperplasia	22	2
Miscellaneous	57	5

Adapted from Weinberg AG, Finegold MJ. Primary hepatic tumors of childhood. *Hum Pathol.* 1983;14(6):512–537.

reveals a well-circumscribed, multilocular, heterogeneous, cystic mass with solid septa and stroma. Biopsy is recommended if cysts are small or appear more solid rather than septated. Complete surgical excision, with a rim of normal tissue (if possible), is the treatment of choice (8).

Focal Nodular Hyperplasia and Hepatic Adenomas

Focal nodular hyperplasia (FNH) and hepatic adenomas are rarely seen in children. Both of these benign lesions have an association with a high-estrogen environment and frequently occur in adolescent girls. Hepatic adenomas are associated with oral contraceptive use. Signs and symptoms may be absent or are nonspecific and include abdominal pain and mass symptoms. A characteristic central stellate scar on CT scan is pathognomonic for FNH. A triphasic helical CT scan is the optimal study to make the diagnosis of FNH. Differentiating FNH from adenomas may require a technetium sulfur colloid scan, which reveals uniform uptake by FNH lesions. Patient suspected of FNH should be managed conservatively. If a diagnosis remains unclear, a liver biopsy may be helpful. If the lesion becomes symptomatic or rapidly enlarging, complete surgical resection may be necessary to differentiate FNH from malignant tumors (8,9).

PRIMARY MALIGNANT LIVER TUMOR

Children with primary malignant liver tumors (PMLTs) often present with an abdominal mass or generalized abdominal enlargement. The child may have pain localized to the right upper quadrant, fever, anorexia, weight loss, jaundice, or vomiting. The first presentation may, on occasion, be an acute abdominal crisis caused by tumor rupture and hemoperitoneum. Paraneoplastic syndrome, such as precocious sexual development, has been associated with PMLTs (10). Anemia and thrombocytosis often occur. This is probably related to the ability of HBL cells to secrete gonadotropin, interleukin-1B, which induces IL-6 production in fibroblasts of endothelial cells (11,12).

Hepatoblastoma

HBL is the most common PMLT occurring in the first 20 years of life and accounts for 1% of all pediatric malignancies and about 60% of PMLTs in the pediatric age group (10,13,14). Median age at diagnosis is 16–19 months. Only 5% of the cases occur in children older than 4 years. As with all PMLTs, there is a male predominance (1,15). HBL has been reported to be associated with a host of conditions, including Beckwith–Wiedemann syndrome, Wilms tumor, adrenal cortical tumors, fetal alcohol syndrome, familial adenomatous polyposis (FAP), prematurity, low birth weight, precocious puberty in boys caused by human chorionic gonadotropin secretion, and thrombocytosis (11,14–18). The cell of origin is thought to be a pluripotent hepatic stem cell (19).

HBL may be histologically classified into six patterns (Table 14.2). Conventional HBLs contain fetal hepatoblasts, embryonal hepatoblasts, or a mixture of the two cell types (Figs. 14.1 and 14.2). Fetal-type hepatoblasts recapitulate the cytoarchitecture of the normal human fetal liver. Cells of the early fetal liver and the cells of fetal HBL are of similar size and configuration. Both proliferate as cuboidal cells with

Table 14.2

Histologic Classification of Hepatoblastoma

Conventional epithelial type (56%)	Mixed epithelial and mesenchymal type (44%)
Fetal pattern (31%)	Without teratoid features (34%)
Embryonal and fetal pattern (19%)	With teratoid features (10%)
Macrotrabecular pattern (3%)	
Small-cell undifferentiated pattern (3%)	

Modified from Jon M. Rowland. Hepatoblastoma: Assessment of criteria for histologic classification. *Med Pediatr Oncol.* 2002; 39(5):478–483.

trabeculae one- to two-cell thick. Both display strong positivity for AFP. Both tissues also display sinusoidal hematopoiesis and a lack of intrahepatic bile ducts (20). Fetal cells are slightly smaller than normal hepatocytes and have a low

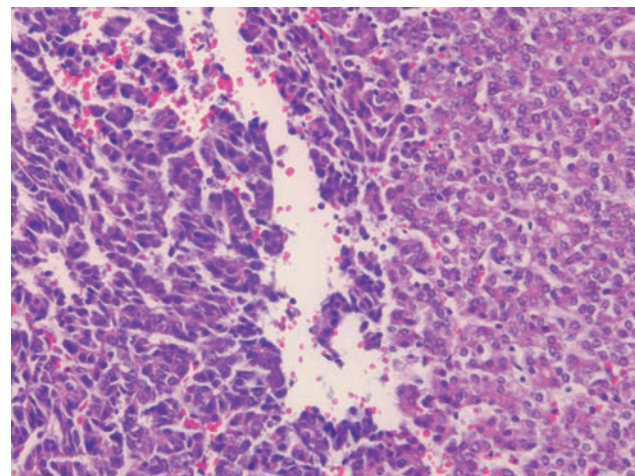


Figure 14.1 Hepatoblastoma, ×20 magnification. (Courtesy Dr John Buchino.)

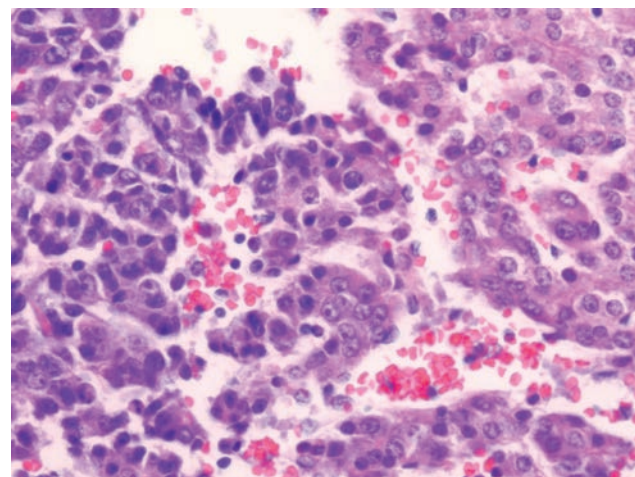


Figure 14.2 Hepatoblastoma, ×40 magnification. (Courtesy Dr John Buchino.)

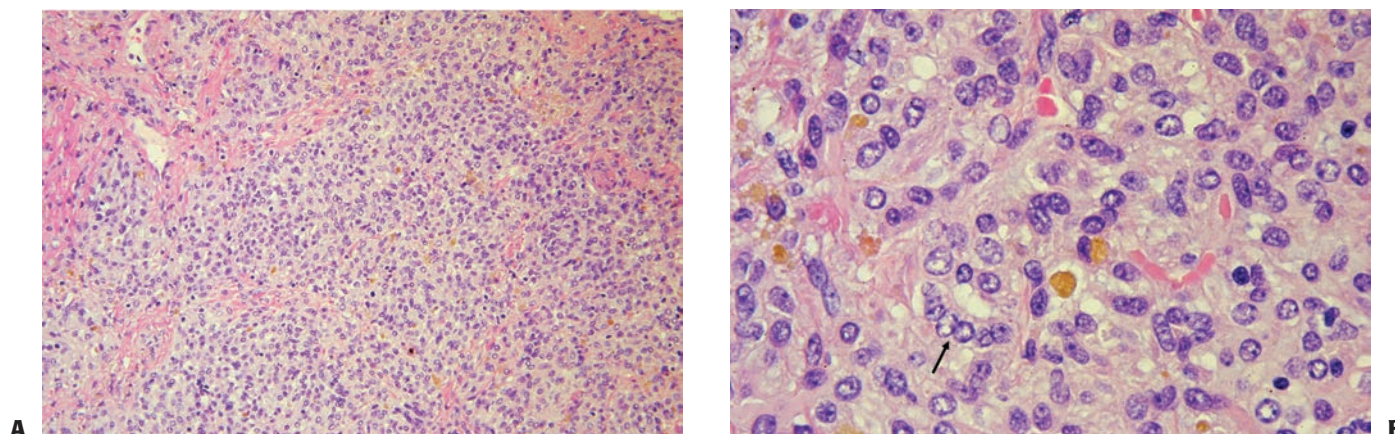


Figure 14.3 Hepatoblastoma. **A:** Fairly well-defined tumor cells arranged in a trabecular pattern and composed predominantly of cells with fetal hepatocyte differentiation pattern. There are trabeculae of cuboidal cells that contain small round nucleus with fine nuclear chromatin and an indistinct nucleolus. The cytoplasm varies from eosinophilic to clear and contains many pigment deposits (hematoxylin and eosin $\times 100$). **B:** A second population of small ovoid cells is arranged in clusters. These cells are of embryonal origin (arrow) (hematoxylin and eosin $\times 400$).

nucleocytoplasmic ratio. In contrast, embryonal hepatoblasts have a higher nucleocytoplasm ratio than do fetal cells, and they also have a compact basophilic cytoplasm (Fig. 14.3). This gives a light-microscopic impression of a higher cell density (1,21–23). Small-cell undifferentiated or anaplastic HBL contains sheets and nests of medium-sized cells, with little or no evidence of hepatoblastic differentiation. There is scant cytoplasm and a high mitotic index. Mixed epithelial and mesenchymal HBL is composed of typical areas of fetal epithelial and embryonal type cells mixed with primitive mesenchyme and various mesenchymally derived tissues (24).

It is unclear whether the recognized histologic subtypes are related to prognosis. The subtypes can occur together within the same tumor in varying composition (25). Some investigators report that in long-term survivors of HBL, the most common histology is the conventional type, with a predominantly fetal cell pattern (31). However, there is no uniformly accepted definition of “predominantly” or “pure” fetal histology (26). Although conventional epithelial tumors constitute 60% of all HBLs, they represent 85% of HBLs in children who have undergone complete tumor resection and are long-term survivors (1,22). Almost no children with anaplastic HBL survive the disease. A Pediatric Oncology Group (POG)–Children’s Cancer Study Group (CCSG) trial showed the distinction between fetal HBL and other histologic subtypes to be of prognostic importance in stage I disease (3-year progression-free survival of 79% vs. 56%, $p = 0.11$) (27). However, not all investigators have confirmed the prognostic importance of histologic subtypes in all stages (21). For example, a large analysis the Japanese Study Group for Pediatric Liver Tumor (JPLT) found no significant influence of HBL histologic classification on outcome (28).

Hepatocellular Carcinoma

HCC, the second most common PMLT in children, accounts for about one fourth to one third of pediatric hepatic malignancies (10). HCC is unusual in children younger than 5 years. The median age of presentation for pediatric HCC is 10–12 years (10,29–31). Approximately 25% of cases in children are associated with cirrhosis (31). Causes that lead to cirrhosis include

biliary atresia, Fanconi anemia, glucose-6-phosphatase deficiency, and hereditary tyrosinemia. HCC has also been reported in association with hemihypertrophy, anomalies of the abdominal venous drainage system, and the use of oral contraceptives. HCC occurs in areas with a high prevalence of hepatitis B viral infection (32). The association of maternal HBsAg seropositivity in children with HCC may be up to 94% in endemic area (32), though the hepatitis B carrier status varies by geographic area. Molecular hybridization studies have shown that viral DNA is integrated into the DNA of cellular lines derived from human HCC and also into morphologically nonmalignant adjacent liver cells (10). Implementation of universal hepatitis B vaccination program starting in 1984 in Taiwan has led to a remarkable decreasing incidence of childhood HCC from 4.5 per 100,000 in 1981–1984 to 1.9 per 100,000 in 1990–1996, indicating the value of hepatitis B immunization as an effective means of controlling HCC (33).

There is a fibrolamellar (FL) histologic variant of HCC, which occurs in the noncirrhotic livers of older children. This variant is characterized by large polygonal neoplastic hepatocytes and lamellar bundles of collagen. Although patient numbers are small, some think that this tumor is associated with a higher frequency of resectability and a good probability of cure. However, others have failed to demonstrate a favorable outcome of the FL variant in children (8,10,16,21,34).

Undifferentiated Embryonal Sarcoma of the Liver

Undifferentiated embryonal sarcoma of the liver is the third most common liver malignancy in children and adolescents, comprising 9–13% of liver tumors. Most are diagnosed at the age of 5–10 years. It may be solid or cystic on imaging, frequently with central necrosis. Distinctive features are characteristic intracellular hyaline globules and marked anaplasia in a mesenchymal background (20).

Embryonal rhabdomyosarcoma arises from bile ducts and usually occurs in children younger than 5 years. It may share some common clinical and pathologic features with undifferentiated embryonal sarcoma of the liver. Clinically, undifferentiated embryonal sarcoma of the liver tends to occur

in older children, often arises in the right lobe of the liver, and does not present with jaundice or biliary obstruction, while bile duct rhabdomyosarcoma occurs more frequently in younger age (median 3.4 years), arises in hilar area, and presents with more jaundice than the former. Surgery alone may achieve local control for undifferentiated embryonal sarcoma of the liver, while surgery and radiotherapy are required for bile duct rhabdomyosarcoma. Chemotherapy regimens used to treat the former differ from those used to treat bile duct rhabdomyosarcoma (35).

DIAGNOSIS

If a hepatic or biliary tumor produces biliary obstruction, there may be elevations of serum hepatic enzymes or bilirubin (36,37). An abdominal ultrasound examination helps to establish the presence of a hepatic mass and differentiates cystic from solid lesions. Ultrasound permits evaluation of the adrenals and the kidneys, helps to exclude these organs as possible primary sites of tumor metastatic to the liver, and allows evaluation of the inferior vena cava for tumor thrombus. Color Doppler ultrasound may be performed to demonstrate the relationship of the tumor to hepatic vessels (38). The technetium-90m sulfur colloid scan is of some value in localizing the tumor to the liver and defining its boundaries. It is a sensitive test, but not specific. CT and MRI provide superior delineation of the mass and show evidence of multifocality (39). On nonenhanced CT, epithelial

HBL is a homogeneous low-attenuation mass. The mixed type is inhomogeneous. Calcifications can be present. Contrast enhancement of the periphery or septa may be seen. On MRI, the epithelial type is homogeneous and hypointense on T1 and hyperintense on T2. The mixed type may be more inhomogeneous and hypointense on T1 and T2, and hemorrhage will show high signal intensity on T1 and T2 (Fig. 14.4). On CT, HCC will show solitary or multiple masses. Calcification can occur. The tumor rim may show enhancement with contrast. On MRI, the T1 images may be isointense or hyperintense. On T2 images, a mosaic pattern (caused by necrosis, hemorrhage, septa, and fatty metaplasia) is common (29). The operating surgeon may request an angiogram to obtain information about the origin and distribution of the right and left hepatic arteries to provide additional information on the vascular supply of the tumor (10). Routine chest radiographs and thoracic CT scans are necessary because 10–20% of patients with HBL and 30% of patients with HCC have lung metastasis at the time of diagnosis (12,18,40,41). Positron emission tomography CT holds promise for better surgical outcomes and greater sensitivity for residual or relapsed disease (42).

A valuable test in evaluating PMLT is the serum AFP. The clinician should note that AFP, synthesized by the fetal liver, may be elevated in pregnant women. AFP levels are high in the normal newborn infant but drop rapidly by the age of 1 month. AFP should be barely detectable by the age of 2 years (18). Approximately two thirds of children with HBL and HCC have

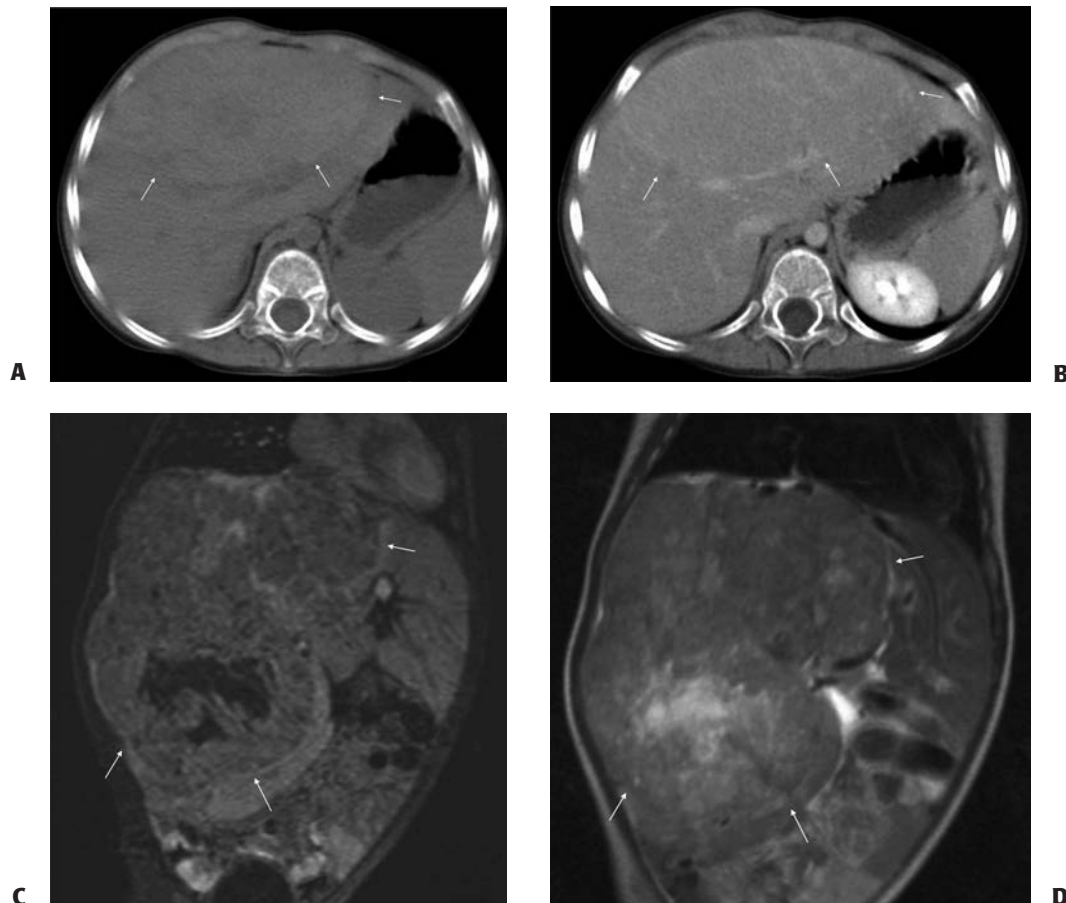


Figure 14.4 A–D: Hepatoblastoma is best visualized on cross-sectional imaging. It is homogeneous and hypointense on T1 and hyperintense on T2 on magnetic resonance images.

an elevated AFP (37). However, the clinician should be cautioned that AFP is not always elevated in HBL or HCC and that this protein may be slightly elevated in benign hamartomas. Absence of AFP elevation may be a poor prognostic sign in HBL; it is associated with the small-cell (anaplastic) histologic type and responds poorly to therapy. For patients with elevated AFP, it may be of value in monitoring the course of therapy (38). Complete resection of HBL or HCC should result in a normal AFP by 2 months postoperatively (17). No change in an elevated AFP after surgery indicates either residual tumor or regenerating normal liver. The diagnosis of growing tumor depends on confirmatory imaging studies. An elevation in the AFP during the follow-up period generally heralds a local tumor recurrence or distant metastasis (37).

Genetic abnormalities are found in HBL. Trisomies 2, 8, and 20 have been reported in tumor samples as well as t (1;4) (q12;34) translocation. The loss of heterozygosity of 11p15 is seen in about one third of cases (12). There is a clear association between HBL and familial adenomatous polyposis (FAP). Germline mutations in APC tumor suppressor gene occur in patients with FAP. One study estimated that 1 in 20 HBLs is probably associated with FAP (43). Increasing data support a role for aberrant transduction of the Wnt/beta-catenin signaling pathway and its molecular targets in HBL tumorigenesis (25,44,45). A study in a mouse model of HBLs induced by toxin exposure detected mutations of the beta-catenin proto-oncogene in 100% of the tumors analyzed (46). Increasing evidence suggests that HBL is derived from a pluripotent stem cell (19). This supports the hypothesis that such tumor may arise from a developmental error during hepatogenesis. Research particularly focused on these developmental processes governing liver maturation and growth may ultimately lead to more effective targeted therapy for this disease.

There are two major staging systems for PMLT, one is from CCSG and POG (Table 14.3), and the other is from 2002 The American Joint Committee on Cancer (AJCC) TNM staging system (Table 14.4) (48). All are based on resectability and, to a lesser extent, microscopic residual tumor (12,49). Figure 14.5 shows that the International Society of Pediatric Oncology Liver Tumor Study Group (SIOPEL) Pretreatment Extent of Disease (PRETEXT) grouping system divides the liver into four parts (40). The clinician must be wary of the pitfalls in the existing staging systems. There are at least two important drawbacks of some of the systems shown. First, the systems are applied at initial diagnosis. If upfront chemotherapy is given and if it produces a substantive tumor response before surgery, then the initial stage may no longer be pertinent. Second, a surgeon's determination of

Table 14.3
Children's Cancer Study Group and Pediatric Oncology Group Staging System for Primary Malignant Liver Tumors (10,12,38,47)

Stage	Description
I	Complete resection of the tumor
II	Microscopic residual disease
III	Macroscopic residual tumor
IV	Distant metastatic tumor

Table 14.4
TNM Staging System

Primary tumor (T)	AJCC TNM staging system		
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Solitary tumor without vascular invasion		
T2	Solitary tumor with vascular invasion or multiple tumors ≤ 5 cm		
T3	Multiple tumors > 5 cm or tumor involving a major branch of the portal or hepatic		
T4	Tumors with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IIIC	Any T	N1	M0
Stage IV	Any T	Any N	M1

From Greene F, Page D, Fleming I. *AJCC Cancer Staging Manual*. 6th ed. New York: Springer-Verlag; 2002, with permission.

resectability is somewhat subjective and varies among practitioners (50).

In the German HBL Study HB94, the following six factors predicted poor prognosis (51):

- Metastatic disease
- Initial AFP greater than 1×10^6 ng/mL
- Extrahepatic and intrahepatic vascular invasion
- Multifocal disease and involvement of both liver lobes
- Stage (tumor, node, metastasis [TNM])
- Poor epithelial differentiation

In the SIOPEL-1 study, only metastatic disease and involvement of all four sectors of the liver predicted poor outcome (25,52,53).

SELECTION OF THERAPY

Surgery

Localized HBL or HCC is curable with complete surgical excision of the tumor. It is also possible to achieve a cure with a near-complete excision in conjunction with adjuvant therapy that is able to further eliminate residual tumor. Tumor resectability is determined by tumor size, the existence of bilobar involvement necessitating resection of more than three liver segments, vascular invasion, or distant metastases (54).

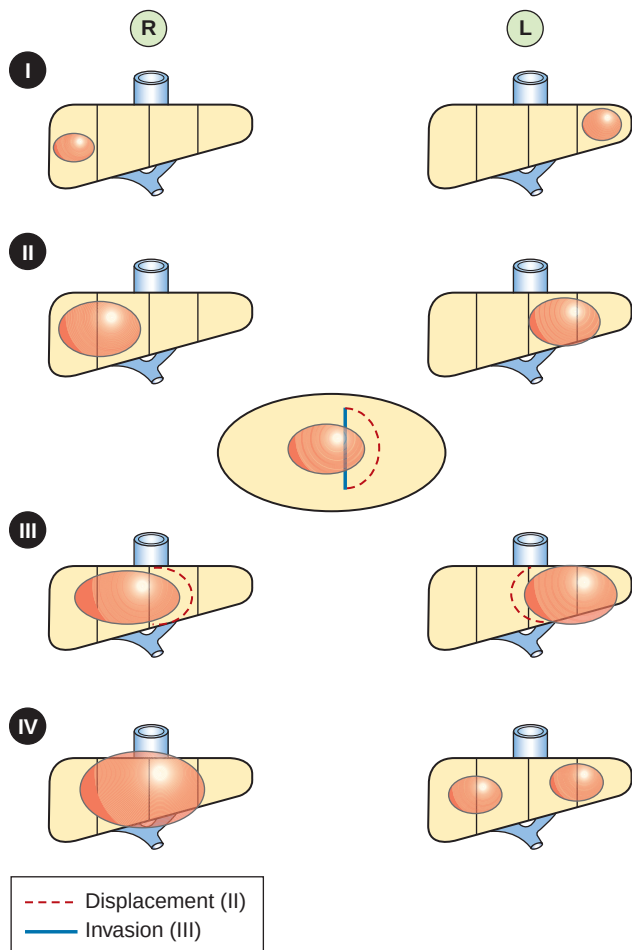


Figure 14.5 The International Society of Pediatric Oncology Liver Tumor Study Group Pretreatment Extent of Disease (PRETEXT) grouping system divides the liver into four parts called sectors. The left lobe of the liver (L) is divided into a lateral sector (segments 2 and 3) and a medial sector (segment 4), whereas the right lobe (R) is divided into an anterior sector (segments 5 and 8) and a posterior sector (segments 6 and 7). Tumors are classified into one of the four PRETEXT categories, depending on the number of liver sectors affected by the tumor. PRETEXT I, one sector involved; PRETEXT II, two sectors involved; PRETEXT III, two nonadjointing sectors free or three sectors involved; and PRETEXT IV, all four sectors involved. Extrahepatic growth is indicated by adding one or more of the following characters: V, hepatic/caval vein; P, portal vein; E, extrahepatic extension; and M, distant metastases. (From Schnater JM, Aronson DC, Plaschkes J, et al. Surgical view of the treatment of patients with hepatoblastoma: results from the first prospective trial of the International Society of Pediatric Oncology Liver Tumor Study Group (SIOPEL-1). *Cancer*. 2002;94(4):1111–1120, with permission.)

Some surgeons believe that therapy should begin with an attempt to resect rather than biopsy. One half to two thirds of patients with HBL have resectable tumors at presentation (54). After chemotherapy, the probability of resection rises to about 90% (55). Only 30–50% of the cases of HCC are amenable to complete resection at presentation because of multilobar involvement or massive tumor size (56).

Many cases are managed with preoperative chemotherapy. Therefore, the surgeon must first deal with the question of whether to perform a biopsy before chemotherapy is

administered in order to histologically confirm the presence of PMLT or accept the diagnosis based on a characteristic clinical presentation, supportive diagnostic imaging, and an elevated AFP (1). When chemotherapy is initiated without a histologic diagnosis, there is about a 4% risk that the patient may not have HBL or HCC. Errors in diagnosis include hemangioendothelioma, angiosarcoma, neuroblastoma, and germ cell tumor (26). Most clinicians prefer to have a histologic diagnosis before treatments are initiated. The classic way to obtain tissue is via an open-wedge biopsy. Some controversy exists over the use of CT or ultrasound-directed needle biopsy as an alternative to the wedge biopsy. Some are concerned that a needle biopsy will cause a significant hemorrhage by disruption of a highly friable PMLT. The International Society of Pediatric Oncology (SIOP) and others believe that the risk is minimal (31,40).

Broadly stated, there are two surgical strategies for treating HBL. The American Intergroup Studies favor primary surgery and adjuvant chemotherapy, except for clearly unresectable tumors. The SIOP prefers biopsy and defers definitive surgery until after preoperative chemotherapy (26). Preoperative chemotherapy reduces the tumor burden in the majority of HBL cases and in a significant number (49%) of patients with HCC (41,57). Many children with initially unresectable HBL may be rendered resectable by preoperative chemotherapy. Many surgeons also believe that PMLTs, after chemotherapy, are less friable and more often encapsulated. For patients who have tumors that are unresectable at presentation, chemotherapy is clearly indicated in an attempt to render the tumor resectable or for palliation. Radiotherapy may also succeed in rendering an unresectable tumor resectable if this goal cannot be achieved by chemotherapy (58).

When the patient comes to definitive surgery, an extensive abdominal incision allowing a large area of exposure is often performed (55). A simple tumorectomy with adequate margins is rarely possible. Rather, hepatic lobectomy or extended lobectomy is needed. Perioperative mortality was reported to be as high as 18–33% in the past (15,59) but is now in the order of 5–10% in specialized centers (56). Surgical complications include severe bleeding, bile leakage, pleural effusion, rupture of the inferior vena cava, cardiac arrest, convulsions, and subhepatic abscess (50). Improved surgical techniques such as vascular reconstruction, ultrasonic aspiration, and dissection under vascular exclusion and improvements in anesthesia, blood product replacement, and postoperative intensive care have produced the significant reduction in operative and perioperative mortality.

In stage IV disease, surgical resection of pulmonary metastases can be considered if they persist after preoperative chemotherapy and if the primary tumor has been rendered resectable by drug treatment (56). In patients with stage I disease at initial diagnosis that recurs with isolated pulmonary disease, surgical resection may result in extended survival. Feusner et al. reported six patients with pulmonary relapses of stage I HBL. Three had concurrent relapses in brain, bone, or abdomen and died of metastatic disease. Three of the six, having recurrence only in the lung, were long-term survivors (younger than 5 years) after metastasectomy and chemotherapy (60). Fuchs et al. also reported good results with aggressive excision of pulmonary metastases (52).

Liver transplantation has an increasing role in children with nonresectable tumors or in those who show chemotherapy

resistance. Otte reported the result of SIOPEL-1 (International Society of Pediatric Oncology), which showed overall survival (OS) at 10 years after liver transplantation to be 85% for the seven children who received a “primary liver transplantation” and 40% for the five children who underwent “rescue liver transplantation” after previous partial hepatectomy (61). They reviewed the world experience (147 cases), the overall survival rate at 6 year after liver transplantation was 82% for 106 patients who received a “primary liver transplantation” and 30% for 41 patients who underwent “rescue liver transplantation”. There is a trend for a better patient survival after living related liver transplantation (62–64). D’Antiga and Czauderna recommended early referral to a transplantation center for patients who had the following characteristics: older patients who had multifocal tumors, high PRETEXT scores (Fig. 14.5), involvement of major liver vessels, and AFP levels <100 ng/mL (53,65).

Chemotherapy

The most important advance in the care of children with HBL has been the discovery of effective preoperative adjuvant chemotherapy in improving surgical and overall outcomes. Cisplatin-based chemotherapy has been successful in the treatment of HBL with a survival rate >90% for children with stage I and II disease (41,57,66–68). Chemotherapy in some cases is able to eradicate pulmonary metastases completely and eliminate multinodular tumor foci in the liver (69).

Only four international groups—the Intergroup (USA/Canada), JPLT (Japan), GPOG (Germany/Austria), and the SIOPEL—were sufficiently large to set up independent studies (Table 14.5).

In 1972, Children’s Cancer Group (CCG) began the initial trial of therapy for hepatic tumors (CCG 831). Patient who had the tumor resected completely received no adjuvant chemotherapy. Children who had residual tumor in one hepatic lobe received sequential chemotherapy (actinomycin D, vincristine, and cyclophosphamide) plus involved-field irradiation. Patients with disseminated diseases received only chemotherapy. Of 40 patients entered in this trial, only 7 were long-term survivors, either with tumor resected completely or with minor residual tumor post-operation and then irradiated (72).

In 1976, CCG trial 881 added doxorubicin and 5-fluorouracil to the three drugs used in trial 831. Adjuvant chemotherapy was given to 24 patients who did not have measurable disease after surgery. Of these, 83% were disease-free survivors with a median follow-up of 30 months, whereas only 12 (44%) of 27 different patients with measurable

disease achieved a response with a median duration of 18 months (72).

CCG trial 823F used cisplatin and continuous-infusion doxorubicin in an attempt to reduce tumor size in children with unresectable or incompletely resected HBL or HCC to allow for subsequent surgery. Thirty-three children with HBL and 14 with HCC were entered in the study. Twenty-six HBL patients completed the initial four courses of chemotherapy, 25 achieved either complete or partial response, and 22 of them had second-look surgery. Of the 22, 16 had complete resections and 15 of them are alive without evidence of disease. In nine of the resected specimens, no viable tumor was identified. Of the 25 children who had a response to chemotherapy, 19 (78%) are alive and disease free. The estimated 2-year survival for the initial 33 patients with HBL is 67%. Children with HCC did not fare as well as those with HBL; however, of the 14 patients with HCC, 12 died of progressive disease and 2 remained free of disease. Only 14% of the HCC patients had complete tumor removal at second-look laparotomy (72).

The Pediatric Intergroup Hepatoma Study INT-0098 (CCG-8881/POG-8945) demonstrated comparable efficacy with cisplatin/vincristine/fluorouracil and cisplatin/doxorubicin in the treatment of HBL. Although equally effective in terms of overall and event-free survival (EFS; $p = 0.219$) (Table 14.6), the combination of cisplatin/vincristine/fluorouracil is significantly less toxic than that of cisplatin/doxorubicin. The results for stage I–III HBL are reasonably good. Patients with more advanced disease, however, do poorly (68,73,74). Replacement of cisplatin by carboplatin in the cisplatin/vincristine/doxorubicin regimen is associated with a decreased EFS (71). For patients with HCC, no differences were found between the two programs for either EFS ($p = 0.78$) or OS ($p = 0.80$). All seven stage I patients were event-free survivors (75,76). Five-year EFS rates for patients with stage I, III, and IV HBL were 91%, 64%, and 25%, respectively, compared with 88%, 8%, and 0% for patients with stage I, III, and IV HCC (76).

The German Cooperative Pediatric Liver Tumor Studies HB-89 and HB-94 treated 141 patients with HBL (Table 14.7). Forty-eight patients were primarily resected, and 14/48 (30%) had micro- or macroscopic residual tumor in the liver. Most (81/141) children were operated after an initial therapy with ifosfamide, cisplatin, and adriamycin. Only 15/78 (19%) cases were recognized as “incomplete resection” ($p < 0.044$). In cases of insufficient tumor response, high-dose cisplatin and adriamycin were added. With a median follow-up of 6 years, disease-free survival (DFS) is 98% for stage I, 55% for stage II, 63% for stage III, and 78% for stage IV. These results underline

Table 14.5
Multicenter Studies in Hepatoblastoma—Comparison of Results

Study	Number of Patients	Complete Resection Rate (%)	5-Year EFS (95% CI) (%)	5-Year Overall Survival (95% CI) (%)
SIOPEL-1 (57)	154	106 (77)	66 (59–74)	75 (68–82)
GPOG (HB-89) (70)	72	66 (92)	72 ^a	76 ^a
US Intergroup (INT-0098) (71)	182	n/a	57/69 ^b	69/72 ^b
JPLT-1 (Japanese) (28)	134	72 ^a	66 ^a	73 ^a

^aOverall CI not provided.

^bResults from regimen A (cisplatin, vincristine, and 5-FU) and regimen B (PLADO) provided separately. CI, confidence interval; GPOG, German Pediatric Oncology Group; n/a = not available.

Table 14.6
Results of the Pediatric Intergroup Hepatoma Study for Hepatoblastoma (CCG-8881 and POG-8945)

Stage	Cisplatin, Vincristine, 5-Fluorouracil			Cisplatin, Doxorubicin		
	Number of Patients	Survival (%)	Event-Free Survival (%)	Number of Patients	Survival (%)	Event-Free Survival (%)
I	22	95	85	22	95	95
II	4	100	100	3	100	100
III	43	70	62	39	65	61
IV	23	45	23	19	36	33

From Ortega JA, Douglass EC, Feusner JH, et al. Randomized comparison of cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric hepatoblastoma: a report from the Children's Cancer Group and the Pediatric Oncology Group. *J Clin Oncol.* 2000;18(14):2665–2675, with permission.

the necessity for preoperative chemotherapy in all HBL (50,52,70).

In POG-8697 (Table 14.7), 19 of 21 patients with stage I or II disease survived disease free at 5 years after five postoperative courses of cisplatin, vincristine, and 5-fluorouracil. Twenty-four of 31 patients with stage III disease achieved a Complete Response (CR) after chemotherapy and surgical excision; actuarial DFS at 4 years is 67% (Fig. 14.6). Those who remained unresectable received 33–39 Gy of local irradiation plus additional chemotherapy. Of the five irradiated patients, three became resectable, achieved a complete resection, and remained alive (47,66).

JPLT Protocol-1 enrolled 145 patients with HBL from 1991 to 1999 (Table 14.5). Preoperative and postoperative

cisplatin and tetrahydropyranyl–adriamycin were administered, and 134 patients were evaluable. The complete resection rates by stage were 89% for stage I, 100% for stage II, 84% for stage IIIA, 40% for stage IIIB, and 58% for stage IV. The 6-year survival rate was 100% for stage I, 96% for stage II, 74% for stage IIIA, 50% for stage IIIB, and 39% for stage IV (28).

In the SIOPEL-1 trial (Table 14.5), 138 patients with HBL received four to six courses of preoperative chemotherapy using platinum and doxorubicin every 3 weeks, followed by surgery. Tumor response, defined as “any tumor shrinkage associated with a serial decrease in serum AFP,” occurred in 82%. Five-year EFS was 66%, and OS was 75% (57).

Table 14.7
Summary of Recent Hepatoblastoma Cooperative Group Studies in Europe and North America

Study	Presurgical Chemotherapy	Chemotherapy	Number of Patients	Outcomes
POG-8697 (66)	No	C5V	73	3-year EFS: stage I (UH) and II, 91%; stage III, 67%; stage IV, 12.5%
POG-9345 (77)	Yes	C5V vs. intensified platinum ^a	33	5-year EFS: stage III, 59% stage IV, 27%
INT-0098 (68)	Selected patients	C5V vs. cisplatin and doxorubicin	182	5-year EFS: stage I (UH) and II, >90%; stage III/IV, >50%
HB-89 (70)	Yes	Ifosphamide, cisplatin, doxorubicin	72	3-year EFS: stage I, 100%; stage II, 50%; stage III, 74%; stage IV, 29%
HB-94 (51)	Selected patients	Ifosphamide, cisplatin, doxorubicin	69	3-year EFS/OS: stage I, 96%; stage II, 100%; stage III, 76%; stage IV, 36%
SIOPEL-1 (78)	Yes	Cisplatin and doxorubicin	160	3-year OS, 75%
SIOPEL-2 (67)	Yes	Cisplatin/carboplatin and doxorubicin	150	3-year OS ^b : SR, 90%; HR, 78%

^aOnly stage III and IV patients enrolled.

^bSR (standard risk) defined as hepatoblastoma confined to the liver and involving no more than three hepatic sectors; HR (high risk) defined as hepatoblastoma extending into all four sectors and/or lung metastases and/or extrahepatic involvement. POG, Pediatric Oncology Group; C5V, cisplatin, vincristine, and fluorouracil; EFS, event-free survival; UH, unfavorable histology; COG, Children's Oncology Group; HB, hepatoblastoma; OS, overall survival; SIOPEL, Childhood Liver Tumor Strategy Group of the Société Internationale d'Oncologie Pédiatrique

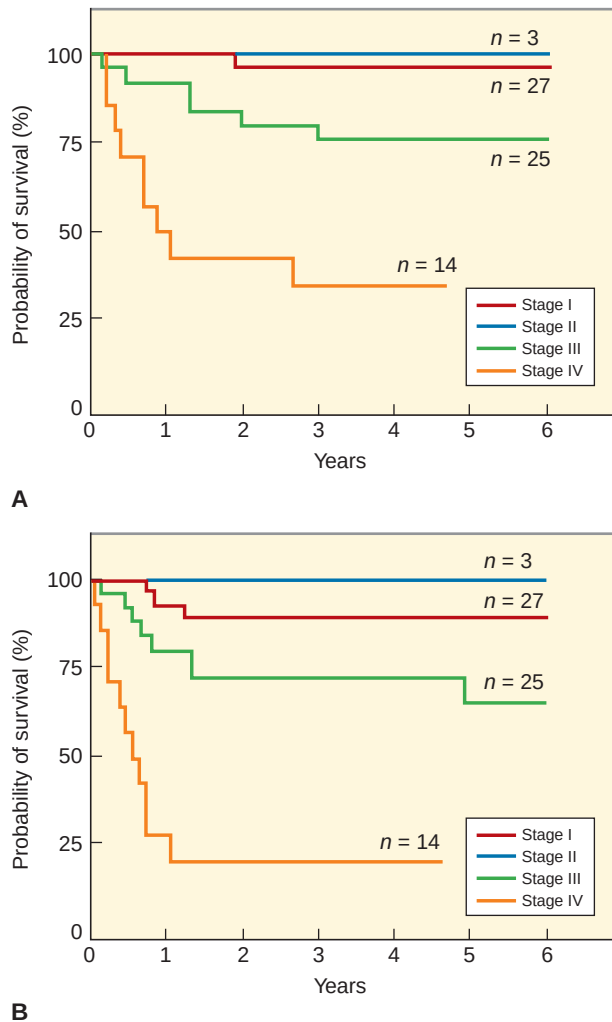


Figure 14.8 A: Disease-free survival and (B) event-free survival, by stage of children with hepatoblastoma in the German Pediatric Liver Tumor Study HB94. (From Fuchs J, Rydzynski J, von Schweinitz D, et al. Pretreatment prognostic factors and treatment results with hepatoblastoma: a report from the German Cooperative Pediatric Liver Tumor Study HB94. *Cancer*. 2002;95:172–182.)

outlined in Figure 14.9. A total of 33 patients were entered and were eligible for analysis. Twenty-two (67%) had stage III and 11 (33%) had stage IV. The 5-year OS was 73% in stage III, with EFS of 59%. In stage IV, the 5-year OS was 27% and EFS was also 27% (44). Complete tumor resection was achieved in 19 (58%) of 33 patients, including 15 (68%) of 22 stage III patients and 4 (36%) of 11 stage IV patients. Five-year EFS for this group was 79% (75).

The Pediatric Intergroup Hepatoblastoma Study POG 9645 was designed to compare the risk of treatment failure for patients with stage III/IV HBL randomized to either C5V (cisplatin + 5-fluorouracil + vincristine) or CC (alternating cisplatin and carboplatin). The 1-year EFS was 37% for CC arm and 57% for C5V ($p = 0.017$). Patients assigned to CC required more blood product support. Random assignment was discontinued early by the Children's Oncology Group Data and Safety Monitoring Committee because the projected improvement in long-term outcome associated with CC was

statistically excluded as possible (71). High-dose chemotherapy with autologous stem cell rescue has been attempted with little success (79).

HCC has epidemiologic and pathologic characteristics different from those of HBL. It usually presented at an older age, involved the liver multifocally, and more related to vertical transmission of maternal hepatitis B virus. HCC is so infrequent in children that these patients have often been treated according to HBL regimens. Surgical resection remains the foundation of curative therapy. Unresected HCC are far less responsive to chemotherapy and carry very poor prognosis.

Thirty-nine children with HCC were registered on the SIOPEL-1 trial and treated with preoperative chemotherapy (cisplatin and doxorubicin). EFS at 2 years was 23%, and 17% at 5 years. Five-year OS, by PRETEXT group, was 44% for stages I and II, 22% for III, and 8% for IV (41). In INT-0098 (CCG-8881/POG-8945) Pediatric Intergroup Hepatoma Study, there were 46 patients with HCC, randomized postoperatively to cisplatin, vincristine, and fluorouracil or cisplatin and doxorubicin. The 5-year EFS rates were 88%, 8%, and 0% for stages I, III, and IV, respectively. There was no difference with either regimen (75). In meta-analyses in adults, a clear benefit of adjuvant chemotherapy in HCC cannot be shown (76).

Meta-analysis of randomized controlled trials in adults with unresectable HCC treated with chemoembolization significantly reduced the overall 2-year mortality rate (odds ratio, 0.54; 95% CI: 0.33, 0.89; $p = 0.015$) compared with best supportive treatment (80). Experience with chemoembolization in children is limited but feasible and effective in inducing surgical resectability of primary hepatic tumors in children (81,82). Selected cases may benefit from chemoembolization as a “bridge” through the pretransplantation waiting (83).

Recently, sorafenib, an oral multikinase inhibitor, which suppress tumor cell proliferation and angiogenesis, was approved by the US FDA for the first-line treatment of HCC after the completion of a phase III trial, Sorafenib versus Placebo in Advanced Hepatocellular Carcinoma (SHARP) for adult patients (84,85). Nevertheless, there are no data on the safety and dosing in children.

Bevacizumab, a monoclonal antibody that exclusively targets vascular endothelial growth factor (VEGF), was evaluated in several phase II trials alone and in combination with chemotherapy in HCC. A survival benefit supports phase III trial of bevacizumab in HCC (86).

Radiation Therapy

Radiation therapy has been used preoperatively and postoperatively as an aid to the curative treatment of HBL and HCC. Its preoperative use has been intended to reduce the tumor burden and increase the probability of resection. Contemporary treatment for HBL favors using chemotherapy alone preoperatively (15,17,36,87), in children who have unresectable tumors after initial chemotherapy, radiotherapy can also be considered (16,58,88). POG-8697, described in the chemotherapy section of this chapter, included five patients in whom radiotherapy was added to chemotherapy when their disease remained unresectable after initial chemotherapy. Three of them ultimately became resectable (47,89).

Some evidence also exists that postoperative radiotherapy is valuable in children who have residual disease after an

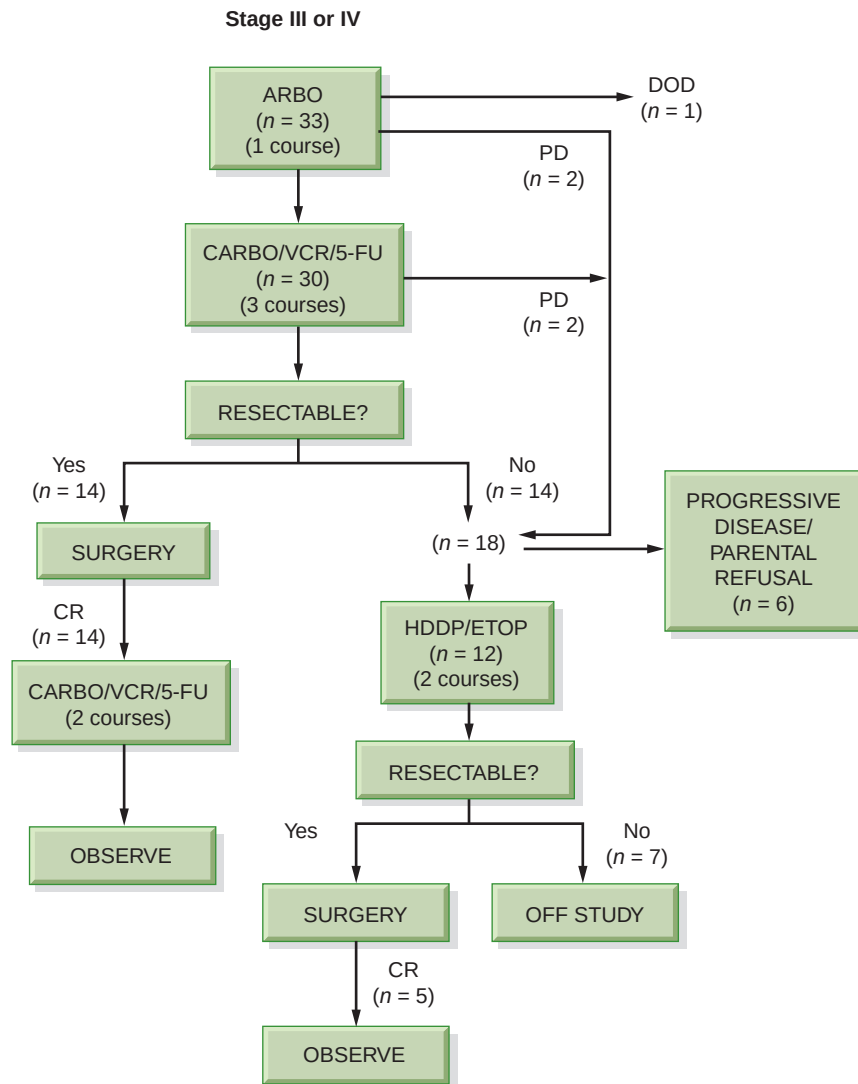


Figure 14.9 The treatment program and patient responses for Pediatric Oncology Group protocol 9345 for stages III and IV hepatoblastoma. CR, complete response; DOD, dead of disease; PD, progressive disease. (From Katzenstein HM, London WB, Douglass EC, et al. Treatment of unresectable and metastatic Hepatoblastoma: A Pediatric Oncology Group Phase II Study. *J Clin Oncol*. 2002;20:3438–3444, with permission).

attempt at resection. A combined CCSG–POG protocol studied 177 children with HBL or HCC. Patients with microscopic residual disease (stage II) received postoperative chemotherapy and 45 Gy of radiation to the tumor bed. The 3-year progression-free survival was 60% for stage II and 22% for stage III (27). The Institute Gustave Roussy administered preoperative chemotherapy, performed surgical resection, and then gave radiotherapy and additional chemotherapy if there was microscopic or macroscopic persistent tumor at surgery. A dosage of 25–45 Gy was given, targeted to the area of postoperative disease only. Seven of nine children were disease free at 22–98 months of follow-up, two patients died, one from local failure and another from both local and distant failure (58). The evidence in favor of the use of irradiation for residual disease is not unequivocal, and we cannot yet determine that chemotherapy by itself would not have ultimately controlled the persistent microscopic disease. No clear treatment policy can be developed and adopted on the basis of the current limited evidence.

When radiotherapy is to be considered preoperatively to improve resectability or postoperatively for residual disease, the defining of tumor volume is crucial. It is essential to spare as much normal liver tissue as possible. Therefore, the radiation oncologist must carefully examine the diagnostic imaging studies and any available operative and histopathologic reports.

The tumor volume should be delineated and covered by portals with a 1- to 2-cm margin. Extra margin (0.5–2.5 cm) is added in the cephalocaudal direction to cover diaphragmatic respiratory excursion. This should be confirmed fluoroscopically. Respiratory gating for external beam radiotherapy may enable a margin reduction on tumor volume. This, in turn, may allow dosage escalation without increasing toxicity (90). In the majority of cases, three dimensionally planned or intensity-modulated fields from a linear accelerator are used. On occasion, the best treatment plan is anterior and posterior fields. If a fair portion of the liver can be spared, then a total dosage of

50–60 Gy would be appropriate. As we described in the previous section concerning POG-8697, preoperative irradiation of an unresectable HBL may convert it to resectability (66).

When postoperative irradiation is given for residual disease after a resection, 45 Gy to a limited area is appropriate for microscopic disease, and 50–60 Gy is appropriate for bulkier residual disease. Full attention must be given to respecting hepatic tissue tolerance to radiation. In adults with unresectable HCC, available retrospective reviews suggest a dosage of 30 Gy as the upper limit for normal liver tissue (91).

If radiotherapy is to be administered to the whole liver for advanced tumor, then parallel-opposed anterior and posterior fields are almost always used. The dosage generally is prescribed to the mid-portion of the liver, and the accepted parameters of liver tolerance to irradiation should not be exceeded. Therefore, with palliative intent for advanced HBL or HCC, 20–25 Gy in 2–2.5 weeks is reasonable. The treatment of metastatic lesions from HBL or HCC can have a palliative effect, and the usual palliative dosages of irradiation (based on the surrounding normal tissue tolerance) may be applied.

Investigational techniques that may have some promise include intraoperative irradiation, regional hyperthermia in conjunction with intra-arterial yttrium-90 microspheres, intra-arterial iodine-131 lipiodol, and iodine-131 antiferritin administered along with chemotherapy (92–94). For patients with more advanced disease, transarterial chemoembolization (TACE) and radiotherapy in combination have been used with promising results. The optimal scheduling of radiotherapy and TACE is unknown. Proton and heavy-ion radiotherapy for HCC have been associated with potentially promising outcomes, perhaps because of their ability to deliver higher tumoricidal doses conformally around the tumor while substantially sparing the surrounding uninvolved liver (95,96). The cost, however, limits their use.

Radiation-induced liver disease (RILD), previously called radiation hepatitis, can be a serious complication of radiation therapy for HBL or HCC. Reactivation of viral hepatitis and precipitation of underlying liver disease also can occur after radiotherapy for HCC (97). RILD is characterized by central liver lobular congestion, sinusoidal congestion, atrophy of the liver plates, and focal necrosis. RILD can occur weeks to months after radiotherapy. One should be particularly concerned about the risk of RILD in patients already compromised by prior hepatic surgery, chronic viral hepatitis, or liver cirrhosis. The laboratory signs of RILD include elevation of alkaline phosphatase and transaminases (97).

The mean liver dose associated with a 5% risk of RILD for patients with HCC is 28 Gy in 2-Gy fractions (98). As the Majority of patients in the analysis by Lawrence of the University of Michigan were having Child A liver function, their results cannot be used to describe the risk of toxicity in patients with Child B or C liver function. Intensity Modulated Radiation Therapy (IMRT), compared to three-dimensional conformal radiotherapy, can reduce the incidental dosages to the spinal cord, kidneys, and stomach. The application of Intensity Modulated Radiation Therapy (IMRT), which uses multiple fields with the mean dosage to the liver being higher than with three-dimensional planning (29.2 Gy vs. 25.0 Gy, $p = 0.009$), should be cautious, especially in patients with compromised liver function.

Is whole-lung irradiation (WLI) appropriate in HBL metastatic to the lung? Data on the subject are sparse. Metastatic disease to the lung should be treated with surgical resection of the metastatic deposits plus chemotherapy. However, there is always a risk of subsequent pulmonary relapse (60). This understanding may be used as an argument in favor of WLI to treat presumed small deposits of well-oxygenated metastatic disease. Based on the experiences from Wilms, Ewing tumor, or osteosarcoma, for example, a total dosage of 12–13 Gy would be considered appropriate for childhood HBL and HCC.

RESULTS AND FUTURE DIRECTIONS

Recent cooperative studies with multimodality treatments have improved OS and EFS for pediatric patients with HBL and HCC in the past two decades. The 5-year survival rates for stages I, II, III, and IV were 95%, 100%, 65–70%, and 36–45%, respectively (Table 14.7). The choices of chemotherapy regimens include vincristine, cisplatin, and 5-fluorouracil, and cisplatin and doxorubicin (68). Doxorubicin is used widely throughout Europe (57). Toxicity in previous North American trials has limited its use (68); however, there are ongoing discussions regarding the reintroduction of doxorubicin in North American clinical trials (73).

Surgery remains the cornerstone of curative treatment for HBL and HCC; preoperative chemotherapy with or without radiotherapy increases the possibility of complete resection. Radiotherapy is recommended in patients who have residual tumor after surgery. As surgical technique advances and better immunosuppressive agents with fewer long-term side effects become more available, a steady improvement in the success of liver transplant patients will likely be observed. In addition, living donor transplantation has also become a promising option (63,99). Ongoing questions are to search for new chemotherapeutic agents with less toxicity and to properly time and prioritize liver transplantation for unresectable cases (61). As more is understood of the molecular and genomic pathways in HBL and HCC, the development of newer targeted therapies may raise new hopes for better control of these dreadful diseases.

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Germ and Stromal Cell Tumors of the Gonads and Extragenadal Germ Cell Tumors

Christian Carrie, and Edward C. Halperin

Gonadal or extragonadal germ cell tumors (GCTs) represent less than 2% of pediatric malignant tumors. They have three important features:

- The origin is related to abnormal migration of primordial germ cells and tumor can occur along this migration path.
- Serum tumor markers allow diagnostic and treatment evaluation.
- The cure rate is high if the clinician respects treatment guidelines.

GCTs result from malignant transformation of a primordial germ cell (Fig. 15.1)

In the human embryo the primordial germ cells are found in the vicinity of the allantoic stalk. From this position the germ cells migrate into the adjoining mesenchyme at 4–5 weeks of gestation. The cells then assume positions in the germinal ridges and migrate along these structures.

GCTs may occur in the ovary, testes, sacrococcygeal region, vagina, retroperitoneum, pelvis, omentum, and mediastinal areas. Extragenadal and testicular sites predominate in children younger than 3 years old. Gonadal sites are most common during and after puberty (1). The main histologic types are germinoma, embryonal carcinoma, yolk sac tumor (also known as endodermal sinus tumor or Teilm tumor), malignant mixed GCTs, and malignant teratomas (sometimes called immature teratomas) (Table 15.1) (2–5). Endodermal sinus tumor typically shows microcystic areas, Shiller–Duval bodies, and periodic acid–Schiff–positive extracellular hyaline droplets. The tumor is often positive, on immunohistochemistry, for α -fetoprotein

(AFP) and cytokeratin (6). Structural abnormalities of chromosome 1 are frequent (1).

Teratomas (from Greek *teratos*, “monster,” and *onkoma*, “swelling”) are the most common pediatric GCTs. Malignant teratomas may develop anywhere along the pathway of germinal tissue migration. By definition, teratomas are composed of tissues derived from two or three germinal layers (tridermal ancestry): ectoderm, mesoderm, and endoderm. Malignant teratomas are so named because of foci of endodermal sinus tumor, embryonal carcinoma, germinoma, or choriocarcinoma. There may also be foci of neuroblastoma, nephroblastoma, or hepatoblastoma. In general, frank malignancy is identified in about 20% of teratomas (5). The distinction must be made between immature teratomas with distinct malignant elements, which warrant aggressive adjuvant therapy, and immature teratomas with primitive neuroepithelium, which can be cured with surgery alone. Immature teratomas are graded by the system of Norris, which also predicts relapse (Table 15.2).

GENERAL ASPECTS OF CLINICAL PRESENTATION, STAGING, AND WORKUP

There is a bimodal age distribution for GCTs, with a peak in children younger than 3 years old and a second peak in children older than 12 years. The male:female ratio is 2:1 (9). Girls predominate in the patient population during the first

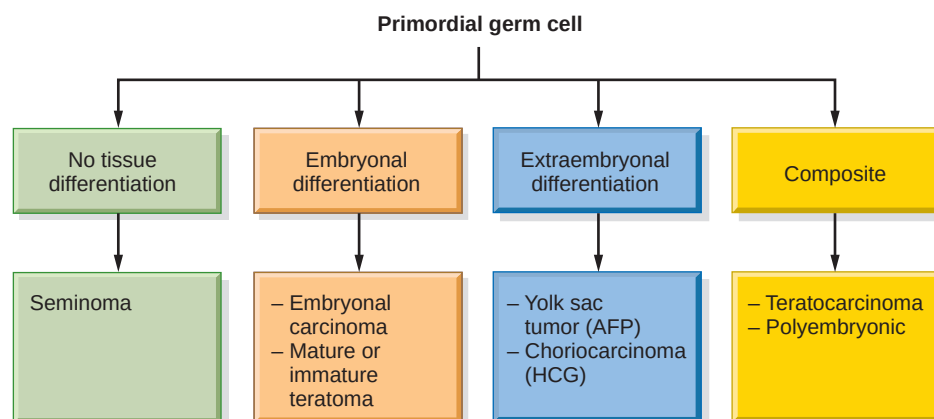


Figure 15.1 Classification of germ cell tumors.

Table 15.1
Biological Characteristics of Pediatric Germ Cell Tumors

Type	Grade	AFP	HCG	Chemotherapy Response	Radiotherapy Response
Dysgerminoma	Malignant	—	+/-	+++	+++
Embryonal carcinoma	Malignant	—	—	+++	+
Yolk sac tumor	Malignant	+++	—	+++	+
Choriocarcinoma	Malignant	—	+++	+++	+
Mature and immature teratomas	Benign to potentially malignant	+/-	—	+	+

AFP, α -fetoprotein; HCG, human chorionic gonadotropin.
Derived from Gobel U, Schneider DT, Calaminus G, et al. Germ-cell tumors in childhood and adolescence. *Ann Oncol*. 2000;11:263–271.

3 years of life because of a female predominance in sacrococcygeal tumors (SCTs). There is an association with intersex disorders (1,10,11). The association between undescended testes and the development of testicular cancer has been established.

The staging workup should include assays for AFP and human chorionic gonadotropin (HCG). AFP is elevated in almost all cases of endodermal sinus tumor and in many other patients with GCTs (12,13). Successful treatment, whether by surgery, chemotherapy, or radiotherapy, is regularly associated with AFP decline consistent with its half life of 5 days in infants 2 months or younger, 33 days in 2- to 4-month-olds, and 5 days in children 8 months or older (1,13,14). AFP falling too slowly, failing to normalize after treatment, or rising generally signifies inadequate tumor response and precedes clinical or radiographic evidence of treatment failure. HCG activity is present in some tumors, particularly choriocarcinoma. The half time of β -HCG is 24–36 hours.

Diagnostic imaging of the pelvis and presacral space is best performed with computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (5). The role of a PET scan is not well established, probably not necessary for nonseminomatous tumor and more useful to identify viable tumor in case of residual lesion after chemotherapy (15). CT is useful to assess the presence of pathologic retroperitoneal lymph nodes and extension of tumor into bone. Imaging may show GCTs to be cystic, solid, or a combination of both.

Table 15.2
Grading of Immature Teratomas

Grade	Description	Approximate Relapse Rate (%)
0	Mature	10
I	Immaturity with PE limited to one lower-magnification field ($\times 40$) per slide	14
II	<4 fields of PE per slide	23
III	>4 fields of PE per slide	33

PE, primitive neuroepithelium.
From Refs. 1, 7, and 8.

Sacrococcygeal and ovarian lesions that are predominantly cystic are less likely to be malignant, whereas solid lesions are more likely to be malignant. However, the correlation is far from perfect. This is particularly important because it argues strongly against using the term *solid teratoma* as the equivalent of *malignant* or *immature teratoma* (4,5,16,17).

Ovary

Of primary ovarian tumors of childhood, about 71% are GCTs, 17% epithelial, and 12% sex cord stromal tumors (1,16,18). The histologic distribution is approximately: mature teratoma, 47%; immature teratoma, 12%; dysgerminoma, 5%; yolk sac tumor (endodermal sinus), 10%; mixed GCTs, 0–24%; and choriocarcinoma, <1% (1,7,19) (Fig. 15.2).

The risk of germ cell malignancy in girls more than 3 years old is 20%. All pediatric ovarian tumors must be considered as malignant. In the series by Germa et al. (19), 46% of girls presented with pain. In the POG/CCG intergroup study 11% of girls present with an acute abdomen due to rupture or torsion (20). The long infundibular pedicle in the



Figure 15.2 Ovarian dysgerminoma.

Table 15.3**Children's Oncology Group Surgical Guidelines for Ovarian Germ Cell Tumor in Pediatric Patients**

- 1 Ascites for cytology or peritoneal washing if no ascites present
- 2 Inspect omentum, resect only if abnormal
- 3 Inspect and palpate iliac and para-aortocaval nodes; perform biopsy only if abnormal
- 4 Inspect and palpate contralateral ovary; perform biopsy only if abnormal
- 5 No violation of tumor capsule in situ for resectable tumors
- 6 Primary resection for localized tumors; perform biopsy only if resection would require sacrifice of other organs and plan for postchemotherapy resection

From Billmire DF. Germ cell tumors. *Surg Clin North Am.* 2006;86:489–503, xi, with permission.

child explains this risk (12,19). Other presenting signs and symptoms included an asymptomatic palpable mass (19%), abdominal distention (36%), and, less commonly, menstrual irregularities, malaise, nausea, vomiting, or vaginal bleeding (9,19,21–30). The stromal Sertoli–Leydig cell tumors may present with defeminization or virilization. Ovarian dysgerminomas are rarely hormonally active or productive of tumor markers. If a patient with an ovarian dysgerminoma is found to have an elevated AFP or signs of hormonal imbalance, there should be a meticulous search of the pathology specimen for elements of other tumor. Preoperative assessment is crucial for the postoperative management. Sample AFP, HCG, and β -HCG must be obtained in all solid ovarian tumors.

Both primary and second-look surgeries are used to treat ovarian GCT. The initial surgical procedure should remove as much tumor as possible with a reasonable possibility of retention of fertility. At the time of laparotomy, the entire peritoneal surface should be examined for the presence of metastasis. Particular attention should be paid to the surfaces of the liver and to the inferior surface of the diaphragm (12). The involved ovary should be removed. Dysgerminoma has a 5–10% incidence of bilaterality (18). For childhood ovarian GCT other than dysgerminoma, the probability of bilateral involvement ranges from 0% to 14% (23). Therefore, the contralateral ovary should be biopsied and, if there is no evidence of malignancy, preserved (29). Palpation and biopsy of all suspicious lymph nodes in the pelvic and para-aortic regions should be done. Peritoneal biopsies and washings (or collection of ascites) for cytology are important to complete the surgical staging (30). When front-line definitive surgery is not

possible or appropriate, chemotherapy can be given followed by second-look surgery (31).

In the POG study, positive ascetic cytology was found among 100 girls despite negative random biopsy samples. Due to this finding the Children's Oncology Group (COG) published new guidelines including peritoneal washing (Tables 15.3 and 15.4).

Ovarian GCTs are lethal malignancies that can kill by early metastasis and rapid invasion of abdominal and pelvic structures. The prognosis of girls with these tumors was poor when they were treated with surgery only or surgery in combination with either radiotherapy or single-agent chemotherapy, except in some cases of dysgerminoma (16). An increasing body of evidence indicates that postoperative chemotherapy has increased the probability of survival (1,4,13,16,19,7,21,22,26–29). Active drugs include cisplatin (P), carboplatin (J), vinblastine (V), bleomycin (B), adriamycin (Ad), actinomycin (A), cyclophosphamide (C), etoposide (E), methotrexate (M), and vincristine (O) (9,32–34). Combinations used include VAC, POMB-ACE-PAV, PVB-ACAd, and PEB (5,10,16). PEB or PVB are most commonly used (7,35,36). A six-drug regimen (VAC, JEB or PEB) or JEB therapy both have achieved 5-year survival rates as high as 90% for all stages (37,38).

The generally accepted standard of care for pediatric ovarian GCT is summarized as follows:

- Benign mature teratomas and immature teratomas: surgery and observation
- Stage I malignant GCT: surgery and observation
- Stages II–IV malignant GCT: surgery and PEB or PVB (1).

Table 15.4**Children's Oncology Group Staging for Pediatric Ovarian Germ Cell Tumors**

Stage	Extent of Disease
I	Limited to ovaries, with no clinical, radiographic, or histologic evidence of disease beyond the ovaries; no malignant cells in ascites or peritoneal washings; omentum grossly normal by visual inspection or pathologically normal if removed; tumor markers normal after appropriate half-life decline (α -fetoprotein = 5 days; β -human chorionic gonadotropin = 16 hours). IA, tumor limited to one ovary; IB, tumor limited to both ovaries
II	Microscopic residual; tumor markers inappropriately elevated; preoperative or intraoperative rupture
III	Retroperitoneal lymph node involvement or metastatic nodule; gross residual or biopsy only; contiguous visceral involvement
IV	Distant metastases, including liver

AFP and HCG are valuable in patient follow-up.

Contemporary treatment programs do not use radiotherapy if initial surgery and, if used, chemotherapy render the child disease free (39). Radiotherapy is reserved for residual disease that cannot be resected at second operation and is not treated with alternative chemotherapy. The persistent tumor volume, generally treated with progressive shrinking fields, is irradiated to 40 Gy (10,13,19,39).

The two principal treatment options in adult patients with stage I dysgerminoma are surgery followed by observation, or chemotherapy with one cycle of carboplatin (40) or para-aortic radiation. To avoid irradiating most girls with ovarian dysgerminoma, the following are the criteria for treatment with unilateral salpingo-oophorectomy alone: unilateral encapsulated tumor (stage I); greatest tumor diameter <10 cm (although this is not uniformly found to be a prognostic sign); no ascites; no evidence of enlarged or abnormal lymph nodes by palpation, lymphangiogram, biopsy, or CT; well-differentiated pure dysgerminoma; and confidence that the patient will attend regular follow-up appointments. Under these criteria, selected patients may be cured with preservation of fertility (24,25,30,35,41).

If ovarian dysgerminoma is locally extensive (beyond stage I) or bilateral, then chemotherapy should be administered (19,33,39). When chemotherapy is used, PEB, as for other ovarian GCT histologies, is selected. Carboplatin alone is not yet a standard in pediatric GCT. In a series from Germa et al. (19), chemotherapy-induced amenorrhea was reversed in 14 of 15 patients after chemotherapy. Three patients attempted to become pregnant: Two had uneventful pregnancies and one had a spontaneous abortion. Whether ovarian failure will ultimately develop in chemotherapy-treated patients remains to be seen, although Mann et al. (13) stated that “in ovarian dysgerminoma, chemotherapy is preferable to radiotherapy to preserve fertility.” Except in very specific cases there is very little role for RT in ovarian germinoma.

For all histologies of ovarian GCTs combined, the reported probability of survival is 60–90%. For the most part, deaths appear to be in stage IV (1,2,13,19,7,21–25, 29,30,33,35,39,42,43). The survival of children with ovarian dysgerminoma is 95–100% when disease is confined to the pelvis or has limited abdominal involvement (2,33,44). Tumor rupture or extensive metastasis reduces the probability of survival (44).

Ovarian stromal and epithelial tumors are rare in children. Stromal tumors of the childhood ovary, including juvenile granulosa cell tumors, often are cured by surgical resection alone (45). These stromal tumors usually present with precocious pseudopuberty in prepubertal girls because of estrogen production by the tumor. The roles of surgery and chemotherapy for ovarian epithelial tumors in adolescents (mucinous or serous cystadenocarcinomas) follow the same guidelines as those for adults (10,27,46).

Inhibin can be used as marker for the follow-up of granulosa cell tumors (47). For Leydig cell tumor, conservative surgical therapy is possible (48).

Testis

Testicular GCTs generally present as a palpable painless mass or with signs and symptoms that simulate infection, torsion, or post traumatic hematoma (49). The diagnostic workup includes testicular ultrasonography, CT of the abdomen and

chest, AFP, and HCG. The most common GCT of the testes in pubertal children is yolk sac tumor (endodermal sinus) (Fig. 15.3) (13,16,49). Less common histologies include embryonal carcinoma, mature, immature, and malignant teratoma and mixed tumor. Prepubertal children more often have non-GCTs such as Sertoli or Leydig cell tumors or sarcomas. Testicular GCTs usually are staged by the COG system (Table 15.4) or the International Union Against Cancer (UICC) 2002 (Table 15.5). Most cases are stage I at diagnosis. Teenagers may hesitate to discuss the presence of testicular mass and tend to have more advanced disease at diagnosis (9,12,49).

Most testicular tumors are suspected before surgery. A radical orchiectomy should be performed with high ligation of the spermatic cord. Transscrotal procedures should be avoided because they can spread tumor and increase lymphatic metastases. If a scrotal biopsy has been done, some authorities advise a hemiscrotectomy (49). Others cite data from adults to argue that there is no increase in the relapse rate in stage I tumors if hemiscrotectomy is not done (50). Regarding pure seminoma, clinical stage I, the European consensus for adults allow three strategies: surveillance with salvage irradiation or chemotherapy at relapse, adjuvant chemotherapy with carboplatin, or adjuvant radiation treatment (15). These options seem to be adaptable for childhood seminoma.

The debate concerning the role of retroperitoneal lymph node dissection in early-stage testicular GCT appears to be resolving in favor of a limited role for the procedure. The older literature indicates that 0–33% of children with GCT have involved retroperitoneal lymph nodes (9,12,51–53). Proponents of retroperitoneal lymph node dissection suggested that it was important in staging and in the removal of small foci of malignant cells and that it possibly improved the chance of cure. Objections to dissection, based on the loss of ejaculatory function, were obviated by the use of the modified retroperitoneal dissection (45). With the widespread availability of serum



Figure 15.3 Testicular yolk sac tumor.

Table 15.5**Children's Oncology Group Staging for Pediatric Testicular Germ Cell Tumor**

Stage	Extent of Disease
I	Limited to testes; completely resected by high inguinal orchiectomy; no clinical, radiographic, or histologic evidence of disease beyond the testes; tumor markers normal after appropriate half-life decline (AFP = 5 days; β -HCG = 16 hours); scrotal orchiectomy with negative margin on cord structures
II	Microscopic residual in scrotum or high in spermatic cord or inappropriately elevated tumor markers after appropriate half-life interval (AFP = 5 days; β -HCG = 16 hours); tumor rupture or scrotal biopsy followed at a later time by a scrotal or inguinal orchiectomy
III	Retroperitoneal lymph node involvement but no visceral or extra-abdominal involvement
IV	Distant metastases, including liver

AFP, α -fetoprotein; β -HCG, β -human chorionic gonadotropin.

tumor marker studies and CT screening, however, it is now clear that the staging node dissection is unnecessary in stage I disease. In children with tumor confined to the testes, where AFP levels normalize within 1 month after orchiectomy and where the chest radiograph and retroperitoneal imaging studies are normal, retroperitoneal lymph node dissection is unnecessary. In one study, 28 patients with stage I testicular yolk sac tumors were treated with radical orchiectomy alone: 24 (86%) were cured; the remaining 4 (14%) relapsed and were rendered free of disease by chemotherapy (52). Both the U.K. Children's Cancer Study Group and the St. Jude Children's Research Hospital (SJCRH) series have almost uniform survival for stage I patients treated with radical orchiectomy alone (14,49). There is no difference in disease-free survival between children with stage I disease who undergo retroperitoneal lymph node dissection and those who do not (12,23,52). Retroperitoneal lymph node dissection may still be appropriate for children with no markers or unknown markers at diagnosis to confirm staging, more aggressive histologies (i.e., embryonal cell), demonstrable moderate-sized nodal metastasis at the time of presentation (i.e., SJCRH stage II), or an elevated AFP after surgery (23,45,54). PET could be useful in this case (55).

The management strategy for testicular GCT is as follows:

- Stage I, surgery alone
- Stages II–IV, surgery followed by PEB

For stage I, chemotherapy is used for documented relapse. The survival for all stages is on the order of 90–100%.

For more advanced disease patients should be treated according to the International Germ Cell Cancer Consensus Group (IGCCCG) recommendation (56).

For a small primary tumor or bilateral testicular tumors one could consider organ-preserving surgery, but this option is still experimental and must be done within a clinical trial (57).

Extragenadal

Extragenadal GCTs usually are found in the midline, consistent with embryonic patterns of migration. The most common sites are the sacrococcygeal, presacral, and buttock region. This is followed by the mediastinal, vaginal, uterine, and prostatic regions. Other reported sites of origin include the neck and face, retroperitoneum, stomach, orbit, pancreas, heart, and pericardium (1,7,58).

Sacroccocygeal Tumor

Sacroccocygeal GCTs may develop early in fetal life (Fig. 15.4). Urinary tract obstruction, compression of the umbilical vessels, and chronic hemorrhage into the tumor and amniotic sac may occur. Prenatal ultrasonography may demonstrate the mass, hydronephrosis, fetal hydrops, or prominent polyhydramnios (5). More than one half of patients with malignant and benign sacroccocygeal teratomas present to medical attention on the first day of life. These children often have other congenital anomalies such as abnormalities of the genitourinary tract or of the lower vertebral bodies (59).

Approximately 60–70% of sacroccocygeal teratomas are unequivocally benign by virtue of the exclusive presence of mature somatic tissue. These lesions in newborns may be cured by surgery. Many are diagnosed by prenatal ultrasonography. Ten percent to 15% of teratomas are composed of a mixture of embryonic or fetal elements in mature structures along with poorly differentiated embryonic tissue. These lesions constitute a category of indeterminate biologic behavior



Figure 15.4 Sacroccocygeal yolk sac tumor.

and are called immature benign teratomas. In the surgical treatment of benign and intermediate-grade sacrococcygeal teratomas in infants, every effort must be made to remove the tumor mass. The early and total extirpation of the tumor and coccyx is necessary. The coccyx should always be removed with the mass because failure to remove the coccyx is associated with a local recurrence rate of 37% (60). However, positive surgical margins of mature or immature SCT are not correlated with an increased risk of local failure (61). Due to the high vascularity of such tumors, surgery can follow a ligation of the sacral artery (62). Only 2–10% of sacrococcygeal region tumors are malignant when removed in infants younger than 4 months old. After 4 months of age, the rate of malignancy rises to 50–90% (5,27,60). Simply put, there are two basic types of sacrococcygeal GCT: large, predominantly benign masses in neonates and pelvic, primarily malignant masses in older children.

A useful classification system for sacrococcygeal GCT has been developed by the Surgical Section of the American Academy of Pediatrics. Type I tumors are primarily external; type II tumors are dumbbell-shaped, with significant external and intrapelvic components; type III tumors have a small

external component, with the majority of the lesion extending into the pelvic and abdominal spaces; and type IV tumors occupy the presacral space and have no appreciable external component. As a general rule, the prevalence of malignancy is lowest in type I tumors and increases as one moves from type II through type IV (59). Malignancy rates by type are 8% for type I, 21% for type II, 34% for type III, and 38% for type IV (1). The malignancy rate also rises with age (Tables 15.6 and 15.7).

Preoperative imaging studies help to determine the lesion's type, and they also evaluate whether the lesion is invading adjacent structures rather than displacing them, a suggestion of malignancy. Only a few malignant sacrococcygeal GCTs are resectable *per primum*. In general, the surgeon obtains an initial biopsy, and chemotherapy is administered. There is evidence documenting complete responses of both metastatic and primary disease to chemotherapy with long-term survival. Unresectable tumors have been rendered resectable, with long-term survivorship reported. If there is a satisfactory reduction of tumor volume, the tumor may be deemed resectable at a later date. The POG (63) and a German protocol MAKKEI (64) did not show any difference

Table 15.6
TNM Classification (UICC 2002)

pT	Primary tumor
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor (e.g., histological scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumor limited to testis and epididymis without vascular/lymphatic invasion: tumor may invade tunica albuginea but not tunica vaginalis
pT2	Tumor limited to testis and epididymis with vascular/lymphatic invasion, or tumor extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumor invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades scrotum with or without vascular/lymphatic invasion
N	Regional lymph nodes clinical
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
pN	Pathological
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumour
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
M	Distant metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph nodes(s) or lung
M1b	Other sites
S	Serum tumor markers

(Continued)

Table 15.6**(continued)**

Sx	Serum marker studies not available or not performed
S0	Serum marker study levels within normal limits
	LDH (U/L) HCG (mIU/mL) AFP (ng/mL)
S1	$<1.5 \times N$ and <5000 and <1000
S2	$1.5\text{--}10 \times N$ or $5000\text{--}50,000$ or $1000\text{--}10,000$
S3	$>10 \times N$ or $>50,000$ or $>10,000$
N indicates the upper limit of normal for the LDH assay.	
Except for pTis and pT4, where radical orchiectomy is not always necessary for classification purposes, the extent of the primary tumor is classified after radical orchiectomy; see pT in other circumstances. TX is used if no radical orchiectomy has been performed.	
According to the 2002 TNM classification, stage I testicular cancer includes the following substages:	
Stage IA	pT1 NO MO S0
Stage IB	pT2, pT3, or pT4 NO MO S0
Stage IS	Any pT/TX NO MO S1–3 S0

AFP, α -fetoprotein; HCG, human gonadotropin; LDH, lactate dehydrogenase UICC, International Union Against Cancer

in survival rate between patients treated by preoperative and postoperative chemotherapy. The 4-year overall survival was 90%. In summary, stage I extragonadal mature and immature sacrococcygeal teratomas and completely resected malignant GCTs are resected and observed. Stages II–IV malignant GCTs are treated with PEB or PVB plus surgery.

Mediastinal GCT

Pediatric mediastinal GCTs account for $<5\%$ of all GCTs (7). They are generally in the anterior mediastinum and can cause superior vena cava syndrome or acute respiratory deficiency (65). Calcification in the tumor is one of the x-ray characteristics (Fig. 15.5).

As the tumor is generally unresectable at diagnosis most patients undergo cisplatin-based chemotherapy first followed by surgery. In a Belgium report, mediastinal GCTs have the worst prognostic of all GCTs with a mortality rate of 28% (66). In the last international analysis, the 2-year survival rates were, respectively, 34% and 84% for nonseminomatous and seminomatous tumors (67).

In general, the survival rate for extragonadal GCT is not as high as for ovarian and testicular (68). The survival rate in the United States for mediastinal lesions is 40–60%. In the recent International Society of Pediatric Oncology (SIOP) and German protocols, the 10-year event-free results are as follows: ovarian, 89%; sacrococcygeal, 81%; testicular, 97%; and all others (except brain), 88% (7,50).

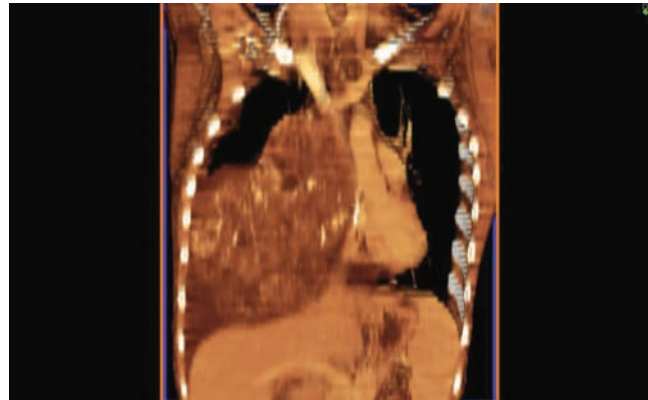


Figure 15.5 Thoracic germinoma.

The Role of Radiotherapy

Radiotherapy is not necessary for children who have a documented complete response to surgery and chemotherapy (39). The local recurrence rate in this particular set of patients is low. In a study by Flamant et al. (21), the majority of children with nonseminomatous malignant GCT (stages III and IV) did not need radiotherapy when aggressive induction chemotherapy was used as a complement to surgery. In 11 of Flamant's cases failing initial therapy, 9 had a local recurrence as the site of first failure. However, when only a partial

Table 15.7

Children's Oncology Group Staging for Pediatric Malignant Extragonadal Germ Cell Tumors

Stage	Extent of Disease
I	Complete resection of any site; coccygectomy for sacrococcygeal site; negative tumor margins; in infants >8 mo old tumor markers are normal after appropriate half-life decline. For infants <8 mo, tumor markers return to normal by 8 mo of life
II	Microscopic residual; lymph nodes negative; tumor markers inappropriately elevated
III	Gross residual or biopsy only; primarily resected but lymph nodes positive
IV	Distant metastases, including liver

response to chemotherapy and surgery is achieved in localized disease, the chance of irradiation achieving local control is only fair. Ablin et al. (39) described 17 children with GCTs of gonadal and extragonadal location who were irradiated for persistent disease after chemotherapy. Radiotherapy failed in the field of treatment in 10 of the 17 cases. The primary site of failure in all seven sacrococcygeal GCTs was at the initial site of tumor. Mann et al. (13) reported irradiating eight patients with GCT in a variety of locations. When obvious disease was present, no sustained responses occurred. There were three survivors who had normal AFP levels at the time of irradiation and who may have been already cured before irradiation. Kersh et al. (24) reviewed the results of radiotherapy in adult and pediatric patients with nonseminomatous GCTs in the mediastinal, retroperitoneal, and sacrococcygeal regions. Local control was obtained in 2 of 11 patients with mediastinal lesions, 0 of 2 patients with retroperitoneal tumors, and 1 of 4 sacrococcygeal lesions. In summary, the results of radiotherapy for patients with persistent disease after chemotherapy are poor, and the radiotherapy literature is based on older forms of chemotherapy. However, it is also clear that with residual unresected disease after chemotherapy, the risk of tumor regrowth at the primary site is almost certain (60). Therefore, we conclude that radiotherapy is worth the effort, albeit with only modest claims for success.

If radiotherapy is used for extragonadal GCT, dosages of 45–50 Gy are recommended, as limited by the tolerance of surrounding normal tissue. The radiotherapy portals are dictated by radiographic imaging studies and surgical exploration. Metastatic lesions may necessitate palliative treatment with local field irradiation.

RESULTS

Survival for stages I–II GCTs at gonadal sites approaches 100%. Survival for stages III–IV GCTs at gonadal sites is about 95%. Extragonadal GCT survival is about 90% for stages I–II and about 75% for stages III–IV (1,68).

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Endocrine, Aerodigestive Tract, and Breast Tumors

Line Claude and Cécile Nozières

ADRENOCORTICAL CARCINOMA

Histology

Adrenocortical carcinoma (ACC) is an aggressive cancer originating in the cortex of the adrenal gland. This chapter focuses on corticosteroidoma. Different types of tumors exist (myxoid adrenocortical carcinoma, carcinosarcoma, oncocytic adrenocortical carcinoma, and clear cell adrenal carcinoma), but are very rarely described in children.

Epidemiology

ACC is rare around the world (0.2% of child cancer) (1–7), except in Southern Brazil (3.5 cases/million children younger than 15 years) (8) due to p53 mutation. The frequency is dependent on the age: 0.4 per million before 4 years and decreases to 0.1 per million after 10 years (9). Sex ratio is 1:5.3 before 4 years and 1:0.8 after 4 years (8).

Genetics

Principal genetic abnormalities associated with ACC are summarized in Table 16.1 (10).

Clinical Aspects

Virilization (pubic hair, clitoromegaly or phallomegaly, acne, deep voice, and hirsutism) is the most common sign of ACC. In the large Brazilian experience, more than 90% of the patients had pubic hair, and more than 80% of girls had clitoris hypertrophy. Other frequent signs are abdominal pain in 50% and Cushing syndrome in 30% (hypertension, centripetal fat distribution, moon face, buffalo hump of the neck, accelerated growth velocity, weight gain, ...) (Fig. 16.1).

Biology

Because the tumor cells may secrete a number of adrenal hormones either alone or in combination (androgens, glucocorticoids, mineralocorticoids, and estrogens), it is possible to establish an endocrine profile of most pediatric ACC. Urinary 17-ketosteroids (17-KS) and 17-OH steroids are elevated in more than 90% of the cases (8).

Molecular Biology

In adult series, Ki-67 marker proliferation, p53 mutation, mdm-2 mutation, and p21 mutation have been identified as associated with ACC but no specific pattern is known. While tumor cell proliferation (Ki-67) correlates with mitotic activity and morphologic index, tumor morphology remains better predictor of metastatic risk (11).

Prognostic Factor

The distinction between benign and malignant ACC is made on cytologic abnormality, tumor weight, and presence of metastases (12,13). Some lesions are frankly malignant on microscopic examination. For those of borderline histologic appearance, one should consider resectability, the extent of capsular invasion, adherence to surrounding structures, the presence of aberrant vessels on angiography, tumor size, and the presence or absence of metastases to distinguish benign from malignant lesions. Well-encapsulated and easily excised tumors may be cured by surgery alone. In the remaining resected but more locally advanced cases, there is a substantial risk of local relapse and distant metastases (7,14,15).

Table 16.1

Constitutional Genetic Abnormalities Associated with Adrenal Cortical Tumours (ACT)

Condition	Tumor Types
Li–Fraumeni syndromes and other germ-line p53 mutations	Adenomas/carcinomas
Hemihypertrophy	Adenomas/carcinomas
Beckwith–Wiedemann syndrome	Adenomas/carcinomas
Carney complex	Primary pigmented nodular adrenocortical disease
Congenital adrenal hyperplasia	Adenomas carcinomas (very rare)
Multiple endocrine neoplasia I	Adenomas carcinomas

From Ribeiro RC, Figueiredo B. Childhood adrenocortical tumours. *Eur J Cancer*. 2004;40(8):1117–1126, with permission.

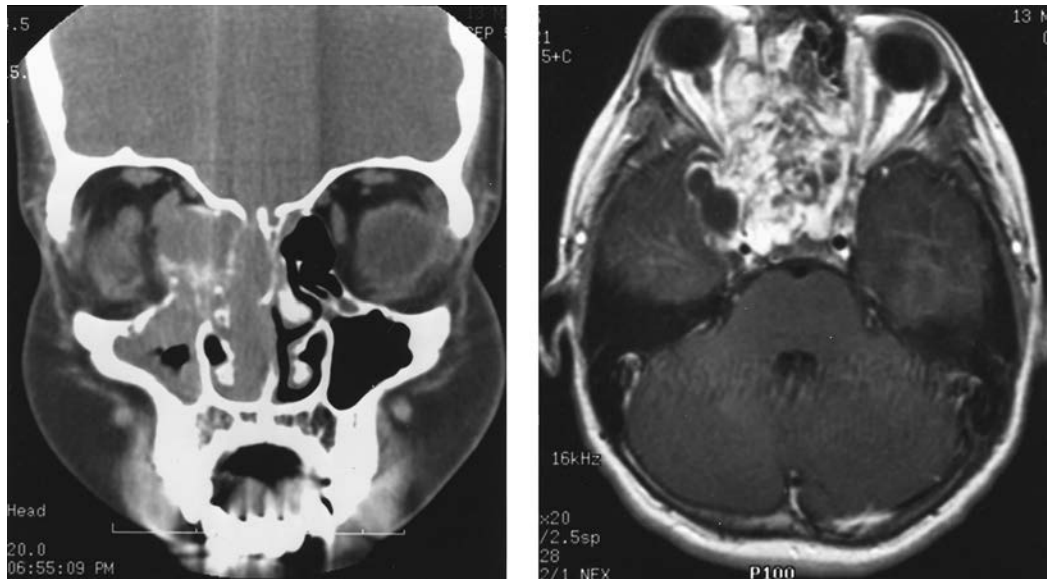


Figure 16.1 Coronal computed tomography (left) and axial magnetic resonance imaging (MRI) (right) of a 13-year-old boy with headaches, diplopia, and right proptosis. The mass-produced destruction of the ethmoid air cells and superior turbinates, mass effect in the right orbit, compression of the right cavernous sinus, displacement of the right internal carotid artery, and displacement of the pituitary. A biopsy proved the diagnosis of juvenile nasopharyngeal angiofibroma. Three-dimensional treatment planning was used to prepare a four-field noncoplanar external beam radiotherapy treatment technique using rigid head immobilization. A dose of 36 Gy at 2 Gy per fraction was administered. One and one-half years after irradiation the symptoms had significantly improved and the mass was smaller on physical examination and MRI. Shortly thereafter the symptoms recurred, and the MRI demonstrated regrowth of the angiofibroma, within and outside the irradiated field. Interferon was administered as antiangiogenesis agent.

While stages are well defined in adults (McFarlane classification (4)), classification is less clear in childhood. Michalkiewicz et al. proposed a classification based on more than 250 patients (9). Factors independently associated with good prognosis in terms of survival include Stage I tumor (tumor completely excised, tumor weight <200 g, and absence of metastasis), virilization alone, age <4 years (9).

Imagery

Imaging studies are of great importance for surgical planning and disease staging. Magnetic resonance imaging (MRI) and tomodensitometry (TDM) are necessary to determine the size of tumor, to detect invasion of local structures, metastasis, and vessels involvement (vena cava, for example).

Due to frequent liver and lung metastasis, TDM is recommended. Brain and bone metastases are rare but possible; technetium bone scan and/or brain MRI should be performed in case of observed symptoms. Positron emission tomography (PET) scan has not been extensively studied, but in a very small series in adults, it can yield additional information in defining tumor metabolic activity and necrosis, and in the earlier detection of metastases in comparison with computed tomography (CT) (16).

Treatment

Surgery

For localized disease, surgery is usually recommended although it is the most important procedure in successful treatment of ACC (8). Tumor friability needs a bloc resection to avoid tumor spillage and rupture of the capsule and to compromise prognosis. Therefore, transabdominal approach is necessary.

Chemotherapy

Patients with residual disease after surgery or with metastatic disease usually receive chemotherapy using different regimens, including mitotane, cisplatin, etoposide, doxorubicin, with poor results (17). At one time, mitotane was considered to be the drug of choice. This drug, an isomer of the insecticide DDD, has adrenolytic activity. It has been used in neoadjuvant to treat advanced metastatic ACC in cases of inoperable tumors, in adjuvant situation for patients at high risk to relapse, and to control symptoms associated with production of adrenal hormones (10). Administration of this drug is associated with toxic effects such as nausea, vomiting, renal and hepatic dysfunction, and neurologic alterations. As in adults series, response rates to mitotane are heterogeneous (0%–56%), highly dependent of serum therapeutic level (14 to 20 µg/mL (17). Association with others drugs, doxorubicin, cisplatin, and 5-fluorouracil (FU), was possible, without evident benefic in tumor response.

Radiotherapy

Radiotherapy (RT) has often been considered ineffective for treatment of ACC. However, old clinical reports have described tumor response rates up to 42% (18), which indicate that ACC is not resistant to RT.

The only series reported with children is Magee's study (12). Fifteen patients including five children were treated for ACC. Nine of them had postoperative irradiation. Three were girls who presented under the age of 2 years with hormonally active tumors and who survived for more than 10 years after gross total tumor resection followed by 30 Gy in 4 weeks. Two of these three patients died of second malignancies arising in the irradiated field. The high frequency of second

primary malignancies is observed in other studies, and it points out the need for close surveillance especially after RT (19).

Recommendation of an international consensus conference was published in 2005 for adults without any data for children. Radiation therapy is recommended in the treatment of bone, brain, and other metastases. It is also recommended in the treatment of symptomatic local recurrences. Concerning adjuvant situations, it should be discussed in case of incomplete local resection. There is no recommendation concerning adjuvant RT in cases of complete resection, and no major evidence to support it (20). However, a more recent study demonstrated the efficiency of adjuvant RT of the tumor bed ($\pm$ bilateral paraaortic lymph node in seven patients due to lymph node involvement) in a retrospective cohort. Fourteen patients (eight in complete resections, two marginal resections, and four unknown) received adjuvant RT (median dose 50.4 Gy, range [41.4–56]. 1.8–2 Gy per fraction, beginning within 8 weeks after surgery in most patients) while 14 were in the control group. Local control was significantly better in the radiation group: 79% at 5 years versus 12% at 5 years without RT ($p < 0.01$), but without impact on survival (21) (Fig. 16.2).

Follow-Up

Consensus recommends hormonal monitoring every 2 months in the first years, followed by monitoring every 4 months in the second years and every 6 months from then on (20). Imaging

studies are indicated only in the presence of hormonal abnormalities in case of functional ACC.

Results

In children, considering all the stages, 5 years of overall survival (OS) ranges from 34% to 54%. Event-free survival (EFS) and OS are very close (9). Stages (quality of resection, tumor weight, and metastasis), age, and virilization are factors significantly associated with survival. In patients with stages III or IV, OS is from 0% to 20% at 5 years. Five years of OS for stages I and II is 80%–100% and 30%–50%, respectively (9).

PHEOCHROMOCYTOMA: PARANGLIOMA

Definition

These tumors arise from the chromaffin cells in the sympatheticadrenal system (22–24). Pheochromocytomas (PHs) are developed from medullary gland, whereas paragangliomas (PGLs) come from extramedullary chromaffin cells (Zuckerkindl organ, bladder, kidney hilar, posterior mediastinum, pericarditis, head, and neck) (25). Adrenal medullary PHs produce epinephrine and norepinephrine, whereas most PGLs (about 10% of cases) produce only norepinephrine. Some of these tumors are nonsecretor. The risk of malignancy is higher for PGL than for PH (26).

Histology

As with many other neuroendocrine tumors, distinction between benign and malignant tumors is difficult. The histologic scaling system “Pheochromocytoma of the Adrenal Gland Scaled Score” uses a range of histologic criteria (vascular and capsular invasion, necrosis, and increased mitotic figures) to determine aggressive behavior, but it cannot predict malignancy. Histologic markers (Ki67, p53) may be indicative of a malignant disease, but none has been shown to be a prognostic marker (27). Malignancy is defined retrospectively by presence of metastases (25).

Epidemiology

The incidence of PH and PGL in the pediatric population is rare, accounting for <1% of childhood cancer, with an incidence of 2 per million (28–30). Two third of pediatric cases occur in boys. The incidence of malignant PH range depends on genetic background from 3% to 36% (31).

Genetic

Classically, it was thought that 10% of PH/PGL cases were hereditary, the remaining 90% being sporadic or nonsporadic. Familial PH/PGL was associated with three endocrine tumor syndromes: multiple endocrine neoplasia 2 (mutation of RET gene, PH, medullary thyroid cancer, and hyperparathyroidism), Von-Hippel-Lindau and neurofibromatosis (NF1) diseases. In 2000, the identification of germ-line mutation in succinate dehydrogenase complex changed this data, whereas mutation in one of six susceptibility genes *VHL*, *RET*, *SDHB*, *SDHC*, *SDHD*, and *NF1* was identified in 24%–27% of cases (32–34). In a pediatric series, this proportion grows up to 40% (30). So, genetic counseling is recommended after diagnosis of PGL/PH.

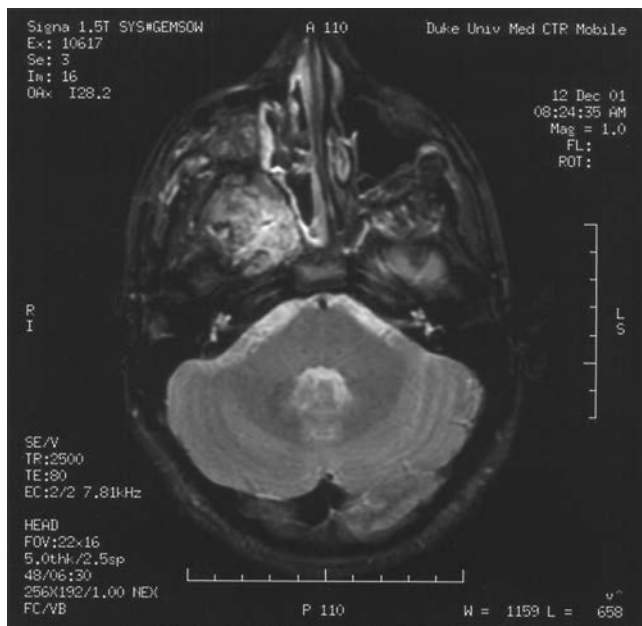


Figure 16.2 A 14-year-old boy presented to the radiation oncology department after multiple surgical and embolization procedures intended to remove and devascularize a juvenile nasopharyngeal angiofibroma. Detailed three-dimensional mapping of the tumor was performed using magnetic resonance imaging accompanied by careful fiber-optic examination. The mass was treated, with a margin, with a mixture of 6- and 15-MV photons to a cumulative dose of 40 Gy. Over the subsequent 2 years, striking regression of the mass was seen. Before RT, the child had been subjected to repeated episodes of bleeding, which ceased after RT.

Clinical Aspect

The classic triad presentation associates headache, sweating, and palpitations, but hormone secretion can be associated with a wide variety of symptoms (fever, nausea, weight loss, fatigue, and headache), although hypertension is the most consistent clinical sign (27). Childhood hypertension can be explained by PH/PGL in 1% of cases. Convulsions and hypertrophic cardiomyopathy can also occur (29). Prevalence of asymptomatic PH is estimated to be 21% more in sporadic tumors. Children with PH have higher incidence of bilaterality higher association with genetic predisposition than adults (29).

Biology

Screening studies include urinary 24-hours and plasma levels. Urinary and plasma levels of normetanephrine, norepinephrine had a high sensitivity (29), 100% in pediatric series. Urinary and plasma levels of epinephrine or metabolites (vanillyl mandelic acid) had lower sensibility (33%–57%) (35).

Imagery

Imaging tests should be employed for localization after biochemical diagnosis is confirmed. TDM and MRI are sensitive to localize the tumor; iodine 131-MIBG scan confirms the functional aspect. 18-F-DOPA TEP is promising for more accurate diagnosis of PGL/PH, particularly in patients with negative MIBG (36,37).

Treatment

En bloc resection is the major treatment of PGL/PH. Appropriate preoperative management is necessary to avoid perioperative complication due to catecholamine secretion. Alpha blockers (i.e., prazosin) and calcium blockers (i.e., nicardipine) are used to reduce hemodynamic instability. Introduction of medical preoperative treatment in 1950 reduced perioperative mortality, from 45% to less than 2% (27).

Laparoscopic resection is preferred to open procedure because it decreases the blood loss during surgery and postoperative length of stay (35). Open procedures are reserved for very large tumors or suspicion of malignancy with capsular effraction or regional disease (27,29).

Chemotherapy was described in malignant disease in one pediatric series using cisplatin and adriamycin. Cyclophosphamide, vincristine, and dacarbazine were used in an adult series (29,38). No randomized studies are available. These combinations of chemo can provide tumor regression and symptom in up to 50% of patients.

External beam irradiation (EBRT) is effective on bone metastases, bones lymph nodes, and brain and spinal cord metastases. Yu et al. reported efficiency of RT in nerve decompression (39).

I-labeled MIBG therapy is the single most valuable treatment after surgery in metastatic disease (31). Symptomatic response was observed in 77%–80% of cases in an adult series, hormonal response in 50 % of cases, and tumor responses in 30%–50% of cases. No benefit was observed on 5-year survival (40,41). There is no consensus of doses to use. The major adverse effect is bone marrow aplasia.

Results

OS and 5-year disease-free survival (DFS) depend on malignancy and genetic abnormalities. Coutant et al. (42), in a

review, found 30 cases of pediatric malignant PHs with 3-year survival rates significantly lower in SDHB mutation than in other cases (34).

A 100% OS and 5-year DFS were found in a series with low malignant rates (35). The probability of long-term recurrence justifies an indefinite clinical and biochemical follow-up (34).

THYROID CARCINOMA

Histology/Epidemiology

According to WHO 2004 classification, thyroid cancers are divided into the following categories:

A. Carcinoma derived from the follicular epithelium:

Follicular carcinoma: no papillary nucleus are seen in these tumors; capsular and vascular invasion is common

Papillary carcinoma: nucleus are typical, with cytoplasmic inclusions

Poorly differentiated carcinoma: includes insular and solid/trabecular carcinoma, with morphology between well-differentiated and poorly differentiated tumors

Nondifferentiated carcinoma: loss of follicular architecture, with aggressive behavior (necrosis, mitosis, vascular invasion, ...)

B. Medullary carcinoma: this subtype derived from C-cells or neural crest—parafollicular cells.

C. Other tumors: lymphomas and metastasis from other cancers

For didactic reasons, three groups of tumors will be separated in next paragraphs:

Follicular, papillary, and poorly differentiated carcinoma

Nondifferentiated carcinoma

Medullary carcinoma

Thyroid carcinoma represents 1% of childhood cancer, 80% in females. Papillary carcinoma represents 90%–95% of pediatric cases, whereas follicular, poorly differentiated, and medullary carcinomas are exceptional; anaplastic forms are practically absent (43,44).

Follicular, Papillary, and Poorly Differentiated Carcinoma

Risk Factors

Risk factors for developing thyroid malignant nodule in children are female sex, postpubertal age, coexisting thyroid disease, family history of thyroid disease, and previous irradiation of the neck. We study in another chapter epidemiologic and specific management aspect of radio-induced nodules of the thyroid (45).

Clinical Aspect

Clinical presentation of pediatric thyroid carcinoma differs significantly from that of adults by delay with the diagnosis. In a Mayo Clinic series, the volume of thyroid nodule was much larger as well as neck node involvement or distant metastases were found more frequently in childhood (90% and 7% of cases, respectively) (43,44). At least 40% of pediatric

differentiated thyroid cancers were multifocal at diagnosis. Lung is the more frequent site of distant metastasis.

Biology

Most children with thyroid carcinomas are euthyroid.

Imagery

Ultrasonography (US) of thyroid gland and neck is the better and less invasive examination to explore thyroid nodule or neck adenopathy. US criteria used to identify malignant nodule in children are controversial. However, irregular shape, hypoechogenic aspect, increased peri- and intranodular vascularization at Doppler US examination are significantly associated with malignancy in nonfollicular neoplasm (46,47). Fine-needle aspiration and cytology of thyroid are justified in nodules > 1 cm diameter or in US suspicious nodules. Accuracy of fine-needle aspiration and cytology of thyroid nodule is less known in childhood than in adults, but “follicular lesion” at cytology indicates need for thyroidectomy, to establish anatomopathologic diagnosis (45,48).

Classification

Tumor node metastasis (TNM) classification was revised in 2004 and is the most used (49).

Prognostic Factor

In papillary thyroid cancer, mutation of RET, BRAF, or RAS, activating the MAP kinase pathway, is found. Contradictory data are reported, but it seems that RET rearrangements are more frequent in children and BRAF mutation is absent. No correlation with a genetic pattern and an aggressive behavior of thyroid carcinoma is established yet. (50).

Treatment

Surgery. According to guidelines of international societies, total thyroidectomy with en bloc dissection of the central compartment is the preferred operation in T1 stage or over followed by postoperative serum thyroglobulin (Tg) levels monitoring and I-131 therapy (51,52). Lobectomy alone was discussed in the past but this less-aggressive strategy leads to higher recurrences due to the high rate of multifocal disease. The extent of lymph node removal is also debated; central compartment dissection is the more consensual, while routine removal of jugular–carotid chains remains controversial (51). Immediate complications of this surgery are permanent hypoparathyroidism and laryngeal nerve injury, described in respectively 12% and 1% in a pediatric series (52,53).

Radioiodine Ablation. After total thyroidectomy, radioiodine ablation (RAI) is performed to destroy thyroid residues and occult distant metastasis or cervical lymph nodes. Chow et al. in a pediatric series showed that postoperative RAI significantly reduces the risk of relapse and 10-year locoregional failure-free survival (54). This data was confirmed by a multivariate analysis of a large pediatric series, independently of surgery or lymph node resection (50).

The American Thyroid Association (ATA) task force recommended RAI ablation from stage I with aggressive features to stage IV carcinoma. To maximize RAI uptake, serum-level thyreostimuline (TSH) should be above 30 mUI/L after L-thyreostimuline. R-TSH injection is not labeled in pediatric. Postoperative L-thyroxin supplementation is necessary.

There is no consensus regarding RAI doses in adult and in children between 30, 100, and 150 mCi or adapted dose to the body weight. In adults, most centers used 100 mCi, but more data are required to determine the minimal effective doses for children on thyroid remnant destruction, recurrence rate, and DFS (50,51).

Consecutive serum levels thyroglobulin measurement allow to confirm the residu or metastatic ablation. (51). Unstimulated and stimulated Tg levels must be undetectable. Raised Tg would provide indirect evidence of presence of functional thyroid tumors. Pediatric differentiated thyroid carcinomas appear to be more radioiodine sensitive than adult carcinomas. RAI could be repeated every 6 months.

Pediatric thyroid differentiated carcinomas appear to be more radioiodine sensitive than an adult, and RAI could be repeated every 6 months. Limits of cumulated doses is not established, but leukemia risks increase between 18.5 and 37 GBq. Early side effects (nausea, vomiting) are more frequent in children than in adults. Bone marrow or pulmonary fibrosis can appear after repeated doses to treat bone or pulmonary metastases. Second cancers are rare but can occur too (50,51).

TSH Suppression. The optimal degree of TSH suppression is debated. In adults, one scheme proposed by Baudin et al. is to suppress TSH levels initially under 0.1 mUI/L and then to allow a TSH levels at 0.5 mUI/L once the patient enters remission (55). This recommendation could be extended for children (51).

External Beam Radiotherapy. There is no place usually for this treatment in local differentiated thyroid carcinoma. Kim et al. have studied the benefit of EBRT in T4 stage (56). No significant difference in survival was found. The 7-year survival rate was 98.1% for no-EBRT group and 90% for EBRT group, but the locoregional control at 5 years was significantly higher after EBRT (95.2% vs. 67.5%) (56).

Bone or soft tissue metastases that are not suitable or do not respond to RAI may be treated effectively with conventional EBRT.

Follow-Up

Follow-up is recommended by TSH, T3I, T4I, and Tg measurement at 3 months, with US of the neck. Tg measurement after R-TSH is performed at 6 and 12 months associated with US of the neck. In cases of persistent relapse disease, repeated lymph node or metastasis removal is possible.

If Tg is undetectable, a 1-year TSH and Tg level, coupled with US of neck seems to be sufficient. If Tg is detectable, TSH suppression must be maintained under 0.1 mUI/L and Tg level has to be followed. Any increase in Tg level during follow-up should lead to US and/or I-131 whole-bone scintigraphy to look for recurrent disease (57).

Result

Results in pediatric series are presented in Table 16.2. Survival rate of children diagnosed with a thyroid cancer is good, 97% in the EUROpean CAncer REgistry–based study on survival and CARE of cancer patients (EUROCARE study)(66), and similar data are reported in the United States (67). Relapse-free survival (RFS) was similar considering the age in a multivariate analysis including treatment-related factors (44). In another pediatric series, RFS rate was 77%, OS 100%, with no statistical difference considering age at diagnosis. This series

Table 16.2

Differentiated Thyroid Cancer in Children from 11 Pediatric Series

Clinical Series											
	Jianping et al. (58)	Harness et al. (59)	Samuel and Sharma (60)	Zimmerman et al. (61)	La Quaglia et al. (62)	Ceccarelli et al. (63)	Schlumberger et al. (64)	Newman et al. (53)	Jarzab et al. (44)	Giuffrida et al. (65)	Collini et al. (43)
No. of patients	14	89	59	58	100	49	72	329	109	48	75
Mean age (year)	NA	12.8	NA	11.9	13.3	14.0	11	15.2	13.6	18.1	14
Female (%)	NA	81	66	69	71	69	71	76	69	71	69
Histology (%)											
Papillary	86	93	63	100	87	90	69	90	71	83	100
Follicular	14	7	32	0	7	8	29	10	29	17	
Medullary	0	0	2	0	0	2	0	0	0	0	
Other	0	0	3	0	6	0	0	0	0	0	
Metastasis (%)	86	88	50	90	71	73	75	74	75	52	12 M+/86 N+
Surgical Procedure (%)											
Total	93	89	83	36	46	0	40	54	74	NA	76
thyroidectomy											
Subtotal	7	11	^a	63	^a	100		46	26	NA	2.5
thyroidectomy											
Subtotal							60				
lobectomy											
Other subtotal		84	NA	84	89	73	83	78	NA	100	
lymph node											
procedure											
Percentage	NA	82	71	17	22	98	42	43	64	NA	100
receiving											
radioactive											
iodine											
Median	6	NA	11	28	20	7.7	13	11.3	5	6.1	16
follow-up											
(year)											
Cancer											
mortality (%)	0	2.2	NA	3.4	0	2.0	17	0.7	0	0	0

NA, data not available.

^aIn these studies, the children who had a total or near-total thyroidectomy were not subgrouped. Expanded and modified from a table in Skinner MA. Cancer of the thyroid in infants and children. *Semin Pediatr Surg.* 2001;10:119–126, with permission.

confirms that outcome of pediatric thyroid carcinoma is independent of prognostic factors often used in adults: extrathyroid invasion, metastasis, and tumor size (43).

RADIATION-ASSOCIATED THYROID CANCER IN CHILDREN

Cancer Survivors

More than 75% of children treated for cancer have been cured, and studies are now focusing on the late effects of treatments for these long-term survivors (68). In the Childhood Cancer Survivor Study, including more than 20,000 survivors of leukemia, central nervous system (CNS) cancer, Hodgkin disease, non-Hodgkin lymphoma, kidney cancers, neuroblastoma, soft tissue sarcoma, and bone tumors, any radiation exposure to the thyroid gland was associated with a 2.6-fold increased risk of thyroid cancer (95% IC 1.1–7.1) (69). Histologic subtype was papillary in 78% of cases. Sixty-six percent of thyroid cancers were diagnosed 10–19 years after the first cancer (median 15–19 years). Risk of thyroid cancer increased with radiation until 30 Gy and decreased after, consistent with a cell-killing effect of radiation at high dose. The dose–response relation differed by age at first cancer diagnosis, and the peak of relative risk was higher if the first cancer was diagnosed after 10 years. Hodgkin lymphoma seems to be a risk factor for thyroid malignancy, independent of radiation dose and age at the time of first cancer diagnosis. Thyroid cancers were usually diagnosed at lower tumor size after Hodgkin disease, due to systematic surveillance of Hodgkin survivors.

Long-term follow-up guideline for survivors of childhood cancer recommends a yearly clinical examination of the thyroid gland. US screening to detect no palpable nodules are discussed (47).

Tchernobyl Accident

After the Chernobyl accident, incidence of thyroid cancer among children increased more than 100-fold and occurred in children less than 5 years old. Risk of thyroid cancer exposed to environmental contamination was linear over the dose range of up to 2.7 Gy, and the excess relative risk was estimated: 1.65 per Gy (IC 95% 1.10–3.20) (69). Pacini et al. have compared post-Tchernobyl thyroid carcinomas and naturally occurring carcinoma in Italy and France (70). In Belarus, thyroid cancers affected younger subjects, were less influenced by gender, were mostly papillary, and had a higher aggressiveness at presentation.

Specific DNA damages were associated at this type of cancer (71). Some of these cases were also explained by chronic iodine deficiency in many of the contaminated areas before the accident.

Medullary Thyroid Carcinoma

Clinical Aspect. Medullary carcinomas account for up to 8% of thyroid cancer in adults (72). It is a tumor derived from parafollicular or C-cells of the thyroid, which can secrete calcitonin. As a consequence, clinical presentation is mainly thyroid nodes with or without diarrhea, due to calcitonin secretion (72).

Genetic. One fourth of the cases are associated with MEN 2A syndrome (MTC, PH, and parathyroid gland hyperplasia),

MEN 2B (MTC, PH, no hyperparathyroidism, and marfanoid status), or familial non-MEN MTC (strong predisposition to develop MTC without other clinical manifestation of MEN 2A), with different mutation of RET oncogene. Even if these syndromes are rare, recognition is important to genetic counseling (73). A strong genotype–phenotype correlation was observed with aggressiveness, time of onset MTC, and presence or absence of other endocrine tumors (73). The primary surgery is curative in the majority of patients with early stages, but up to 80% of patients with palpable disease have nodal involvement.

Treatment. Genotype–phenotype correlation and clinical presentation are the basis for recommendation to prophylactic thyroidectomy in childhood (73). Three levels of risk were defined in a codon-based genotype–phenotype correlation.

Transforming potential of level 3 (codon 918 and 883 in MEN 2B) and level 2 (e.g., codon 634 in MEN 2A) mutations are well established, and total thyroidectomy is recommended, respectively, as early as possible, preferably before the first years of birth and before the age of 5 years (73).

For level 1 (FMTC, codon 804 or 891 MEN 2A), age at prophylactic surgery is discussed, when calcitonin level rises before 5 or 10 years of age (73).

Distant metastases are observed in up to 25% of cases. Reoperation is the best treatment, but cytotoxic chemotherapy drugs such as cyclophosphamide and vincristine have been tested, with a poor response rate (72). Interferon- γ or somatostatin analogs are used to improve diarrheal symptoms. Thyroid kinase inhibitors, such as vandetanib, sorafenib, motesanib, or sunitinib, have been studied in this indication based on the inhibition of RET protein. Phase II trials are promising; they showed partial response or stabilized disease according to RECIST criteria.

Local invasion can be eventually treated by external beam radiotherapy, with poor results (72,74).

AERODIGESTIVE TRACT

Juvenile Nasopharyngeal Angiofibroma

Epidemiology

Juvenile nasopharyngeal angiofibroma (JNA) is a rare benign neoplasm of the nasopharynx. It represents 0.5% of all head and neck tumors (75) with an incidence of 1 per 150,000. It predominantly affects adolescent boys and men between the ages of 14 and 25 years, rarely after 5 years (76–78).

Both male predominance and time of occurrence (adolescence) suggest a link of JNA with hormonal status (79). Hormonal disorders have been reported in patients with JNA. Moreover, androgen and estrogen receptors have been identified in tumor tissue. Studies on genetic and molecular changes are going on to better define the pathology.

Histology

JNA is a benign but locally aggressive vascular tumor, developed from the posterolateral wall of the nasal cavity. JNA may extend to the nasal cavity, the maxillary, involve the skull base, and extend intracranially. JNA tends to extend along natural foramina and fissures, spreading toward the paranasal sinus (ethmoid, sphenoid, and maxillary) and through the pterygopalatine fossa laterally. This growth in soft tissue

spaces is limited only by bone, which can be eroded by pressure. The vascular structures of the basisphenoid region can be involved, especially in the area of the sphenopalatine foramen (80). Intracranial extension has been reported in 10%–20% of all cases before the era of modern neuroimaging. JNA's etiology and pathogenesis remain unknown. Origin of JNA are discussed : main retained causes are vascular or fibrous.

JNA is a nonencapsulated benign tumor composed of a proliferating and irregular vascular component within a fibrous stroma (81–84). Some angiogenic markers, growth factors, and proliferation markers have been found to be associated with the pathogenesis of JNA, and some were also described in vascular anomalies (85–87). In recent immunohistochemical studies, vascular endothelial growth factor (VEGF), its transcriptional regulator hypoxia-inducible factor-1 (HIF-1), and other proangiogenic factors have been localized in JNA stromal cells, suggesting that deregulated vessel growth is driven by stromally derived growth factor (88–91).

Clinical Aspect

Patients with JNA usually present with recurrent painless spontaneous epistaxis, nasal obstruction, facial deformation, and nasal discharge. Less frequently, a reduced sense of smell, snoring, headache and facial swelling, and cranial nerve palsies can lead to JNA diagnosis (92,93).

Imagery

The tumor mass is usually seen on CT as a well-delineated and high-density lesion that display a homogeneous enhancement. A mass in the posterior nasal cavity and pterygopalatine fossa is the first constant sign. The erosion of bone behind the sphenopalatine foramen with extension to the upper medial pterygoid plate must also be checked. Good bone imaging on CT is essential to show invasion of the cancellous bone of the sphenoid. MRI scans are particularly useful in analyzing the intracranial and intraorbital extension. CT and MRI usually permit the estimation of extent, avoiding the dangers of biopsy. The characteristic features on MRI are due to the high vascularity of the tumor causing signal voids and strong postcontrast enhancement. The vascular supply may come from the internal maxillary, accessory meningeal, ascending pharyngeal, or ascending palatine arteries. MRI shows the preoperative soft tissue extent of angiofibroma optimally, but its more important application is to provide postoperative surveillance to show any residual or recurrent tumor, record tumor growth or natural involution, and monitor the effects of RT (94,95). Due to possibility of asymptomatic relapses, a CT or/and MRI is recommended about 4 months after surgery, to rule out posterolateral or extranasopharyngeal recurrences. Spontaneous evolution of residual masses should also be evaluated on successive CT/MRI examinations (96).

Prognostic Factor

The reported rate of recurrences following treatment varies between 0% and 57% (84,97,98). The main predictor of recurrence seems to be the invasion, while the deeper the extension, the larger the potential tumor remnant likely to be left following surgery. In a retrospective study on 55 males treated for JNA, size of tumor and type of invasion were

predictive for relapse: Invasion to anterior infratemporal fossae (ITF) and/or to pterygomaxillary fossae, to posterior ITF or intracranial extension were associated with recurrences in 2 of 15, in 8 of 18, and in 8 of 12 cases, respectively. Tumors less than, greater than, or equal to 6 cm were associated with zero and with 18 recurrences, respectively ($p = 0.006$) (99). Similarly, a retrospective review of 44 cases treated between 1985 and 1996 was published. Invasion of the skull base affected two thirds of the patients, and the rate of recurrence was 27.5%. Extensions to the infratemporal fossa, sphenoid sinus, base of pterygoids and clivus, cavernous sinus, foramen lacerum, and anterior fossa were correlated with more frequent recurrence (95).

Treatment

Surgery and EBRT are the two main definitive treatments for JNA. They can have a complemented interest in the management of JNA.

A wide variety of scales and staging systems have been described (Table 16.3). While the treatment of small JNA is well recognized to be surgical, local infiltration (especially to the infratemporal region) often leads to propose RT due to the risks of surgery (107,108).

Chemotherapy. Chemotherapy with doxorubicin and dacarbazine or vincristine, actinomycin, and cyclophosphamide has been used for recurrent lesions that are not amenable to additional surgery or irradiation with some success (109,110). Flutamide has also been tested in neoadjuvant JNA treatment, with poor results; the mean tumor reduction was 11% in a small series of seven patients (111).

Surgical approach.

Radical Surgery There are several surgical approaches: transpalatal, lateral rhinectomy, and craniofacial resection, with infratemporal approach. Preoperative hormone therapy such as flutamide (112) and embolization before surgery are still discussed. With adequate operative exposure and resection, 70%–100% of the patients are cured without adjuvant treatment.

Endoscopic Resection The use of an endoscopic approach to treat small JNA is supported by good results from a number of operative series published in recent years (113,114). For instance, 20 young patients were treated for JNA using three different surgical approaches between May 1998 and January 2007. Nine patients were managed using endoscopic approach, five were treated through midfacial degloving, and six patients had a transpalatal approach. Preoperative angiography with embolization was performed in all nine patients who underwent endoscopic approach, and three patients were treated by midfacial degloving technique. Endoscopic approach, assisted by preoperative embolization, led to less intraoperative blood loss, shorter duration of surgical procedure, shorter length of hospital stay, and no complications, compared with the conventional techniques (115). Another study identified 65 patients treated for JNA, mean age 15 years. Six consecutive patients underwent successful resection of JNA by way of an endoscopic approach since 2001. Compared with the conventional surgery group, the endoscopic group had less intraoperative blood loss (225 vs. 1250 mL), a lower occurrence of

Table 16.3**Six Proposed Staging Systems for Juvenile Nasopharyngeal Angiofibroma**

Chandler et al. (100) and Jacobsson et al. (101)	
Stage I	Tumor confined to nasopharynx
Stage II	Extension into nasal cavity or sphenoid sinus
Stage III	Extension into one or more of the following: antrum, ethmoid sinuses, pterygomaxillary and infratemporal fossae, orbit, or cheek
Stage IV	Intracranial extension
Fields et al. (102)	
Stage I	Tumor confined to nasopharynx or nasal fossae
Stage II	Extending into the sphenoid sinus or pterygomaxillary fossae
Stage III	Extending beyond stage II limits into maxillary sinus, ethmoid sinuses, orbits, infratemporal fossae, cheeks, or palate
Stage IV	Intracranial extension
Sessions et al. (103)	
Stage IA	Limited to posterior nares or nasopharynx
Stage IB	Extension into one or more paranasal sinuses
Stage IIA	Minimal spread into pterygopalatine fossa
Stage IIB	Occupation of the pterygopalatine fossa displacing posterior maxillary wall; possibly erosion into orbit
Stage IIC	Extension through pterygopalatine fossa into infratemporal fossa or cheek
Stage III	Intracranial extension
Andrews et al. (104)	
Type I	Tumor limited to the nasopharynx and nasal cavity. Bone destruction negligible or limited to the sphenopalatine foramen
Type II	Tumor invading the pterygopalatine fossa or the maxillary, ethmoid, or sphenoid sinus with bone destruction
Type IIIa	Tumor invading the infratemporal fossa or orbital region without intracranial involvement
Type IIIb	Tumor invading the infratemporal fossa or orbit with intracranial extradural (parasellar) involvement
Type IVa	Intracranial intradural tumor without infiltration of the cavernous sinus, pituitary fossa, or optic chiasm
Type IVB	Intracranial intradural tumor with infiltration of the cavernous sinus, pituitary fossa, or optic chiasm
Fisch (105)	
Type I	Tumor limited to the nasopharynx and nasal cavity with no bone destruction
Type II	Tumor invading the pterygomaxillary fossa, maxillary, ethmoid, and sphenoid sinus with bone destruction
Type III	Tumors invading the infratemporal fossa, orbit, and parasellar region remaining lateral to the cavernous sinus
Type IV	Tumor with massive invasion of the cavernous sinus, optic chiasm region, or pituitary fossa
Radkowski et al. (106)	
Type IA, IB, IIA, IIB	Same as the system of Sessions et al.
Type IIC	As in Sessions et al. or posterior to pterygoid plates
Type IIIA	As in Sessions et al., erosion of skull base, and minimal intracranial
Type IIIB	As in Sessions et al., erosion of skull base, extensive intracranial with or without cavernous sinus

complications (1 patient vs. ≥ 30 patients), shorter length of hospital stay (2 vs. 5 days), and lower rate of recurrence (0% vs. 24%) (116). In long-term results of the endoscopic approach, a retrospective study of 21 consecutive patients undergoing endoscopic resection of JNA showed, with a mean follow-up of 52 months (range of 5–120), 71.4% of the patients were free of disease after one endoscopic resection (117). Three patients (14.3%) developed a recurrence with the need for further treatment at 6, 14, and 23 months, respectively. Two of the three recurrent tumors were successfully resected endoscopically; one case was treated with gamma knife.

Radiotherapy. RT has been well described as an efficient treatment for advanced disease or in case of relapse after surgery. Dose ranging from 30 to 50 Gy at 1.8 to 2 Gy per day give excellent results (Table 16.4) considering the more recent studies available (102,109,118–121). RT techniques are not well described. In recent series, patients are usually treated in conformal RT, or with intensity modulation, using a head holder. Inadequate treatment fields are the major cause of local failure (124). Proper mapping of the tumor volume is crucial, using CT and MRI (fusion) to establish the treatment volume, including cranial extension if necessary. The margins are not clearly defined in the

Table 16.4**Radiotherapy for Juvenile Nasopharyngeal Angiofibroma: Most Recent Studies**

Reference	Year of Report	Number of Cases	Dosage Range (Gy)	Local Control	Follow-up
Fields et al. (103)	1990	13 ^a	35–52	11/13 (85%)	2–25 years
Gullane et al. (118)	1992	7	30–35	3/7 (42%)	7–10 year
Kasper et al. (122)	1993	9 ^f	30–35	9/9 (100%)	3–15 year
Wiatrak et al. (119)	1993	3	36–50.4	3/3 (100%)	1.7–4.5 year
Ungkanont et al. (123)	1996	2	35–45	1/2 (50%)	
Reddy et al. (120)	2001	15	30–35	13/15 (85%)	2.5–24 year
Lee et al. (121)	2002	27	30–55	23/27 (85%)	3–42 year
McAfee et al. (76)	2006	22	30–36	20/22 (91%)	2–30 year
Roche et al. (93)	2007	73 with stereo 4 with stereo	14–16 25–50	3/3 (100%) 4/4 (100%)	3–5 year 1.5–20 year

^aSome of these patients had relapses after surgery rather than primary radiotherapy.

literature. Recently, McAfee et al. took approximately 2-cm margins around the tumor for the treatment planning with excellent local control (76). Late effects, especially the risk of malignant cancer, neuroendocrine dysfunction, cataract ..., must always be considered but these effects remain quite rare and should be weighted against the risk of surgery in case of advanced disease. A large retrospective study on 130 patients treated over a 41-year period (1960–2000) was published. Twenty-seven patients received radiation (30–55 Gy) as first treatment (121). Fifteen percent of the irradiated patients developed relapse 2–5 years later. Fifteen percent of the patients developed significant late complication, including growth retardation, panhypopituitarism, temporal lobe necrosis, cataracts, and radiation keratopathy. Two of the patients developed in-field cutaneous basal cell carcinomas but were at risk for skin tumors. Second malignancies have been observed in other series. Cummings et al. reported one patient who developed thyroid carcinoma after 35 Gy (124). The main visual complication after RT is cataract formation, while optic neuropathy and retinopathy are uncommon at conventionally fractionated doses between 30 and 36 Gy. Cummings et al. reported cataract development in 2 of 55 patients (3.6%) (124). Lee et al. observed cataracts in 3 patients on 27 (11%) (121). Cummings examined the comparable risk factors associated with surgery and RT and found that the relative risks of significant complications were similar with both treatment modalities (124). Intracavitary RT has been used rarely (125) but not used anymore due to major bleeding and inadequate coverage of the treatment volume (124).

Nasopharyngeal Carcinoma

Many of the principles established in adults apply to childhood nasopharyngeal carcinoma (NPC). However, childhood NPC should be distinguished from the adult form by several points, detailed below.

Histology

The World Health Organization (WHO) has classified NPC into three subtypes: type I is keratinizing squamous cell carcinoma, type II is nonkeratinizing epidermoid carcinoma,

and type III is undifferentiated carcinoma. The malignant origin is epithelial, but in tumor types II and III, lymphoid, plasmoid, and eosinophilic cell infiltration are common. The most common histologic type seen in children is undifferentiated carcinoma, with a high incidence of locoregionally advanced disease (126–129).

Epidemiology

NPC represents 1% of all childhood cancers, and 40%–50% of all malignancies involving the nasopharynx in children (130–132). The classic age incidence is bimodal with a first peak of incidence at 10–20 years and a second at 40–60 years (133–137). The incidence of NPC varies according to racial and geographic factors. Undifferentiated NPC is an endemic tumor that is common in southern parts of China, Southeast Asia, Alaska, and the Mediterranean Basin. In children, the median age of NPC development is 13 years, with a male predominance (sex ratio 1.8:1) (138).

Genetic

Individuals who have human leukocyte antigen A2 Bsin2 haplotype, Aw19, Bw46, and B17 types were found to have an increased risk of NPC leading to a genetic determinant of NPC (139,140).

Clinical Aspect

The tumor initially develops in the walls of the nasopharynx without any symptoms, explaining the usually late diagnosis. The most common presenting symptom is a painless mass in the upper neck. Of 484 confirmed NPC cases reported in Malaysia from July 1, 2007 to February 29, 2008, 225 were newly diagnosed cases. Among them, the most common presenting symptom was the presence of neck lumps (42%) (141). Other series report upper neck nodes in about 70%–90% of cases (138). Local tumor effects can include nasal obstruction, blood-tinged drainage, bleeding, and conductive hearing loss or serous otitis. When the tumor invades the base of the skull through direct extension, the cranial nerves are frequently involved leading to symptoms (drooping of the upper eyelid, eye pain, loss of vision, double vision, difficulty swallowing, spasms of masticatory muscles, disturbances of taste and voice, ...).

Metastasis Involvement

About 20% of the patients have metastasis at diagnosis (142). Among them, metastatic regions include the bones (60%–70%), liver (about 30%), lungs (about 20%), bone marrow (about 20%), and mediastinum.

Biology

NPC in childhood is distinguishable from the adult form of the disease, while Epstein–Barr virus (EBV) infection association has been well described in childhood (143,144). EBV has been identified as a causative agent in several patients. High antibody titers of immunoglobulin G (IgG) and immunoglobulin A (IgA) against early antigen or viral capsid antigen are commonly seen in patients with NPC, particularly those with the undifferentiated form of the disease. Circulating EBV DNA load may be a useful prognostic marker in endemic regions. However, for a definitive diagnosis, an endoscopic examination and a biopsy from primary tumor should be done.

Imagery

Contrast-enhanced cranial CT and MRI are useful to assess the extent of local tumor growth and base of skull involvement. A heterogeneous mass (primary tumors and lymph nodes) with a part of necrosis has been reported as characteristic in adults (145). It is less defined in childhood. Thirteen patients, 30 years old or less, with undifferentiated NPC were reviewed in terms of CT and MRI findings. The signal intensity of tumors was slightly higher than that of muscles in six cases and isointense to that of muscles in two cases on T1-weighted images. In all cases, the signal was higher than that of muscle and lower than that of cerebellar gray matter on T2-weighted images. Internal signals were homogeneous in both pre- and post-gadolinium-enhanced MR images in all cases. (146).

Recent publications have shown the superiority of fused PET/CT over PET alone and conventional imaging to do an accurate staging and to impact on patient management. PET/CT response after therapy and its place in the follow-up need to be prospectively evaluated, especially in children. A large prospective study on adults (8) assessed the usefulness of fluorodeoxyglucose (FDG)-PET in initial M staging of NPC. Three hundred patients with NPC were compared in terms of staging. Conventional workup (CWU) included chest radiography, abdominal US, and skeletal scintigraphy and was compared with FDG-PET staging. About 20% patients were found to have distant metastases. FDG-PET was more effective than CWU ($p < 0.001$) to find them, especially for detecting bone ($p < 0.001$) and chest metastases ($p < 0.001$). It was equally effective for detecting hepatic metastases than abdominal ultrasound (142). However, its real impact on therapeutic management needs to be prospectively evaluated.

Prognostic Factor

TNM stage is the major prognostic factor for NPC. Locoregional invasion may extend to cranial nerves and the base of the skull, which increases the risk of local failure after RT (147).

Classification

New criteria for classifying NPC were defined in the seventh edition of the American Joint Committee on Cancer (AJCC)

staging manual (Table 16.5). Several classifications for NPC have been done, but the most popular in Western countries is the AJCC staging system (148). The fifth edition of this classification was designed to merge the best predictive factors of the fourth edition. Another staging system is most frequently applied to Asian populations, described by Ho and al. (149).

NPC prognosis is essentially based on initial TNM stage. For example, between 1990 and 2000, 81 pediatric patients from Mumbai, median age 14 years, with a diagnosis of NPC were treated. Of the 81 patients, 32 (39%), 21 (26%), and 28 (35%) had T1–T2, T3, and T4, respectively. Ninety-one percent had nodal metastasis. Thirty patients (37%) had lymph nodes >6 cm, and 45 (56%) had bilateral nodes at presentation. Nodal status had a significant impact on DFS ($p = 0.021$) and OS ($p = 0.006$) (132).

Treatment

Indications. Type of treatment depends on the NPC stage. Stage I patients usually receive exclusive RT, while stages II and III patients are treated with chemotherapy and RT. Stage IV patients usually receive CT.

Stage I. Exclusive RT remains the standard treatment of the initial stage I patients, without node involvement, leading to a 10-year survival rate (150).

Stages II–III. The place of chemotherapy remains controversial in the initial management of localized NPC. In adults, phase III trials and meta-analysis comparing induction chemotherapy with RT alone (151–154) did not show any improvement in OS, despite a significant reduction in local and distant failures (152,153). In addition, excess treatment-related deaths were only observed in the induction chemotherapy trials (155).

In contrast, recent trials and meta-analyses have confirmed the role of concomitant chemotherapy with RT in locoregionally advanced NPC. The last meta-analysis of chemotherapy in nasopharynx carcinoma (MAC-NPC) was performed by the Collaborative Group. Eight randomized trials compared chemotherapy plus RT versus RT alone in locally advanced NPC. All trials used conventional RT and cisplatin-based chemotherapy. A total of 1753 patients were included. A significant benefit was found for OS (6% at 5 years) and EFS (10% at 5 years) with the addition of chemotherapy. The benefit on survival was essentially observed when chemotherapy was administered concomitantly with RT (155). Concomitant (cisplatin-based) chemoradiotherapy now appears to be the standard treatment for locally advanced (T2B and more) and/or node positive (Np) patients in adults (156).

In children, some large studies tend to demonstrate the same results (157). As an example, some of them are presented below. Fifty-two patients, 18 years, with stages I–IVB NPC, received RT dose of 60–66 Gy in 2-Gy fractions to the nasopharynx and cervical nodes. Among them, 22 also received chemotherapy with cisplatin and 5-FU. Three-year DFS with concurrent chemotherapy was 82% compared to 40% for patients treated with RT alone ($p = 0.001$) without impact on 3-year OS. Thirty-three patients, median age 14 years, were also treated for stages I–IVB NPC. Thirteen patients (39%) received RT alone and 20 patients (61%) had chemotherapy and RT. The addition of chemotherapy had no significant effect on locoregional control but did reduce the

Table 16.5
Staging System for Carcinoma of the Nasopharynx

American Joint Committee on Cancer staging system

Primary Tumor	
T1	Tumor confined to the nasopharynx or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension
T2	Tumor with parapharyngeal extension (posterolateral infiltration of tumor, i.e., beyond the pharyngobasilar fascia)
T3	Involves bony structures and/or paranasal sinuses
T4	Intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space
Nodes	
N1	Unilateral nodes, 6 cm or less, above the supraclavicular fossa, and/or retropharyngeal lymph nodes 7 cm or less (unilateral or bilateral)
N2	Bilateral nodes, 6 cm or less, above the supraclav fossa
N3a	Lymph node greater than 6 cm
N3b	Extension to the supraclav fossa (defined as the triangular region described by Ho, bounded by the superior margin of the sternal head of the clavicle, the superior margin of the lateral end of the clavicle, and the point where the neck meets the shoulder. This includes some of level IV as well as V.)
Distant Metastases	
N3a	6 cm in dimension
N3b	Extension to supraclavicular fossa
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases
Stage	
I	T1 N0
II	T1–T2 N1, T2 N0 (i.e., T2 or N1)
III	T3 N0–2, or T1–3 N2 (i.e., T3 or N2)
IVA	T4 N0–2
IVB	N3
IVC	M1

Data from Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

development of distant metastases (16% vs. 57%, $p = 0.01$). Combined modality therapy improved 10-year DFS (84% vs. 35%, $p < 0.01$) and survival (78% vs. 33%, $p < 0.05$) over radiation alone (126).

Of 165 patients reviewed between 1978 and 2003, median age 14 years, 12.7% patients were treated with RT alone, while 87.3% received chemotherapy and RT. The median follow-up time was 48 months. In multivariate analysis, patients treated with RT alone had poorer locoregional relapses-free survival ($p = 0.0001$) as well as DFS than patients treated with chemotherapy and RT ($p = 0.002$) (158). Optimal regimen during RT has not been set up so far. Most chemotherapies are cisplatin-based combinations, used weekly or once every 3 weeks. The question to add induction chemotherapy followed by concomitant chemoradiotherapy remains controversial; it may be the best strategy to reduce distant metastasis. In adults, several phase II studies (39–41) have shown good results on a limited but poor prognostic population (T2B, 3, 4, and/or N+) selected on good performance status, but further studies are needed, especially in children due to a high risk of toxicity (159–161).

Stage IV Treatment of metastatic disease is based on chemotherapy. Anthracyclines and bleomycins, which are active in this peculiar epithelial head and neck cancers, were

the first agents used in chemotherapy regimens. To date, platinum-based regimens are the standard chemotherapy for metastatic NPC patients, and cisplatin–5-FU combination remains the most used in first-line treatment (162). For example, clinical characteristics, treatment regimens, survival, and late complications in patients with NPC were retrospectively evaluated on 84 patients, mean age 13 years, with NPC. Chemotherapeutic regimens involved cyclophosphamide from 1972 to 1982; vincristine, cyclophosphamide, epirubicin, and actinomycin-D protocol from 1982 to 1999; and cisplatin, methotrexate, and 5-FU with leucovorine rescue after 1999. A total of 78.5% of the patients were at advanced stage (stages III and IV). The survival rates (80%) were higher with the cisplatin-combination regimen (129,130,138,163).

Radiotherapy

Radiotherapy Dose. The optimum dose for local control NPC in children is not precisely known. Doses greater than 65 Gy have been shown to achieve better local control in some studies (128,129,130,148,163), but others have not shown any correlation between the dose of radiation, rate of local relapse, and survival time (130,164–166). Generally, doses ranging between 50 and 70 Gy are recommended for

patients older than 10 years, and a 5%–10% reduction in this dose is recommended for children younger than 10 years of age (130). Daily fractions of 1.8–2.0 Gy, 5 days a week are usually proposed in children. The spinal cord, brain stem, and optic nerve are shielded after 45–50 Gy, and the posterior lymphatic chains are treated with electron beams. The lower cervical and supraclavicular regions are treated with a single anterior portal and a median shield to protect the larynx and the spinal cord, with doses of 45–50 Gy.

One of the ongoing questions in children is to reduce the RT dose to lymph nodes and/or to the nasopharynx area in case of good response to chemotherapy, to limit the late effects of high-dose RT. For instance, a French study was recently published. Thirty-four children were treated for AJCC-TNM stage IV NPC. After chemotherapy, cervical nodal irradiation was reduced (<50 Gy) in the 15 cases of a good response to chemotherapy ($\geq 90\%$ of initial tumor volume). Nasopharyngeal RT was kept at a dose of 59.4 Gy. The overall prognosis was not influenced by the dose of local RT delivered or response to initial chemotherapy, but EFS was better in patients with a good response to chemotherapy. The cervical local failure rate was low despite RT dose reduction in the case of a good response to neoadjuvant chemotherapy (167). In all cases, before the beginning of RT, dental evaluation and prophylaxis or treatment is necessary. Baseline neuroendocrine testing and audiograms are also useful for the assessment of late effects.

Radiotherapy Volumes. Liu et al. have well discussed the major interest of CT and MRI in the delineation of clinical target volumes (CTVs) (168,169). The CTV should include the nasopharynx, half (posterior) of nasal cavity, entire sphenoid sinus, and posterior ethmoid sinuses. Posterior limit is usually at the anterior part of medullary canal, and inferior limit is represented by oropharyngeal wall to the midtonsillar fossa (169). CTV should also encompass basioccipital bone, cavernous sinus, base of skull, pterygoid fossae, posterior one third of the maxillary sinus, retropharyngeal nodes, bilateral cervical nodes, and supraclavicular nodes. If the tumor has invaded the base of the skull, the superior border should be raised to include all of the pituitary gland, the base of the brain in the suprasellar area, the adjacent middle cranial fossa, and the posterior portion of the anterior cranial fossa. Sham et al. have shown that the protection of pituitary gland did not lead to increase local failure if the skull base was not involved (170).

Radiotherapy Technique. Due to the superiority of conformal 3D technique versus 2D technique in terms of volume coverage, and probability of tumor control, conformal RT has become the standard technique for NPC since years (171).

In adults, it has been well described that intensity modulated radiotherapy (IMRT) substantially improved head- and neck-related symptoms and quality of life of patients with NPC without decreasing local control (172,173). In the same way, IMRT may provide improved local control in children with less late sequelae (128). Thirty-six children, median age 14 years, with localized NPC, were included in Uzel's study. All of them were treated with a combination of chemotherapy and RT. Nineteen underwent IMRT and 17 underwent conformal RT. They have shown that IMRT significantly reduces and delays the onset of acute toxicity

(grade 3 toxicity of skin, mucous membrane, and pharynx), resulting in improved tolerance and treatment compliance for children with NPC. IMRT also permitted a superior target coverage and normal tissue sparing compared with CRT (174). However, pediatric series should be really followed carefully: Louis et al. have also reported a little pediatric series ($n = 5$) of NPC treated by IMRT and concomitant platinum-based chemotherapy. With a median follow-up of 6.3 years, all patients experienced three or more long-term toxicities, including hypothyroidism, xerostomia, hearing loss, and dental disease (175).

Hyperfractionation. Experiences with altered fraction schedules in NPC remain limited in adults, and exceptionally described in children. In adults, hyperfractionation and accelerated fractionation have not demonstrated formally an increase of the survival efficacy (176), but local controls are usually better (177). However, the high rates of toxicity limit the development of NPC (178,179), especially in children. For example, Teo and colleagues reported increased risk of temporal lobe injury in adults with NPC after altered-fractionated RT (176).

Results

Results in childhood NPC are presented in Table 16.6

Late Effects

A number of acute and late adverse events can occur after RT for NPC, especially in children. The more common acute toxicities include grades 2–3 skin reactions and mucositis leading to dysphagia and weight loss. Considering late effects of treatment in children with NPC, studies are scarce. The more frequent are late endocrine effects caused by hypopituitarism (stunted growth, thyroid dysfunction [73%], and fertility defects), reported in 30% of long-term survivors, other effects include xerostomia, chronic sinusitis, dental caries, hearing loss, and neck fibrosis. Second malignancies, encephalopathy, osteoradionecrosis, cranial nerve dysfunction, hypoplasia, and fibrosis of facial bones occur less frequently (128,148,163,183).

Esthesioneuroblastoma (or Olfactory Neuroblastoma)

Epidemiology

Esthesioneuroblastoma (EN) accounts for 3% of endonasal neoplasms. It is rare in children (184), but 20% of all EN are found in patients under 20 years (185,186). A bimodal distribution has been described, with a first peak incidence at 10–20 years and a second one at 50–60 years. No sex predominance is known.

Histology

EN is an aggressive malignant tumor derived from the olfactory specialized neuroepithelium of the upper nasal cavity (187). Histologic features include small, round neuroepithelial cells arranged in rosette or pseudorosette patterns, separated by fibrous elements. In cytology, fibrillary cytoplasm and smooth nuclear contours are usual; mitotic figures are generally absent (188). The diagnosis needs a combination of parameters, including microscopic aspect and immunohistochemical stains. The tumor may be positive for chromogranin, synaptophysin, S-100 protein, and neuron-specific

Table 16.6**Survival in Childhood Nasopharyngeal Carcinomas: Studies During the 1990s and 2000s**

Year of Report (Reference)	Number of Cases	Treatment	T1–T2	Combined	T3–T4
1990 (130)	57	R ± Ch	61%	49%	
1995 (180)	10	R or R + <i>cis</i> -DDP + 5-FU		8/10	
1996 (138)	13 (T1–T2)	R		R: 47% 10-year FFS	
	35 (T3–T4)	R + <i>cis</i> -DDP/5-FU R + Bleo + <i>cis</i> -DDP + Epi		R then Ch: 54% 5-year FFS Ch then R: 72% 3-year FFS	
1996 (181)	6 stage IV	R + <i>cis</i> -DDP + 5-FU or R + Cy + <i>cis</i> -DDP			
1997 (182)	1 (T1–T2) 4 (T3–T4)	R R + BACON R + UICC2 or R + UICC2 + V		4/5	
1999 (127)	65	R (34) R + Cy	58%		69% n_{0-1} 28% n_{2-3}
2000 (132)	33	R + Epi + Bleo + <i>cis</i> - DDP R (13) or R + T6		58%	
2000 (183)	11 (all stage IV)	R + <i>cis</i> -DDP + Bleo + 5-FU	91% at 75 mo		
2001 (126)	33	R (4) or <i>cis</i> -DDP R + CAV Ch or 5-FU		63%	
2001 (128)	32	R + 5-FU + <i>cis</i> -DDP R (10) or R + 5-FU + <i>cis</i> -DDP (6) or R + Epi + Bleo + <i>cis</i> -DDP (3) or R + MTX + Bleo + <i>cis</i> -DDP (3)	73%		
2007 (157)	52 22	R R + <i>cis</i> -DDP + 5-FU		40% 3-year DFS 82% 3-year DFS	

5-FU, 5-fluorouracil; BACON, bleomycin, doxorubicin, lomustine, vincristine; Bleo, bleomycin; CAV, cyclophosphamide, doxorubicin, and vincristine; Ch, chemotherapy, not otherwise specified; *cis*-DDP, cisplatin; Cy, cyclophosphamide; DFS, disease-free survival; Epi, epirubicin; FFS, failure-free survival; MTX, methotrexate; RT, radiotherapy; T6, actinomycin, cyclophosphamide, bleomycin, vincristine, methotrexate, and oidiomycin; UICC2, bleomycin, methotrexate, cisplatin, and vinblastine; V, vincristine.

enolase (189). A histologic grading system is based on degree of differentiation, cellular anaplasia, and mitotic rate. This is a four-level system that is frequently simplified into low-grade (Hyams grades I and II) and high-grade (Hyams grade III and IV) neoplasms (190). Pathogenesis is not well known; however, nitroso derivatives (191) and viral induction (192) have been discussed in the pathogenesis.

EB has also been described as a member of Ewing sarcoma and peripheral primitive neuroectodermal tumor (PNET) family, while the EWS/FLI1 translocation has been shown in EB cell lines (193).

Clinical Aspect

Longstanding unilateral nasal obstruction, present for months, sometimes for years, is the most common complaint (>50%). Less frequent complaints include recurrent epistaxis, headache or sinus pain, loss of smell, facial mass, proptosis, diplopia, excessive lacrimation, and inappropriate secretion of antidiuretic hormone (194,195). Lacking specific early symptoms, patients are usually late diagnosed.

Imagery

Contrast-enhanced CT (<5-mm thick slices) is necessary to obtain local information, especially concerning the paranasal cavities involvement. ENs are solid and aggressive nasal cavity tumors; erosion of osseous structures can be seen (orbit, ethmoid, ...). MRI is often necessary because it is more sensitive to explore intracranial involvement (196).

Classification

The most commonly used classification is Kadish staging system (Table 16.7) (197). About one third of the patients are in group B, half of them in group C. Neck node involvement has been reported in 10%–50% of the patients (194,198–200). Metastatic disease at presentation occurs in 10%–50% of patients, depending on the study reviewed (201–203). In case of metastatic disease, the lesion area in 20%–30% patients involves the subepithelial endocrine cells (SNCs) that grow through the cribriform plate and invade the anterior basal cranial base metastatic disease, 20%–30% will involve the SNC by growing through the cribriform plate and invading the

Table 16.7**Kadish Staging System (194)**

Group A	Tumor confined to the nasal cavity
Group B	Tumor involving the nasal cavity and paranasal sinuses
Group C	Tumor extension beyond the nasal cavity and sinuses

anterior basal cranial base. It can then metastasize to brain parenchyma or leptomeninges (202). Other metastases are less frequently found in lung, liver, or bone (204).

Treatment

Due to low incidence of EB, even in adults, it is difficult to evaluate the efficiency of treatment strategies. The optimal option is matter of debate. Different options include surgery alone, RT alone, both surgery and RT, chemotherapy, and sometimes high-dose chemotherapy with autologous bone marrow transplantation. In general, multimodality treatment offers the best survival rate, particularly with more advanced disease. Studies concern mainly adults but often include a few children.

Surgery Outcomes improved significantly with the advent of craniofacial resection in the 1970s, providing a more complete surgical resection (205). Surgical extirpation can usually be accomplished, but obtaining standard oncologic negative margins in this area of critical functional anatomy is not without great morbidity to the patient. Craniofacial resection allows en bloc resection of tumor including the cribriform plate, with direct visualization of intracranial extension and protection of the brain and optic nerves. DFS increased from 40% to 80% when compared extracranial resection with craniofacial resection in one published study (205). Complications include infections, cerebrospinal fluid leak, and optic injury (205). If cervical disease is present at diagnosis, complete neck dissection can be discussed (206). Due to surgical morbidity and frequent indication for adjuvant therapies, other strategies have been studied: treatment with smaller surgical margins followed by postoperative radiation, the use of neoadjuvant chemotherapy followed by surgery and postoperative radiation, and the use of chemoradiation without surgery (207–212). A recent meta-analysis of individual adult's data has been published, concerning 361 patients treated between 1992 and 2008. A greater published survival rate for endoscopic surgery compared to open surgery ($p = 0.0019$), even when stratifying for publication year ($p = 0.0018$), was found. Review of Kadish tumor staging for each modality showed that larger tumors were more often treated with an open approach, but open and endoscopic survival measures were comparable (213).

Radiotherapy. Multiple retrospective studies have demonstrated an improved outcome with the addition of radiation before or after surgery (214).

Delivering RT in preoperative situation offers several theoretical advantages including a better tumor oxygenation

while the blood supply is intact, leading potentially to a better radiation efficacy. An easier definition of the tumor volume is also clear before surgery. On small studies, RT has been shown to provide a valuable complement to radical craniofacial resection, leading to reduction in tumor burden in two thirds of the patients. Patients experiencing reduction in tumor volume by neoadjuvant therapy demonstrate an improved prognosis (215).

Radiation in postoperative situation is now strongly accepted as an important modality for treatment of advanced EN (216–218). Broich et al. reviewed the literature and reported 62.5% survival with surgery alone and 72% survival with combined surgery and radiation at 5 years (214).

Exclusive Radiation Therapy. Radiation portals are typically arranged using CT-based planning and simulation, with fusion of MRIs to the treatment planning CT, in order to more accurately define soft tissue and/or brain parenchymal extension. Typically, fields may include the entire nasal fossa, maxillary sinuses with extension into the ethmoid, sphenoid sinuses, and the anterior cranial fossa. Elective treatment of ipsilateral neck is controversial and likely not indicated without risk factors for evidence of extension to the neck nodes. Radiation dose tolerances of critical structures must be respected in the treatment planning process (219). Total RT dose ranges from 50 Gy for microscopic disease to 55–60 Gy for gross disease administered in 1.80/2.00 Gy per fraction. IMRT can be a good option for EBRT due to the proximity of organs at risk combined with the high dose to be delivered. On 13 patients, Zabel et al. reported that the IMRT plans gave equal dose coverage and allowed more effective sparing of normal tissues in all the cases (220). In addition, it has been recently published that proton beam radiation therapy has allowed for dose intensification to the target volume with relative sparing of adjacent normal tissues, especially for bulky or unresectable diseases (221,222). Finally, radiosurgery could be another treatment modality for definitive treatment and for local relapse. It allows the benefit of single fraction treatment, with good efficiency according to small series. In particular, small local relapses after previous RT may be ideally treated with this technique (223).

Chemotherapy The role of chemotherapy, especially in a multimodal approach, is not well defined, in particular in pediatric population. Chemotherapy has been studied in the neoadjuvant and adjuvant situations in small numbers of patients. Mainly cisplatin-based regimen, associated with cyclophosphamide, vincristine, or etoposide, has been used with various efficiency (210,224–226). However, some studies tend to recommend chemotherapy in stage C disease. For example, routine use of cyclophosphamide and vincristine in combination with radiation and surgery has demonstrated improved survival in a study carried out by University of Virginia (224). A retrospective study on 19 patients <20 years has shown a benefit of multimodal treatment regimens combining surgery and chemo- and RT for pediatric patients with EN Kadish stage C. Chemotherapy appears to improve resectability, EFS, and OS (227).

High-dose chemotherapy with stem cell rescue has been reported as primary and salvage therapy, with good results in small series, after RT (228).

Table 16.8
Local Recurrence Rates in Retrospective Series of the Treatment of Esthesioneuroblastoma: Combined Adult and Pediatric Series

Author (Reference)	Surgery Alone (%)	Surgery and Preoperative or Postoperative Radiotherapy (%)
Argiris et al. (229)	40	63
Dulguerov and Calcaterra (203)	86	40
Eich et al. (204)	—	17
Elkon et al. (230)	44	0
Foote et al. (200)	59	8
Gruber et al. (231)	—	46
Kadish et al. (197)	50	0
O'Connor et al. (232)	75	29
Resto et al. (194)	33	11
Crude average ^a	55	24

^aCrude average does not account for variations in age, stage, number of patients, or details of therapy between retrospective series. The “surgery alone” patients generally have lower-stage disease. In view of the higher relapse rate in these more favorable patients, the role of radiotherapy is reinforced.

Results

The results are presented in Table 16.8. A meta-analysis—combined data from 37 small retrospective studies (386 patients) was published in 2001, comparing outcomes by treatment modality. OS at 5 years was 45% (mean). Survival by treatment modality was 65% for surgery plus RT, 51% for RT plus chemotherapy, 48% for surgery alone, 47% for combination of all three modalities, and 37% for RT alone. Higher histopathologic grade and the presence of cervical lymph node metastases were poor prognostic factors (203). Although recurrence can occur with high frequency even after prolonged time interval, long-time survival can be improved after aggressive salvage therapy. Therefore long-term follow-up is mandatory (233). Recurrence can occur even 15 years after treatment. Therefore, long-term follow-up is essential (234).

MALIGNANCIES OF THE ORAL CAVITY, OROPHARYNX, HYPOPHARYNX, AND LARYNX

Epidemiology

Limited data are available in the literature on the incidence of childhood cancer of the head and neck worldwide. The national German Childhood Cancer Registry have reported one of the largest studies, on 370 malignancies of the head and neck in children under the age of 15 between 1994 and 2003 (199 boys and 171 girls). The overall incidence of malignancies of specific sites of the head and neck in Germany is 4.48 per 100,000 children. The most frequently observed entities, representing primary tumors, are soft tissue sarcomas (0.39/100,000), lymphomas (0.09/100,000), and thyroid carcinomas (0.07/100,000). The most commonly affected organs

are the thyroid (1.21/100,000), orbital region (0.91/100,000), nasopharynx (0.66/100,000), tonsils (0.43/100,000), and paranasal sinuses (0.14/100,000) (235).

SALIVARY GLAND TUMORS

Epidemiology

Salivary gland tumors (benign or malignant) represent only 1% of head and neck tumors (236,237). Only 5% of salivary gland cancers arise during childhood (238,239). Carcinomas of the salivary glands represent 0.08% of cancer in the pediatric population (240).

Pathology

Fine-needle aspiration biopsy is a well-tried technique for the diagnosis of salivary gland mass (241,242). Among epithelial tumors of the salivary glands, mucoepidermoid carcinoma (MEC) and adenoid cystic carcinoma (ACC) are the most frequent histologic types in adults and children.

MEC as Second Tumors

MEC of the salivary glands represents 6% of the second cancers and is also known to arise as a second malignant tumor in adulthood (243,244).

In a French retrospective study on 18 patients, 11 had a previous history of a nonsalivary malignancy tumor (245). All except one had initially received chemotherapy with alkylating agents, including cyclophosphamide in nine patients. External RT was also performed in seven patients, with a dose range of 10–55 Gy. MEC occurred within or close to the original radiation treatment field in all seven cases (245).

Clinical Aspects

The most frequent clinical presentation is an isolated, hardened, noninflammatory, painless, and slow-growing tumefaction (246). A descriptive, retrospective, and multicenter French analysis of a series of 18 patients younger than 20 years with MEC treated from 1980 to 2000 has shown that the first symptom in all cases was noninflammatory, painless solid tumefaction in the area of a salivary gland. One parotid tumefaction was associated with facial palsy (245).

Treatment

MEC has a good prognosis in young patients. Differences in OS, specific survival, and DFS do not seem statistically significant between the primary MEC tumors and the second cancers. Surgery is the primary treatment of choice in the majority of cases, with the addition of adjuvant RT ± chemotherapy when the diagnosis is a high-grade tumor and/or when the malignancy presents as a large mass or is associated with local tissue invasion (247). Definitive surgery gives very good local control rates in the literature (248,249). A systematic neck lymph node dissection is recommended in patients with advanced-stage disease, and high-grade tumors neck lymph node metastasis is detected in 50% of these cases (250–252). In children, postoperative RT is not well codified due to the risk of late sequelae, but it seems justified in patients with advanced-stage disease and high pathologic grade tumors, which have the worst prognosis in MEC, especially in children.

INFANTILE SUBGLOTTIC HEMANGIOMAS

Congenital subglottic hemangioma (SH) causes life-threatening airway obstruction during the first few months of life. After an asymptomatic neonatal period, the infant presents a characteristic biphasic stridor as the lesion progressively obstructs the subglottic space. In 80%–90% of cases, these symptoms appear in the first 6 months of life. The involutional process generally begins at 12 months of age and continues until the SH regresses completely. The mortality rate of recognized and untreated cases justifies active treatment. Aim of therapy is to restore normal respiration, attempting to preserve the child's voice and alter the quality of life as little as possible.

Treatment

Modalities of treatment are still discussed. The most common technique is endoscopic excision with carbon dioxide laser, used alone or combined with other therapeutic techniques. A retrospective study was carried out on all cases of infantile SH treated in the Department of Otolaryngology, Toronto, between 1980 and 2000. A retrospective review of 36 patients was performed to assess the current practice and treatment options in use. Besides this a retrospective comparative study of a previous cohort of 51 patients with SH was performed in which patients were treated either by tracheostomy alone, tracheostomy and CO₂ laser, systemic steroids and CO₂ laser with no tracheostomy and intralesional steroid injection, CO₂ laser therapy, or both, followed by intubation. Resolution of the SH was achieved in about 90% of cases. However, a transitory tracheostomy was required in more than half of the cases. The time to resolution of SGHs does not appear to be reduced by laser therapy compared with treatment by tracheostomy alone. Intralesional steroid injection or laser therapy together with intubation was associated with avoidance of a tracheostomy in 66% of cases (253).

Although RT is known to be efficient, it carries a risk of inducing second thyroid cancer later in life, leading to limit its use. A series of 11 patients with SH has been reported; conventional RT was utilized in the first 7 patients. A radioactive gold grain directly was placed into the lesion in the last four patients, leading to minimal thyroid gland irradiation compared to treatment by conventional RT. It was successful in the four patients but larger trials are warranted (254). When RT is used, a dose range between 3.5 and 5 Gy at 0.5–1.5 Gy per fraction is delivered. When dealing with a life-threatening situation, one should be prepared to use irradiation if other treatment modalities are either inapplicable or unsuccessful.

OESOPHAGEAL CANCERS

Esophageal carcinoma may develop in children; it may arise spontaneously, years after chemical burns in the setting of Barrett esophagus (255), and, in one reported case, in association with Cornelia de Lange syndrome (256). Both squamous cell carcinoma and adenocarcinomas have been reported. They are managed similarly to those in adults (257). The rare case of esophageal sarcoma (leiomyosarcoma, carcinosarcoma, and malignant schwannoma) may be treated with preoperative or postoperative irradiation (258). Palliative RT is occasionally necessary for leukemia or secondary or

primary lymphomatous infiltration of the esophagus (244,245). Other rare esophageal neoplasms include leiomyoma, desmoid, and teratoma (259,260).

GASTROINTESTINAL MALIGNANCIES

Primary gastrointestinal (GI) malignancies are exceptional in childhood and adolescence, with limited information from Asian populations. Non-Hodgkin lymphoma is the most common malignancy of the stomach in childhood (see Chapter 8). As a group, leiomyosarcoma and leiomyoblastoma are the second most common gastric malignancies in children (261–264). The average size of a gastric leiomyosarcoma in childhood is 6–7 cm in diameter. Infiltration of tumor to adjacent structures, including the liver or nodal metastasis, may occur (262). Therapy of gastric leiomyosarcoma begins with surgery. The operative bed and the upper abdomen are common sites of tumor recurrence. Postoperative EBRT is justifiable when there is a particularly high risk of local recurrence created by positive surgical margins or posterior penetration. However, the efficacy of adjuvant RT in this setting is not proven. Gastric adenocarcinoma is rare in children (261,265). It may occur de novo or in association with Peutz–Jeghers syndromes (266). There is epidemiologic evidence that long-standing *Helicobacter pylori* infection and chronic gastritis are involved in the development of a variety of gastric malignancies including adenocarcinomas, lymphomas, and mucosa-associated lymphoid tissue lymphomas. Acquisition of infection in childhood appears to be a risk factor for development of neoplasia as an adult. However, there is no evidence at present that the treatment of all *H. pylori*-infected children would influence the risk of gastric malignancy decades later (267). Rhabdomyosarcoma, Hodgkin disease, malignant teratoma, GI stromal tumor, and nerve sheath tumors also may occur in the stomach (268). (See Chapters 7, 11, and 12.)

PULMONARY NEOPLASM

Epidemiology

Pulmonary neoplasms are unusual in the pediatric age group and represent a wide spectrum of pathology (269). Some are similar to adult lesions and some are specific to childhood. An American study on patients 25 years of age has reported the relative incidence of primary and metastatic lung tumors in children and adolescents through a single-institution case series. A total of 204 pediatric lung tumors were diagnosed and analyzed. About 83% were secondary lung lesions, 10% were benign lesions, and 7% were primary malignant lesions.

Pathology

Adult lung cancers (adenocarcinoma, epidermoid carcinoma, ...) are exceptional in childhood. The most common primary lung malignancies in children are pleuropulmonary blastoma (PPB) and carcinoid tumor and less frequent ones are peribronchial myofibroblastic tumor and other myofibroblastic lesions, sarcomas (270), mesothelioma, and inflammatory pseudotumor (plasma cell granuloma) of the bronchus. Metastatic lung tumors are relatively common in

children and also comprise a spectrum of cancers different from the adult population (269–271).

Clinical Presentation

Symptoms are quite nonspecific. Cough, fever, pulmonary infection, respiratory distress, weight loss, pain, and hemoptysis are the more frequent symptoms (271).

Pleuropulmonary Blastoma

PPB is the most frequent malignancy associated with lung cysts, usually in early childhood (272). This neoplasm is histologically characterized by primitive blastema and a malignant mesenchymal stroma that often presents multidirectional differentiation. The early form of the disease, cystic type I PPB, is a multilocular cyst form with variable numbers of primitive mesenchymal cells beneath a benign epithelial surface. Rhabdomyoblasts and cartilage nodules are seen in more than 40% of the cases (273). Type I PPB can present a great resemblance to some developmental lung cysts, making the diagnosis sometimes difficult.

Genetic

A constitutional genetic predisposition is currently studied. It is suggested by the early age of diagnosis, the association of PPB, and renal tumors (cystic nephroma for instance) together in patients and/or family members (274).

Diagnosis

PPB in children aged <5 years is usually present as respiratory tract infection or pneumothorax. PPB appears commonly as a solitary parenchymal mass on chest radiograph and CT (275). Large masses in the right hemithorax with heterogeneous low attenuation, pleural effusion, contralateral mediastinal shift, lack of chest wall invasion (276), and pneumothorax can be seen (277). Rarely, PPB (especially in PPB types II and III) at diagnosis presents with metastatic sites of involvement such as brain, bone, liver, pancreas, kidney, and adrenal glands (278,279). A study on 39 patients showed that the cumulative probability of cerebral metastasis by 5 years from diagnosis reached 11% for type II patients and 54% for type III patients (280).

Treatment

Most cases are managed initially with surgery while total resection is associated with better outcomes (281). However, the tumors often are large and locally extensive, making complete surgical excision uncommon (282–285). Thoracic irradiation has been used for the postoperative treatment of patients with large tumors or positive margins (30–55 Gy) (285). One should also consider RT for the treatment of local tumor recurrence, where the situation is grim but not hopeless (284,285). Several reports describe the need for combination chemotherapy for PPB without any consensus on the optimal regimen (286–290). Recurrences after type I PPB are usually advanced types II or III neoplasms with a poor prognosis. Salvage after types II and III recurrence is poor (about 40% in the best series). A rigorous surveillance schedule after type I PPB diagnosis might detect early recurrence (291).

Results

Despite the introduction of multimodal therapy (surgery, chemotherapy, and occasionally RT), the prognosis for PPB patients remains poor. The actuarial 2-year overall and event-free survival rates are about 60% and 40% (279), respectively. According to previously published data, almost all recurrences of this disease tend to occur within 24 months of diagnosis, and with a few exceptions, within 36 months of diagnosis (292,293). Therefore, careful and strict follow-up for 3 years is needed in patients with PPB. Brain metastases are the most common distant lesion and usually have a poor prognosis (279,280). In terms of prognostic factors, on retrospective studies, total resection of PPB performed at any time of treatment appears to provide a better outcome, whereas extrapulmonary involvement at diagnosis worsens the prognosis (294).

CARCINOID AND MUCOEPIDERMOID BRONCHIAL TUMORS

Endobronchial tumors are rare in children and often misdiagnosed as benign conditions resulting in delayed definitive treatment. Although the true incidence of this entity is unknown, bronchial adenomas alone may account for 5% of all primary pulmonary neoplasms in children (295).

The malignant lesions include bronchial adenomas, carcinoids, MECs, and ACCs. Bronchogenic carcinomas are reported rarely in childhood (271,296,297). The most common endobronchial tumor in children and adolescents is carcinoid (271). Carcinoid tumors can be divided into typical and atypical forms with the latter exhibiting histologically malignant features and aggressive clinical behavior. This histologic and clinical distinction is not as clear in the pediatric age groups as it is in adults because of the limited pediatric experience with this pathology (298).

Because of the abundant vascularization, endoscopic removal of these lesions can be hazardous and currently is not recommended. A retrospective analysis of all patients treated for a carcinoid or mucoepidermoid tumor in France between 1984 and 2001 was performed to determine the characteristic features and outcome of carcinoid or mucoepidermoid tumors in children (299). There were 11 cases of carcinoid tumor and 6 cases of mucoepidermoid tumor. Twelve and six patients were presented with evidence of bronchial obstruction and hemoptysis, respectively. Fiber-optic bronchoscopy confirmed the presence of a bronchial tumor in all cases, and endobronchial biopsies were diagnostic in 11 of 12 cases. Complete surgical resection (lobectomy in 15 patients and pneumonectomy in 2 patients) was performed in all cases without preoperative chemotherapy or RT. With a mean follow-up of 4 years, no death was observed. In two patients, auscultation asymmetry and an episode of hemoptysis revealed the recurrence of a mucoepidermoid tumor; a child was successfully cured by removal of the tumor and chemotherapy and RT. The authors recommend a biopsy for diagnosis and a complete surgical removal as treatment of choice. Long-term results are excellent but a clinical follow-up is recommended.

NEOPLASMS OF THE PANCREAS

Primary neoplasms of the pancreas are rare in childhood. A retrospective review of the Memorial Sloan-Kettering was undertaken of all patients less than 21 years of age with malignant pancreatic tumors since 1967. Seventeen patients were identified mainly with pancreatoblastoma ($n = 5$) and solid pseudopapillary tumor ($n = 7$), and more rarely with acinar cell carcinoma, nonfunctioning pancreatic endocrine neoplasm, malignant VIPoma, and PNET (300). Another more recent study has reported that malignant pancreatic neoplasms were identified in 58 patients. They have reported an age- and population-adjusted incidence of 0.021 (females) and 0.015 (males) per 100,000. Asians had the highest incidence. The main frequent tumors were classified as exocrine in about half of the patients, endocrine in one third, or sarcomas in the rest (8%). Exocrine tumors included mainly pancreatoblastoma and solid-cystic tumor (SCT), less frequently ductal adenocarcinoma, and acinar cell carcinoma. Ductal adenocarcinoma, SCT, acinar cell carcinoma, sarcomas, and endocrine tumors were more common in children older than 10 years, whereas pancreatoblastoma was more common in younger children. Almost half of the patients presented with distant metastasis (301).

Among pancreatic tumors in childhood, pancreatoblastoma is one of the more frequent types. It is characterized by well-formed acinar areas along with squamoid corpuscles and zymogen-like granules. Because these organoid structures are similar to the pancreatic anlage, pancreatoblastoma is thought to originate from pancreatic multipotential primordial cells (302). Positive staining by periodic acid-Schiff, γ -trypsin, and γ -keratin are common (303). About two thirds of cases have been associated with a high level of γ -fetoprotein (302–305).

Main causes of diagnosis are abdominal pain and diarrhea (306). Abdominal mass, hypoglycemia, and jaundice can also be seen (302,307). Imaging findings indicate usually a well-defined heterogeneous large mass in the pancreas or mesentery. Pancreatoblastomas are heterogeneous and often multilocular with hyperechoic and enhancing septa (308).

Localized, nonmetastatic tumor that can be completely resected is generally cured (307,309). In some cases, unfortunately, the tumor is clearly malignant, with local invasion, recurrence, and metastasis. About 35% of patients present with metastases, and 50% die of tumor (300,303). A resectable tumor without metastases can be treated with surgery alone. If the tumor secretes γ -fetoprotein, this marker can be used along with CT and ultrasound for the follow-up. The role of RT in managing pancreatoblastoma is not clearly defined. Griffin et al. reported a case of locally recurrent pancreatoblastoma treated with 46.2 Gy. Six weeks after irradiation, exploratory laparotomy was performed. Multiple biopsies showed no evidence of tumor. The girl was cured 2 years after the diagnosis (310). Therefore, it is possible to infer that some cases of pancreatoblastoma may be curable by radiation. However, in most cases in which RT is considered is because of tumor spillage at the time of surgery or positive surgical margins. Radiation therapy has been used to render unresectable tumors resectable, to treat local regional recurrent

tumor, and as postoperative therapy for microscopic disease and tumor spillage. A dosage of 40–50 Gy seems appropriate (302,305,309). A variety of chemotherapy programs have been used to shrink unresectable tumors, to treat metastatic disease, or as adjuvant therapy. There have been some notable successes in rendering unresectable tumors resectable. Cyclophosphamide, vincristine, 5-FU, adriamycin, mitomycin-C, cisplatin, etoposide, ifosfamide, actinomycin D, bleomycin, vinblastine, and epirubicin have been used. Cases are so rare that firm statements regarding the indications and specifics of chemotherapy treatment policy are inappropriate (300,305,309).

Pediatric pancreatic neoplasms carry a variable prognosis. Both female sex and surgery were good independent predictors in the recent large Perez's study on 58 children treated for pancreatic tumors. A significant difference in 15-year survival was seen considering tumor type. Ductal cancers had the worst prognosis (23% survival) and SCT the best one (100% survival) (301). The roles and impact of chemotherapy and radiation remain undefined (300).

NEOPLASM OF THE APPENDIX

Carcinoids are the most common neoplasm of the appendix in children. Almost all appendiceal carcinoids are incidental findings, usually 2 cm in diameter or less and are found in specimens removed because of appendicitis or during abdominal surgery. Metastasis to lymph nodes occurs in less than 5% of pediatric cases. Some assert that the risk of metastases is related to tumor size and local invasion. Surgical excision is the treatment of choice. For the typical small tumor, appendectomy is curative. Some authors favor hemicolectomy in tumors larger than 2 cm, for invasive lesions, or for nodal metastases. Others advocate a resection restricted to the cecum as an alternative. The overall prognosis of appendiceal carcinoid tumors is excellent. Radiotherapy is almost never used (311–313).

SMALL BOWEL NEOPLASMS

Non-Hodgkin lymphoma is the most common malignancy of the small intestine in children (see Chapter 8). Ewing tumors have also been described rarely (314). Small intestine adenocarcinoma develops *de novo* or in association with Peutz-Jeghers syndrome. Surgery is the initial treatment. Nonfixed jejunal and ileal lesions usually are treated with surgery alone. As a general rule, RT should not be used for routine adjuvant treatment of small bowel carcinoma when the primary tumor is in a mobile part of the small bowel. In the retroperitoneal fixed portions of the duodenum, where local recurrence after surgery is a risk, an argument may be made for postoperative irradiation. Unresectable tumors may be treated with palliative irradiation for pain and bleeding. The survival rate for small bowel adenocarcinoma is poor. Sarcomas of the small bowel are treated with surgery (314). Adjuvant RT is discussed when there are close or positive surgical margins. Small intestinal carcinoids are treated surgically (313). Palliative RT may be used for liver metastases.

COLORECTAL MALIGNANCIES

Colorectal carcinoma accounts for 2% of malignancies in adolescents and has been reported in children as young as 9 months of age. In Japan, for example, one to three pediatric colon carcinomas are identified annually (315,316). Based on the published reports, which are small clinical trials or case reports, most CRC in children is sporadic (315–317), but it can also arise in the setting of predisposing conditions, such as GI polyposis syndromes, nonpolyposis familial cancer syndromes, and inflammatory bowel disease. They also may occur as second malignant neoplasms after treatment of childhood leukemia, rhabdomyosarcoma, Wilms tumor, or Hodgkin disease (318).

Carcinomas of the colon and rectum in childhood present with pain, vomiting, anemia, a palpable mass, hematochezia, diarrhea, or constipation (315–317). Because of the lack of specificity of the symptoms and the rarity of the disease, the possibility of a child having colorectal carcinoma is rarely considered, and the interval between clinical complaints and diagnosis often is long (317,319,320). As a consequence, involvement of regional lymph nodes, distant metastases, and inoperability are common in children (317).

In a review of the Japanese literature concerning children less than 15 years old, 48% of the patients were disease-free survivors (315). This is attributed to a delay in diagnosis resulting in more advanced disease (321,322). It is generally felt that when a carcinoma arises in ulcerative colitis, a total colectomy should be performed.

As a result of its rarity in children and the lack of prospective pediatric studies, recommendations for therapy are primarily extrapolated from adult clinical trials. Complete surgical resection with aggressive lymph node dissection is essential for cure, and neoadjuvant chemotherapy may be used in an effort to render unresectable lesions resectable. Active agents in adults with CRC include FU, folinic acid (leucovorin), oxaliplatin, and irinotecan. Furthermore, newer targeted therapeutic agents, such as bevacizumab and cetuximab, have added additional efficacy to the standard chemotherapy backbone but no trials have been done in pediatric population till now.

BREAST CANCER

Malignant lesions of the breast in children are rare. The most common form of breast cancer occurring in young girls (or boys rarely) is juvenile secretory carcinoma. Approximately 100 cases have been reported in the literature (323). The malignant cells are characterized by abundant secretion of mucin and mucopolysaccharide-containing materials (324–326). A unique pathologic feature is the presence of a thick-walled capsule that is thought to be caused by a desmoplastic reaction around the tumor. This may be responsible for its cystic appearance on ultrasound (327). Surgery is the treatment of choice but there is little consensus, however, about the extent of surgery. A sufficient number of case reports of local recurrence suggest that local excision alone may not constitute adequate therapy, and mastectomy has been advocated as standard treatment (323,328,329). Richard et al. reported, in a literature review of 33 reported cases with follow-up in adult females, that 33% of patients treated by less than simple mastectomy demonstrated local recurrent disease

(329). Sentinel lymph node biopsy seems to offer an approach to stage the axillary lymphatic basin with a lower complication rate than formal dissection and is recommended by some authors (330). For others, mastectomy with sentinel lymph node biopsy or axillary lymph node dissection is recommended in any male case due to more relapses (331). The prognosis is excellent in this benign tumor, and no RT or chemotherapy is generally necessary. There is minimal experience with lumpectomy and RT.

Primary breast carcinoma is exceedingly rare in the pediatric age group. Infiltrating ductal, lobular, medullary, and inflammatory carcinomas have been reported in young girls. With almost no data available in children, we would be cautious about varying from the principles of clinical management set by adult oncology (327).

Four cases of breast carcinoma in women under 20 years were retrospectively described in a recent study (332). Various histologic types were found: (1) invasive ductal carcinoma associated with fibroadenoma, (2) secretory carcinomas, and (3) invasive lobular-type carcinoma. Surgery was performed in the four cases. Only one patient received adjuvant chemotherapy. After follow-up ranging from 76 to 126 months, three patients are alive and disease-free and one has disseminated metastatic disease.

There have been case reports of primary non-Hodgkin lymphoma, rhabdomyosarcoma, ACC, radiation-induced spindle cell sarcoma, and cystosarcoma phylloides of the breast in children (325–327,333). Reported breast metastases in children include hepatocarcinoma, non-Hodgkin lymphoma, rhabdomyosarcoma, Hodgkin disease, neuroblastoma, and adenocarcinoma (334).

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Langerhans Cell Histiocytosis

Edward C. Halperin

HISTORICAL BACKGROUND

Paul Wilhelm Heinrich Langerhans (1847–1888) was born in Berlin. His father and his two brothers were physicians. While still an undergraduate, Langerhans used Cohnheim's gold chloride staining to identify a novel nonpigmentary epidermal dendritic cell. When he was 21 years old, he described this finding in an 1868 paper titled “*Über die Nerven der menschlichen Haut*” (on the nerves of the human skin) (1). Langerhans initially regarded these cells as intraepidermal receptors for extracutaneous signals of the nervous system. He later changed his mind and in 1882 wrote that “my cells are in no way essential for nerve endings” (2). Langerhans studied medicine with Heckel and Virchow. He defended his thesis, “*Contributions to the Microscopic Anatomy of the Pancreas*.” In 1869, he identified a cell in the human pancreas, now called Langerhans islets. After his thesis defense, Langerhans demonstrated that cinnabar was taken up by white blood cells but not red blood cells. This opened the door for Aschoff's concept of the reticuloendothelial system.

In 1874, Langerhans became Professor Extraordinarius in Freiburg. Unfortunately, 1 week later he was diagnosed with renal tuberculosis (TB). He was released from his duties at the university and he left for Madeira. He continued to do research on the flora and fauna of the Atlantic Islands and Madeira. His contributions were of such high quality that in 1909 a polychaete worm was named after him. Langerhans practiced medicine whenever his health allowed. The majority of his patients were German and British citizens who lived on the island for health reasons, usually TB. Langerhans died of progressive renal degeneration caused by TB in 1888. He published two papers on TB, undoubtedly influenced by his own condition and by the fact that his mother had died of TB and his half brother had also contracted the disease (3–5).

In 1893, Dr. Alfred Hand Jr, a 25-year-old resident at the Children's Hospital of Philadelphia, reported the case of a 3-year-old boy with “a history of great thirst and polyuria... undersized and puny.”

At autopsy, a yellow spot about the size of a five-cent piece was noticed near the right parietal eminence. When the skull-cap was removed, this spot was seen on the inner side as well, and the entire thickness of the bone there was soft and movable.... The lymphatic glands... all through the body were greatly enlarged.... The liver and spleen were enlarged and firm, and the former had minute gray nodules in its substance.... Microscopical sections showed nodular masses of small, round-celled infiltration in the liver, spleen, kidneys (5).

Hand suspected that he was dealing with a case of TB. In 1921, he noted the similarity of his original case to ones subsequently reported by Schuller, Christian, and Kay. Eventually, the term *Hand-Schuller-Christian disease* or *triad* was used to describe a disease occurring in children more than 2 years old characterized by exophthalmos, lesions in the bones of the skull, and diabetes insipidus (DI). The full triad was rarely seen, and the prognosis was good (6,7).

In 1924 and 1933, Letterer and Siwe described what they perceived to be an entity distinct from Hand-Schuller-Christian disease. *Letterer-Siwe disease* generally occurred in children less than 2 years old. The diagnostic criteria included splenomegaly, hepatomegaly, lymphadenopathy, anemia, and a hemorrhagic diathesis. The prognosis was poor (5–7).

In 1940, Otani and Ehrlich (8) described a granuloma of bone simulating a primary neoplasm. Eventually, the solitary eosinophilic granuloma was described as occurring in children more than 2 years old, characterized by a solitary, usually bony site of involvement, and an excellent prognosis (6,7).

In 1953, Lichtenstein argued that eosinophilic granuloma of bone, Letterer-Siwe disease, and Hand-Schuller-Christian disease were related manifestations of a single nosologic entity (5,7). He used the name *histiocytosis X* to refer to a spectrum of diseases of the mononuclear phagocyte (histiocyte). The X referred to the unknown etiology and pathogenesis of the disease or diseases. The diseases formerly grouped under the heading “Histiocytosis X” are now called *Langerhans cell histiocytosis* (LCH).

DEFINITION, PATHOGENESIS, AND PATHOLOGY

LCH is an accumulation or proliferation of a clonal population of cells bearing the phenotype of a Langerhans cell that has been arrested in early stage of activation and is functionally deficient. Langerhans cells along with lymphocytes, eosinophils, and normal histiocytes form infiltrates typical for the disease, which may be found to a varying extent in multiple or single organ(s). LCH can affect the skin, bone, lymph nodes, ear, gums, lungs, gastrointestinal tract including the liver, and the central nervous system (CNS) by causing DI.

The Langerhans cells are a family of related cells characterized by their dendritic morphology and multiple thin-membrane projections. Dendritic cells constitute 0.2% of white blood cells in the blood and are present in even smaller proportions in tissues such as the skin. Because of their rarity, their true function eluded scientists for nearly a century after

Langerhans first identified them in 1868. In 1973, Ralph M. Steinman of Rockefeller University rediscovered the cells in mouse spleens and recognized that they are part of the immune system (9). The cells were unusually potent in stimulating immunity in experimental animals. He renamed the cells *dendritic* because of their spiky arms, or dendrites. The subset of dendritic cells that occur in the epidermis of the skin are commonly still called Langerhans cells. In normal anatomy, Langerhans cells are found in the epidermis and skin appendages, in squamous mucosal epithelium such as the buccal mucosa, vagina, cervix, and esophagus, and in the spleen and lymphatic system. Dendritic cells attack invading bacteria, digest them, and display their antigens on the surface. Antigen-bearing dendritic cells travel to lymph nodes or the spleen, where they interact with other cells of the immune system, including B cells, which make antibodies, and killer T cells, which attract microbes and ingest them.

LCH cells cause tissue damage by infiltration and excessive production of cytokines and prostaglandins. Cells produce interleukin-1 (IL-1) and prostaglandin E₂, which can cause bone resorption through osteoclast activation. IL-1 may cause release of IL-2 and gamma interferon from helper-inducer T lymphocytes, leading to the stimulation of other lymphocytes and histiocytes. Tissue injury results from the local immune response as the collection of immune cells impairs normal tissue structure and function (10). On microscopic evaluation, the lesions of LCH are found to be consistent with Hand's original description: a pleomorphic infiltrate of lymphocytes, eosinophils, polymorphonuclear leukocytes, and Langerhans cells (Fig. 17.1). A more definitive diagnosis is made when electron microscopy shows Birbeck granules or when light microscopy shows that the Langerhans cells are ATPase positive; stain for S-100 protein, CD11, and CD14, anti-CD1 marker (also called the T6 surface marker), and α -D-mannosidase; and bind peanut lectin (11,12) (Table 17.1). Birbeck granules are membranous cytoplasmic structures, of unknown function, 200–400 nm wide and shaped like tennis rackets (11,13,14) (Fig. 17.2).

Lesional cells of LCH may represent Langerhans cells arrested in early stage of activation. Immunohistochemical expression of fascin, a protein that is a marker for dendritic

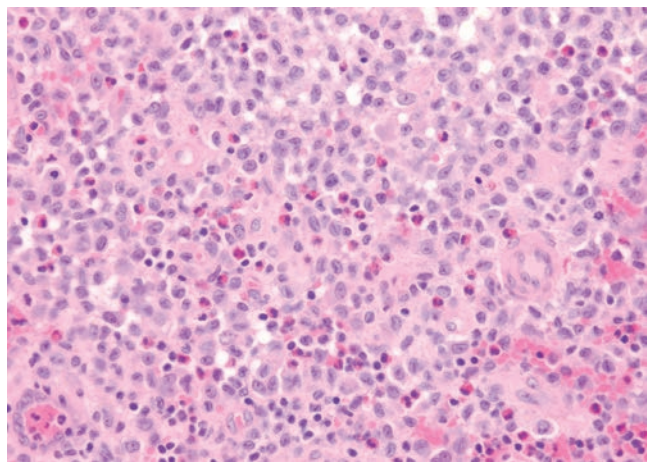


Figure 17.1 Langerhans cells characterized by plump nuclei frequently having longitudinal folds surrounded by ample cytoplasm. Numerous eosinophils are scattered throughout the tumor.

Table 17.1

Immunophenotype of Langerhans Cell Histiocytosis

Marker	Percentage of Cases Positive
CD1a	~100%
S-100	~100%
CD21	~0%
CD35	~0%
CD68	<50%
Lysozyme	~0%

From Usami GN, Westra SJ, Younes S. Case 13-2003: a 14-month-old boy with hepatomegaly, perianal lesions, and a bony lump on the forehead. *N Engl J Med*. 2003;348:1692–1702, with permission.

cells, is observed in many cases of LCH. This immunoreactivity for fascin supports LCH's pathogenesis from cells of the dendritic system (12).

Until recently, the disease generally was not thought to be monoclonal in origin. It was argued that the individual cells do not show atypia and that the disease lacked the usual histologic criteria for malignancy. Therefore, LCH was generally considered to fall within the realm of reactive immunologic disorders or perhaps to be of infectious origin. However, viral and immune causation theories generally have lacked supporting evidence. In 1994, Willman et al. (15) provided evidence that LCH is a clonal proliferative disorder. These investigators studied 10 lesions from patients with LCH and found that they all contained clonal populations of cells. The proportion of clonal cells corresponded to the proportion of lesional Langerhans-like cells, whether from solitary lesions or extensive multisystem disease (16). Yu et al. (17) reported similar findings by flow-sorting CD1a-positive cells from three patients. The hypothesis that LCH arises from somatic mutation of DNA in a normal Langerhans or precursor cell must be considered (16). The evidence of a genetic mutation or mutations leading to LCH is circumstantial. On average, patients with multiorgan LCH are younger than those with single-bone disease. In the rare instances of familial LCH, all the affected members have multiorgan disease. These two observations,

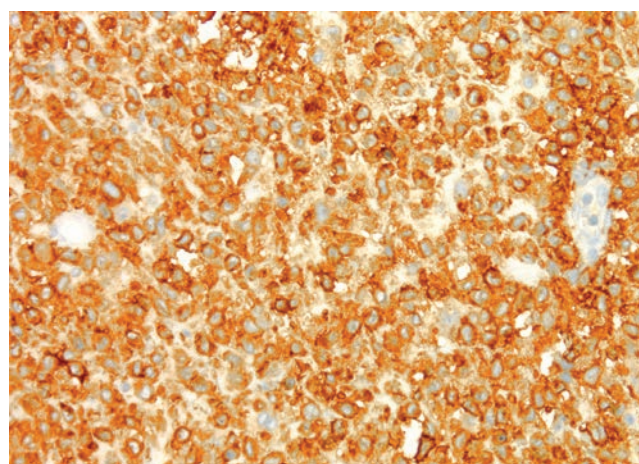


Figure 17.2 Langerhans cells stain positive with CD1a antibody.

reminiscent of the pattern of heritable versus nonheritable retinoblastoma, suggested to Egeler the possibility that LCH's behavior was explicable by Knudson's two-hit hypothesis and a tumor suppressor gene (18). (The two-hit hypothesis is discussed in detail in Chapter 5.)

The distinction between calling LCH malignant and considering it a reactive immunologic disorder is important. Classification has significant consequences for how the clinician thinks about and manages the disease. If one believes that LCH is primarily a malignancy, then radiation therapy (RT), cytotoxic chemotherapy, and even bone marrow ablation and transplantation seem to be acceptable primary therapies. However, if one thinks about LCH primarily as a reactive disorder, then at least initially one would be likely to use more conservative and less toxic therapies, including expectant observation. For the clinician, the truth lies between these two classifications. Most cases of LCH are not life-threatening and can be managed with minimal therapy. There are a few instances of the disease running a fulminant and fatal course, a situation that calls for an aggressive response.

CLINICAL PRESENTATION, DIAGNOSTIC EVALUATION, AND STAGING

The annual incidence of LCH is approximately 0.5 to 2.0 cases per 100,000 children per year. There is a male predominance, with 56–66% of patients male, and 50% of cases diagnosed between the ages of 1 and 15 years (12,13,19–21).

The form of clinical presentation is related to the child's age (19–33) (Tables 17.2 and 17.3). In children less than 2 years old, there may be a widespread seborrheic rash (Fig. 17.3). The rash is often most pronounced on the scalp and in the groin. Petechial hemorrhages in the involved skin are characteristic. Erosive intertrigo in the groin, axilla, and perianal region is a common feature. Ulceration and secondary skin infection may occur. Involvement of the mastoid and middle ear may present as a chronic draining otitis. The infant may be irritable, with a diminished appetite and failure to thrive. Palpable lymphadenopathy may be seen secondary to LCH infiltration. Liver involvement is common in disseminated LCH. Hepatomegaly, elevation of liver enzymes, increased

Table 17.2

An Overview of the Clinical Presentation of Langerhans Cell Histiocytosis in Several Recent Clinical Series

Aspect of Langerhans Cell Histiocytosis Studied/Origin of the Data	Manchester Children's Tumor Registry, United Kingdom, 1954–1998, Published in 2007 (34)	Department of Pediatrics of The Karolinska Hospital, Sweden, 1962–1989, Published in 2005 (35)	Hospital das Clinicas, Universidade Federal de Minas Gerais, Brazil, Published in 2007 (36)
Number of patients in the series	117	49	33
The most five commonly involved disease sites at presentation	Bone, 67%	Bone, 86%	Bone, 70%
	Skin or mucocutaneous, >37% ^a	Skin or mucocutaneous, >39% ^a	Lymph nodes, 49%
	Lung, 10%	Lymph nodes, 18%	Skin or mucocutaneous, 33%
	Lymph nodes, 19%	Ears, 16%	Hepatomegaly, 27%
	Hepatomegaly and or splenomegaly, 16%	Splenomegaly, 10%	Splenomegaly, 21%
Single-organ system involvement vs. multisystem organ involvement at presentation	Single, 44%	Single, 55%	Single, 30%
	Multi, 56%	Multi, 45%	Multi, 70%
Age at diagnosis	Median: 2 years	Mean: Single system, 5.7 years Multisystem, 2.0 years	Median: 2.5 years
Survival from initial diagnosis	At 5 years Overall: 71%	At 35 years Overall: 90%	At 16 years Overall: 86%
	Overall for those presenting with bone disease alone: 93%	Overall for those presenting with single system disease: 100%	Disease free: 31%
	Overall with liver or spleen involvement at diagnosis: 25%	Overall for those presenting with multisystem disease: 77%	

^aThese series report only the percentage of skin involvement so we may infer that if mucocutaneous involvement was included, then the percentage would be higher than what is reported for skin alone.

Table 17.3
Sites of Bone Involvement in Langerhans Cell Histiocytosis: A Summary from the Published Literature

Author	Slater	Kilpatrick	Sessa
Reference	(149)	(27)	(38)
Number of patients	639	263	40
Bone(s) involved			
Skull, including mandible	51%	73%	80%
Ribs	14%	16%	38%
Pelvis	13%	18%	20%
Vertebrae	10%	16%	50%
Upper extremity	7%	12%	5%
Lower extremity	18%	33%	30%
Other	9%	20%	15%

The percentages shown represent patients with this/these bone(s) involved/total number of patients in series *not* patients with this/these bone(s) involved/total number of bony sites involved.



Figure 17.3 Truncal rash and hepatosplenomegaly in an infant with Langerhans cell histiocytosis. (From Berry CL, ed. *Paediatric Pathology*. Berlin: Springer-Verlag, 1991, with permission.)

conjugated bilirubin, ascites, edema, and failure to thrive may be attributable to liver disease or involvement of the gastrointestinal tract. Diarrhea may be the result of abnormal bile acid metabolism or malabsorption (14). Splenomegaly may be accompanied by anemia, leukopenia, or thrombocytopenia (39). In children more than 2 years old, the most common presenting symptoms are related to bone involvement (Table 17.3). There is localized pain, with or without an associated soft tissue mass. Involvement of the orbital bones may cause exophthalmos. LCH may produce premature eruption of the teeth or tooth loss because of gum and mandibular disease (39). Back pain and loss of vertebral height may be seen. Spinal cord compression is rare.

DI is the most common complication of CNS involvement. The incidence varies, in different reports, from 11% to 50%. Magnetic resonance imaging (MRI) may show lesions in the posterior pituitary or the pituitary stalk (40). The mechanism of injury is thought to be either infiltration of the meninges adjacent to the posterior hypothalamic–pituitary axis or direct involvement of the brain. DI often is associated with skull lesions, which may be seen before the DI (23,38,41–44). This may be important because if the index of suspicion for DI is high, and it is diagnosed early, then a few authors believe prompt irradiation may reverse or ameliorate the DI. Lung and oral mucous membrane involvement with LCH often occurs in patients in whom DI develops (41). In a Dutch–German–Austrian study, 3 of the 93 patients (3%) with primary localized disease and 16 of the 106 patients (15%) with dissemination of LCH at diagnosis had DI (41). In a series of patients from London's Hospital for Sick Children, DI was more common among children with multi-system disease (12 of 32) than among those with disease apparently confined to bone (3 of 20). Fourteen of the 15 children with DI had bone disease involving the skull. The cumulative risk of developing DI during the first 4 years after presentation with LCH was 42% (42). In a series from San Francisco, 25% of patients developed DI (25).

Pulmonary LCH has been reported in infants and older adults. However, it affects primarily adults in their twenties and thirties. Chest CT demonstrates multiple nodules with a predominance in the upper lobes. If bronchioalveolar lavage yields more than 5% LCH cells, then the procedure is diagnostic. The cells are CD1a positive. In adults, the natural history of LCH is variable. It is often associated with cigarette smoking, and patients who continue to smoke progress to end-stage fibrotic disease or develop extrapulmonary complications. Smoking cessation is the most effective therapy (45).

Skull lesions often are the first sign of LCH. Often very slow growing, they may be single or multiple and can occur without other bony involvement. Although they have a predilection for the temple area, they can be found anywhere on the skull. On plain radiographs they will appear as punched-out lesions. With time they can develop a sclerotic border (46). Calvarial lesions can have epidural extension. They may extend beneath the dura into the brain parenchyma.

A diagnostic radiograph skeletal survey should be performed to assess the extent of bony involvement (Fig. 17.4). In LCH, conventional skeletal surveys are complementary to isotopic bone scans (46). Both are often used (47). In skeletal radiographs, LCH produces a focal area of rarefaction. The lucent area begins with the medullary cavity and extends to



Figure 17.4 Langerhans cell histiocytosis (LCH) involving the left second rib in a 5-year-old girl. The lesion was painful. The involved portion of the rib was subtotally resected and was diagnostic of LCH. This localized, unifocal bone lesion was adequately treated with surgery alone. There was no recurrence of LCH.

involve the inner table of the cortical bone. MRI may show that the area of bone abnormality is larger than suspected from other studies. Preliminary data suggest that PET scanning may identify active lesions and differentiate them from healed lesions after treatment (48).

In disseminated LCH, cerebral involvement may occur (49). There can be meningeal involvement with formation of large plaques of subdural tumor and/or intraparenchymal lesions. The most common sites for intraparenchymal disease are the hypothalamus and cerebellum. Less common locations are the frontal and temporal lobes (50). Occasionally, LCH can first present to medical attention as an isolated, unifocal lesion of the CNS. The hypothalamus is the most common site for this rare situation. In such cases, the diagnosis is made after surgical exploration and biopsy (49–51).

LCH has a variable prognosis, and a system of grouping patients by predicted outcome is a valuable guide for the clinician (52–54). Patients with localized disease (skin, bone, or lymph node) have a good prognosis and often require minimal or no treatment. In contrast, multiple organ involvement, which is particularly frequent in children <2 years of age, has the risk of a poor prognosis (Table 17.4). Lahey and coworkers (29,30,55) found a striking difference in survival between patients with and without organ dysfunction. Of the 50 patients without organ dysfunction, 33 (66%) responded to chemotherapy and 2 (4%) died. In 33 patients with dysfunction of one or more of the three organ systems, only 11 (33%) responded to chemotherapy, and 22 (67%) died.

The stage distribution of LCH at presentation is almost certainly influenced by referral patterns. A children's hospital is likely to see a higher proportion of advanced disease than a community hospital. In the Children's Hospital of Philadelphia series, 33 of the 64 patients (52%) had localized disease at presentation, 22 (34%) had multifocal disease without organ dysfunction, and 9 (14%) had multifocal disease with evidence of organ dysfunction (21). In a series by McLelland et al. (22) of 58 children, 14 (24%) had single-system disease,

Table 17.4

Organ System Involvement in Langerhans Cell Histiocytosis

Organ	Percentage of Cases
Bone	80%
Skin	60%
Liver, spleen, and lymph nodes	33%
Bone marrow	30%
Lungs	25%
Orbits	25%
Oral cavity and teeth	20%
Ears	20%
Endocrine system	
Diabetes insipidus	15%
Growth failure	<1%

From The Histiocyte Society. LCH-III (2nd version, January 2002). Treatment Protocol of the Third International Study for Langerhans Cell Histiocytosis. The Histiocyte Society; 2002, with permission.

22 (38%) had multisystem disease without organ dysfunction, and 22 (38%) had multisystem disease with organ dysfunction (22).

SELECTION OF THERAPY

In many cases LCH can take an indolent course or spontaneously remit. If there is no organ dysfunction or systemic effects threatening the child, it may be possible to use minimal or no therapy. Asymptomatic lesions in older patients with disease confined to one organ system often are best managed by observation (52–54). One should carefully balance the risks of treatment against the apparent course of the disease. The potentially toxic effects of therapy should not be engendered unless absolutely necessary (53,54,56–63). In Table 17.4, the authors outline a conservative management strategy for LCH. A detailed discussion of the particulars of the therapy follows.

Surgery

Regression of an isolated LCH bone lesion with no further treatment after the initial fine needle aspiration biopsy has been reported. It is possible that a small amount of mechanical perturbation of an LCH lesion is sufficient to initiate its regression without further treatment. Pediatric Oncology Group (POG) Study 8047 evaluated the response rate of LCH bone lesions to incisional or excisional biopsy. The study was open to patients less than 21 years old with no more than two bone lesions and no systemic involvement by LCH. Open biopsy was recommended, with curettage when possible. Needle biopsy was performed for vertebral lesions, and excision was performed for expendable bone. Surgery proved highly effective: 20 of the 23 lesions (87%) were controlled without local LCH relapse (57).

Solitary bone lesions may be treated surgically. There is an equal probability of local control with biopsy, curettage, or excision (57,63). A wide excision may be considered in an expendable bone such as the clavicle, ribs, or tip of the scapula. In nonexpendable bone locations, a small, mill-like biopsy

instrument allows a tissue diagnosis and access to the medullary cavity for a curettage. Relative contraindications to curettage are situations in which the procedure would result in loss of function, severe orthopedic deformity, or poor cosmetic result. A curettage should not be performed at the axis, atlas, or femoral neck because of the risk of bone instability. Gingival curettage may be useful for gum disease.

Direct Injection of Steroids

Methylprednisolone (40–80 mg) or depomedrone may be injected into some bone lesions under fluoroscopic guidance (70). Because the transient expansion of the medullary cavity causes extreme pain, the procedure should be performed under general anesthesia (Table 17.5). One cannot be certain whether responses are obtained from the steroids or from the disruption of the microenvironment caused by the needle (71–78).

Radiation Therapy

The use of radiation therapy (RT) to manage localized bone or soft tissue LCH is decreasing. This trend is attributable to a better understanding of the prognostic factors predicting the behavior of LCH, an appreciation of the frequency of disease remission after minimally toxic therapy, and concern about the long-term ill effects of radiation, albeit at low dosages (14). The complete response rate of solitary LCH in bone to curettage or excision is 70–90% (57–59,62,63). There is no evidence that immediate postoperative irradiation improves these results. Asymptomatic bone lesions with sclerotic margins often resolve spontaneously and RT usually is not necessary (57). If the clinician obtains follow-up radiographs of the child with bony LCH, evidence of healing is common. Meyer et al. (40) described radiographic lesion improvement in 14 out of 15 patients with multifocal LCH (93%) and 7 out of 8 patients with unifocal LCH (88%). A change from a nontrabecular to a trabecular pattern, evolution of sclerosis in a nonsclerotic lesion, and loss of distinct

margins indicate healing (59). Minimum time from diagnosis to evidence of mild healing was 3 months, although complete resolution often takes longer (57).

Postoperative irradiation should be reserved for patients who have no clinical or radiographic signs of local healing. In addition, RT may be indicated for local relapse after surgery when the relapsed bone is the sole site of recurrent disease, where curettage is not appropriate because of the risk of fracture (i.e., a lytic lesion of the femoral neck; mandibular involvement producing a loose, painful tooth, and reluctance to eat) or poor cosmesis (i.e., the orbital bones) (40,60,61, 79,80), when the potential compromise of critical structures from expansile bone lesions (spinal cord compression, pressure on the globe or optic nerve) demands a reliable and rapid response, or for pain relief. The success rate of RT for bony LCH is extremely high (Table 17.6).

Vertebral lesions should be considered a special situation. Partial or complete collapse (vertebra plana) of a vertebral body may be asymptomatic (Fig. 17.5). These asymptomatic lesions generally do not warrant therapy because partial regrowth usually occurs irrespective of treatment. However, if a vertebral lesion is painful, it may be irradiated (111).

In patients with multifocal LCH or with organ dysfunction, local RT may have a place. Lesions that are painful despite chemotherapy should be considered for local RT (112). Disfiguring bone or soft tissue lesions or bones at substantial immediate risk for fracture may also be appropriate for local RT.

Recalcitrant skin lesions may be treated with electron beam or orthovoltage photon therapy, but this should almost never be necessary in view of the other available agents (44,79,113).

The value of RT for LCH-associated DI is controversial. Greenberger et al. (79) reported 21 patients irradiated for DI. They noted a complete reversal of symptoms in four patients with discontinuation of pitressin for 2, 5, and 25 years. A complete response to RT was observed in three of four patients

Table 17.5
Treatment of Localized Langerhans Cell Histiocytosis of Bone with Intralesional Corticosteroid Injection

Author (Reference)	Anesthesia Needed: General/Local	Speed of Pain Relief (Weeks)	Speed of Resolution of Bone Disease (Months)	Complete Responders/Total Number of Patients	Complications
Cohen et al. (73)	8/1	1	2–4	8/9	None
Scaglietti et al. (74)	9/0	<1	2	9/9	None
Nauert et al. (92)	10/2	1–2	NS	12/12	None
Ruff et al. (150)	1/0	NS	NS	1/1	None
Capana et al. (70)	11/0	2	3	11/11	None
Fradia et al. (151)	3/0	NS	NS	3/3	None
Wirtschaffer et al. (75)	1/0	NS	NS	1/1	None
Jones et al. (71)	1/0	NS	NS	1/1	Abcess
Kindy-Degnan et al. (76)	NS	1	12	1/1	None
Egeler et al. (152)	8/0	1–2	3–6	8/8	Osteomyelitis

NS, not stated.

Modified from Egeler RM, Thompson RC Jr, Voute PA, et al. Interlesional infiltration of corticosteroids in localized Langerhans cell histiocytosis. *J Pediatr Orthop.* 1992;12:811–814; and Egeler RM, Nesbit ME. Langerhans cell histiocytosis and other disorders of monocyte-histiocyte lineage. *Crit Rev Oncol Hematol.* 1995;18(1):9–35.

Table 17.6
Results of External Beam Radiation Therapy for Langerhans Cell Histiocytosis of Bone

Year of Publication	First Author	Number of Patients Reported	Dose of Radiotherapy Administered (Gray)	Follow-Up Period (Years)	Complete Response Rate or Local Control Rate (%)
1960	McGaran (58)	8	3–35	3–13	8/8 (100%)
1965	Pfeifer (66)	10	20	0.5–14	10/10 (100%)
1965	Bopp (68)	10	7–31	2–12	2/10 (20%)
1966	Oshsner (67)	20	6–10	?	20/20 (100%)
1970	Davidson (69)	5	4.5–7.5	0.25–1.5	5/5 (100%)
1970	Fowles (81)	11	?	1–35	11/11 (100%)
1970	Lindenbaum (82)	1	12	0.8	1/1 (100%)
1970	Winkelmann (83)	9	?	2–5	9/9 (100%)
1971	Rodrigues (84)	1	10	?	Partial response
1973	Von Koppenfels (85)	39	6–30	?	39/39 Complete and partial response
1974	Metha (86)	1	10	?	1/1 (100%)
1977	Mukadam (87)	14	15–20	?	14/14 Complete and partial response
1979	Sweet (88)	1	38	?	1/1 (100%)
1980	Gmelin (89)	14	20–30	0.6–8	11/14 (79%)
1981	Greenberger (54)	8	4–20	4–25	8/8 (100%)
1981	Pereslegin (90)	93	4–14	1–25	115/118 (97%)
1982	Wester (91)	12	?	0.5–3	11/12 (92%)
1983	Nauert (92)	24	3–35	?	20/24 (83%)
1983	Shelby (93)	1	10	0.3	0/1 (0%)
1984	Rawlings (94)	13	6–25	0.1–25	13/13 (100%)
1986	Hauk (95)	1	30–45	12	(100% “regression”)
1987	Anonsen (96)	8	?	Median 6	8/8 (100%)
1987	Selch (97)	1	15	3	1/1 (100%)
1988	Mackenzie (98)	11	?	1–20	9/11 (82%)
1988	Rivera-Luna (99)	17	?	1.7–7	17/17 (100%)
1990	Selch (26)	16	6–15	1–13	14/16 Complete and partial response (88%)
1991	Wiegel (100)	17	6–42	0.3–33	17/17 (100%)
1992	El-Sayed (65)	15	6–35	1–20	13/15 (87%)
1993	Fiorillo (101)	8	8–10	0.3–2.3	8/8 (100%)
1994	Irving (102)	9	?	4–10	7/9 (78%)
1995	Kilpatrick (27)	106	?	0.3–50	100/106 Complete and partial response (94%)
1996	Willis (24)	37	?	0–40	37/37 (100%)
1997	Floman (103)	13	?	1–17	6/13 (46%)
1999	Dornfeld (104)	1	10	0.3	1/1 (100%)
1999	Braier (105)	15	?	0–8	14/15 (93%)
2000	Heyd (106)	2	12.6–14	0.3–6	2/2 (100%)
2003	Ghanem (107)	8	?	2–15	6/8 (75%)
2007	Sarkar (108)	1	?	?	“Favorable response”
2008	Saliba (109)	2	?	3	2/2 (100%)

This table is modified from the work of Heyd et al. (106) and Olschewski et al. (110) and additional material was added. Some of the reported series include patients who were also treated with surgery, steroids, or chemotherapy. In some reports, a range of doses is given for the treatment of just one patient. This is because multiple bony sites were irradiated in one patient using different doses.

treated within 1 week of the onset of symptoms. Only 1 of the 15 patients responded when the duration of symptoms before RT exceeded 2 weeks. However, Smith et al. (114) reported no response in seven patients irradiated for DI. Broadbent and Chu (116) have reported six patients with DI who failed to

respond to irradiation. Selch and Parker (26) irradiated two patients with DI 3 months after the onset of symptoms. Neither of these patients responded. There were no responses among seven patients treated with chemotherapy with or without irradiation by Willis et al. (24). El-Sayed and Brewin (73) reported

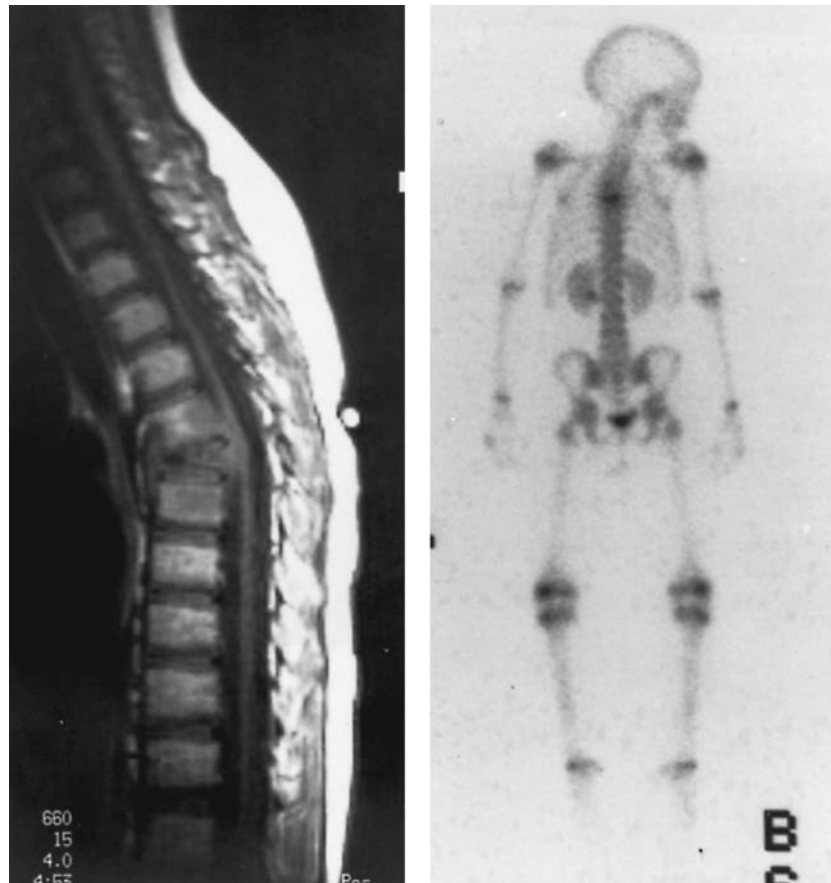


Figure 17.5 A: Magnetic resonance imaging scan and (B) bone scan showing complete vertebral collapse (vertebra plana) secondary to Langerhans cell histiocytosis (LCH) in 1992. No therapy was given beyond a needle biopsy to establish the diagnosis. Pain resolved over a month. Typically, healing includes fusion to adjacent vertebrae. The child remains without evidence of recurrent LCH.

successful radiotherapy of two patients with DI. Grois et al. (115) found that none of the five patients treated with 10 Gy of radiotherapy to the pituitary within 1 month of the occurrence of DI was able to decrease the desmopressin dosage. Some have discounted the value of RT for DI without contributing additional supporting data to the literature (18,38,114,153).

The largest series of DI in LCH has been reported by Minehan et al. (43) and Kilpatrick et al. (27) from the Mayo Clinic. In 45 evaluable patients, the principal findings were as follows: 10 of the 28 (36%) irradiated patients had a complete or partial improvement in their DI, as opposed to none of the 17 nonirradiated patients; 6 patients were complete responders, 5 of whom were irradiated within 14 days of the diagnosis of DI; 77% of all patients with LCH and DI had a non-CNS head and neck site involved with LCH; computed tomography (CT) or MRI improvement in a pituitary–hypothalamic mass did not correlate well with improvement in DI; and in 12 of the 28 patients (43%) irradiated for DI, growth hormone (GH) deficiency or parhypopituitarism developed. Minehan et al. (43) did a literature review, to which we can add published patients they did not include, to generate an overall response rate of less than 25% of DI to radiation (26–27,38–44,76,116). We believe that RT is worth considering in DI if symptoms are of recent onset (approximately 1 week). Others recommend RT even for long-standing DI in the hope of preventing local disease progression and additional neuroendocrine dysfunction.

Focal LCH involving the brain can be treated successfully with radiotherapy. On rare occasions, LCH may diffusely involve the parenchyma of the brain (50). The true incidence of this event is not known. Brain involvement of this sort occurs in the most aggressive form of the disease. On MRI, cerebral LCH may demonstrate parenchymal masses that intensively enhance after gadolinium is administered. Other patients may show diffuse infiltration of brain structures without tumor formation. A retrospective review by Hund et al. (51) identified 36 histologically evaluated cases of cerebral LCH with an extrahypothalamic localization. Sixteen of the patients had cerebral involvement during the course of the previously diagnosed LCH, whereas 20 patients had cerebral LCH without a history or symptoms of systemic disease before the neurologic presentation. Solitary brain lesions were treated by surgery in 13 patients. Six remained free of disease for up to 2 years of follow-up. In another six, follow-up was not reported. One patient died 4 weeks after resection of a posterior fossa mass. In an additional six patients, surgery was followed by RT (10–41 Gy) because of recurrence of a lesion or incomplete resection. In five of the six patients, the lesions disappeared and did not recur for up to 2 years of follow-up. In three patients with multiple lesions, the disease was controlled by radiation or chemotherapy for up to 3 years. In others, regression, relapse, or new lesions occurred despite various treatments. Eight of the 36 patients died; 4 had multiple intracranial lesions, and the remaining 4 had localized lesions. Although it is difficult

to draw firm conclusions from the available literature, some suggestions may be made: Dural and choroid plexus lesions probably are best treated by resection. Solitary interparenchymal lesions may also be resected. RT after biopsy (if necessary for diagnosis) is a reasonable alternative to surgery.

Chemotherapy

In the first three editions of this book, we stated that in multifocal LCH the indications for systemic therapy are controversial. Because there was no agreement on the important prognostic factors in LCH, the selection of patients needing chemotherapy was difficult (117–120). The lack of a uniformly applied staging system made comparison of specific chemotherapy programs difficult.

Many clinicians were reluctant to use chemotherapy in multisystem disease because of the study of McLelland et al. (22). Forty-four children with multisystem disease, including 22 with organ dysfunction, were treated conservatively. Five had no treatment, 1 received topical nitrogen mustard only, 2 received radiotherapy alone, and 36 were treated with prednisone. Of these 36 children, 21 were given cytotoxic drugs later when disease progressed despite prednisone. The 2-year mortality rate (36% with organ dysfunction, 0% without organ dysfunction) was no different from that of historical studies using aggressive upfront systemic cytotoxic chemotherapy. The rate of development of DI in the group of McLelland et al. was 36%, which is higher than that in some but not all other series of the era (22,114,116).

From the 1970s to the 1990s, the reported complete and partial response rates of advanced LCH to prednisone and a wide variety of single-agent cytotoxic chemotherapeutic agents (chlorambucil, cyclophosphamide, etoposide, vinblastine, and vincristine) were between 50% and 100% (22,23,117–122). (These data are reviewed in Table 17.6 in the third edition of this book.) Relapse after initial therapy was common (71). By the early 1990s, if systemic therapy was elected for LCH, then the consensus view was to begin with high-dose steroids, usually prednisone. If that failed, then most clinicians opted for either etoposide or vinblastine as a single agent.

There are now several large cooperative group studies that offer guidance in selecting appropriate patients for chemotherapy.

AIEOP-CNR-H.X*83

This prospective multicenter trial included 12 different Italian institutions (53,123). The objectives were to determine the outcome of patients therapeutically stratified according to the presence or absence of organ dysfunction, to test the efficacy of different single-agent chemotherapy approaches in patients with a good prognosis, and to determine the incidence of disease-related disabilities before and after treatment.

In children with a single lesion, treatment was variable and consisted of either incisional biopsy, curettage, total excision, RT, or chemotherapy. This good-prognosis group consisted of immunotherapy with crude calf thymic extract and then sequential single-agent chemotherapy. First-line treatment in patients was vinblastine. Poor responders then received doxorubicin, and patients in whom doxorubicin failed were placed on etoposide. The poor prognostic group, consisting of patients with organ dysfunction, were treated with vincristine, cyclophosphamide, and prednisone.

Of the 90 eligible patients, 84 were evaluable. The 16 patients with mono-ostotic LCH or a paravertebral intradural mass are alive. All had initial complete responses, and 15 were recurrence free 3–6 months after diagnosis. Fifty-four patients with systemic disease but without organ dysfunction received good-prognosis chemotherapy. Thirty-four achieved a complete response with vinblastine. The multiagent program for the poor prognosis group was given to 11 patients. Only 2 achieved complete response and were recurrence free at 36 and 66 months, respectively.

The overall survival for the 84 evaluable children was 93% at 48 months. Survival at 48 months was 100% for the 60 children more than 2 years old and 79% for the 24 children less than 2 years old. All 73 children without organ dysfunction were long-term survivors, and the 11 patients with organ dysfunction had a 46% survival rate at 12 months. Of the total 90 eligible patients, 18 developed DI. One patient developed acute nonlymphocytic leukemia (ANLL) 2 years after diagnosis and treatment with vinblastine and etoposide.

DAL-HX83

This trial accrued 106 patients from institutions in Austria, Germany, and the Netherlands from 1983 to 1989 (25,41,53,56,124). Disseminated disease was defined as the presence of multiple LCH lesions of any type or combination, with the exception of multiple skin lesions. Group A patients were those with multifocal bone disease: lesions in multiple bones or more than two lesions in one bone. Group B patients either had soft tissue involvement with or without bone lesions and without signs of organ dysfunction or patients with a single-bone lesion and a biopsy-proven contiguous soft tissue mass, regional lymph node involvement, or endocrinologic disabilities. Group C patients had dysfunction of liver, lung, or the hematopoietic system.

All patients with disseminated disease received chemotherapy immediately after diagnosis with prednisone, vinblastine, and etoposide. Thereafter, all patients received continuous oral 6-mercaptopurine (6 MP) for 46 weeks. Patients in group A received prednisone and vinblastine. Patients in group B received continuation treatment with prednisone, vinblastine, and etoposide. Patients in group C received continuation therapy with those three agents plus methotrexate.

Complete resolution was achieved in 86% of all patients at 4 months. In group A, 25 of the 28 patients (89%) achieved initial complete resolution of LCH. Recurrence occurred in only three children (12%). In group B, 52 of the 57 patients (91%) achieved resolution of disease. Twelve patients (23%) had recurrent disease. In group C, 14 of the 21 patients (67%) achieved resolution of disease. Of these 14 patients, 6 (42%) developed a recurrence. Disease-free survival was 88% in group A, 73% in group B, and 64% in group C ($p < 0.05$). DI developed in 15% of patients.

DAL-HX90

DAL-HX90, a follow-up to DAL-HX83, made moderate changes including less aggressive induction therapy utilizing fewer initial doses of etoposide for group C patients. Methotrexate was eliminated from group C continuation. These changes produced no significant difference in outcome.

LCH Trial 1

In the Histiocyte Society's first LCH randomized trial, 447 patients were registered (53,122). All patients with disseminated multisystem LCH received high-dose methylprednisolone. One hundred forty-three patients were then randomized to receive either etoposide (69 patients) or vinblastine (74 patients). Vinblastine and etoposide were equivalent in response at week 6 of therapy, response at the last evaluation, toxicity, probability of survival, frequency of disease reactivation, and risk of DI. After 6 weeks of treatment, 53% of patients were drug responders. Reactivation of disease after a complete response occurred in 58% of these patients after a median of 9 months. Overall, 4-year survival was 78%; 91% in responders to initial therapy versus 34% in initial nonresponders (ISS). In general the results of the LCH trial 1 (LCH1) were compared unfavorably with those of the DAL-HX83/90 studies. The response rate was lower, and the activation rate was higher. Polychemotherapy given for 1 year appeared superior to 6 months of monotherapy.

LCH2

The results of the LCH1 and the DAL-HX studies formed the basis of the Histiocyte Society's LCH2 study, which opened in May 1996. This randomized trial to compare the effect of oral prednisolone combined with vinblastine with or without the addition of etoposide in high-risk patients defined as those with multisystem disease with at least one of the organ systems involved. Low-risk patients were more than 2 years old without involvement of the hematopoietic system, liver, lungs, or spleen (124). High-risk patients were randomized between initial treatment with vinblastine and prednisone versus vinblastine, prednisone, and etoposide. All high-risk patients received 6 MP in continuation. Low-risk patients were all treated with vinblastine and prednisone and did not receive 6 MP.

LCH-II was an international randomized trial which randomized 193 patients to treatment arm A which consisted of 6 weeks of daily prednisone and weekly vinblastine followed by 18 weeks of daily 6-mercaptopurine with vinblastine/prednisone pulses v. these drugs plus etoposide which was added in arm B. Considering all 193 randomized risk patients, there were similar outcomes: rapid (6 weeks) response (arm A vs arm B: 63%/71%), 5-year survival probability (74%/79%), disease reactivation frequency (46%/46%), and permanent consequences (43%/37%). Patients <2 years of age without risk organ involvement had 100% survival and >80% rapid response. Risk organ involved patients not responding within 6 weeks had highest mortality. The more intensive arm B reduced mortality in risk organ involved patients. Comparison of risk organ involved patients in LCH-I and LCH-II confirmed that increasing treatment intensity increased rapid responses (from 43% in arm A LCH-I to 68% in arm B LCH-II; $p = .027$) and reduced mortality (44% in arm A LCH-I to 27% in arm B LCH-II; $p = .042$). (125)

JLSG-96

The Japanese Langerhans Cell Histiocytosis Study Group conducted a protocol that enrolled patients with newly diagnosed multifocal LCH. There were 32 patients with single-organ disease and 59 patients with multiorgan disease. All received induction therapy with cytarabine, vincristine, and prednisolone for 6 weeks followed by 6 months of maintenance with cytarabine, vincristine, and methotrexate. Patients found to be poor responders during induction

therapy were then switched to doxorubicin, cyclophosphamide, vincristine, and prednisolone.

In the single-organ disease group, the 5-year overall survival was 100%. Seventy-six percent of patients with multiorgan disease had some response with initial induction and 63% achieved good response by the end of maintenance. Of the responders, 46% had a sustained remission (53).

LCH3

LCH1 and LCH2 showed that "risk" organ involvement (hematopoietic system, spleen, liver, and lungs) and poor response to initial chemotherapy are the crucial prognostic factors for LCH. Age <2 years at diagnosis was not of independent prognostic importance. Since VP-16 has not been proven beneficial and is leukemogenic, it has not been included in LCH3 (125). The current histiocytosis treatment protocol is described in Table 17.7 (125,126).

Salvage Therapy

The LCH1S study was established to study salvage therapy for patients who did not respond to initial chemotherapy (52,53,120). No superior strategy has been demonstrated for patients who failed to respond to steroids and vinblastine or etoposide.

Some of the agents that have been used are as follows:

2-Chlorodeoxyadenosine (2-CdA) is a purine analog resistant to the enzyme adenosine deaminase (ADA) but not to the enzyme deoxycytidine kinase (DCK). ADA has an essential role in the intracellular degradation of purine nucleosides derived from DNA breakdown. Normal mature lymphocytes and monocytes express high levels of DCK. In vitro studies have shown that 2-CdA is a highly selective anti-monocyte agent that causes decreased monocyte function and viability and decreased IL-6 secretion. Because tissue histiocytes are derived from the same stem cells as circulating monocytes, 2-CdA may be a rational agent for treating patients with histiocytic disorders. In a report by Rodriguez-Galindo et al. (127), five out of six patients with multisystem LCH achieved remission with 2-CdA. Hampshire et al. reported a complete/partial response rate of 63% in 16 adults with LCH. Median response duration was 3 years (128). Although the efficacy of 2-CdA in treating LCH probably results from its direct effects on histiocytes, the drug also may interfere with the immune abnormalities that are part of the pathogenesis of LCH. 2-Deoxycoformycin (2-DVF) is a nucleoside analog. 2-DCF is given as a weekly intravenous push injection and a handful of LCH patients have been treated. Thalidomide is an oral medication that has been used for the treatment of cutaneous oral LCH lesions in adults. Etanercept is a soluble TNF receptor and Fe fusion protein has been used in the treatment of LCH with little benefit.

Cyclosporine (an immunosuppressive drug) long used in bone marrow transplantation (BMT) has similarly proved of little use in LCH (129).

Bisphosphonates, including pamidronate and clodronate, have been associated with improved pain control for LCH bone lesions.

Table 17.7
Management Strategy for Langerhans Cell Histiocytosis Based on LCH 3

Stage of Involvement	Anatomic Site	Symptoms	Recommended Options for Therapy
Localized disease with organ dysfunction	Bone or soft tissue	None	If the diagnosis is not established, then excisional biopsy (or biopsy and curettage) is already established, then expectant observation is appropriate
Localized disease with dysfunction or single-system “low-risk” disease	Bone, soft tissue, or skin	Pain or disruption of function	Disease in noncrucial bone and soft tissue sites can be managed by biopsy, excision, curettage, or steroid injection; at some sites, such as adjacent to the eye, ear, or spine or in critical weight-bearing bones with the potential to fracture, or for relapse after more conservative therapy, consider systemic steroids or local irradiation; symptomatic skin disease may be treated with topical nitrogen mustard, although some authorities prefer systemic therapy
Multifocal, no organ dysfunction	Any sites	None	Complete absence of symptoms in this situation is rare, but if the child is truly asymptomatic, then expectant observation is felt to be appropriate by some authorities; others begin chemotherapy
Multifocal, with organ dysfunction (high-risk systems/organs are hematopoietic, liver, spleen, or lungs except for single system/lung) and single-system multifocal bone disease and localized special site involvement	Any sites	Fever, weight loss, failure to thrive, local symptoms from bone and soft tissue lesions	Patients may be stratified into groups; group 1: multisystem “risk” patients (with involvement of $\geq$ risk organs, hematopoietic, liver, spleen, lungs except for single-system lungs); group 2: multisystem “low-risk” patients (multiple organs involved but without involvement of “risk” organs); and group 3: single-system “multifocal bone disease” and CNS lesions with intracranial soft tissue extension or vertebral lesions without intraspinal soft tissue extension. Group 1 patients are treated with PDN, VBL, and 6MP or PDN, VBL, MTX, and FA; Group 2 patients are treated with PDN and VBL for 6 vs. 12 weeks; Group 3 patients are treated with PDN and VBL.

PDN, prednisone; VBL, vinblastine; MTX, methotrexate; 6MP, 6-mercaptopurine; FA, folinic acid.

Modified from The Histiocyte Society. LCH-III (2nd version, January 2002). Treatment Protocol of the Third International Study for Langerhans Cell Histiocytosis. The Histiocyte Society; 2002, with permission.

Other agents under investigation include interferon alpha, monoclonal CD-52 antibody, and monoclonal CD1a antibody.

Skin Therapy

Skin involvement is a common component of multisystem LCH in younger children. Skin symptoms may include pruritus, ulceration, purulent exudation, odor, and painful defecation caused by anogenital involvement (23,130–132). Sheehan et al. (131) treated 16 patients with symptomatic cutaneous LCH with a topical nitrogen mustard solution made by adding tap water to nitrogen mustard

powder and applying it daily to the skin with a watercolor brush. A complete or partial response was obtained in all cases. In patients who do not respond to topical nitrogen mustard or if cells are very sensitive to ultraviolet radiation, PUVA can be effective in controlling skin disease. Mayou et al. (132) successfully treated a case of cutaneous LCH in an adult with oral etoposide (143). Concerned about the mutagenicity of nitrogen mustard, these authors labeled the topical use of that compound for LCH as “retrogressive.” Systematic corticosteroids have been advocated for the treatment of children with persistent or recalcitrant skin disease (23).

Liver and Bone Marrow Transplantation

In some children, liver failure from LCH is the cause of death. There are a few case reports of successful orthotopic liver transplantations. These patients did not appear to have active LCH at the time of the transplant (23,133,134).

There have been a small number of children with refractory LCH, despite chemotherapy, who have been successfully treated with autologous bone marrow rescue, unrelated cord blood, stem cells, or other forms of allogeneic BMT. A variety of conditioning programs have been used, including the treatment of many patients with programs that include total body irradiation (TBI, e.g., 2–2.25 Gy per fraction daily or twice daily to 12–15.75 Gy) or combinations of cyclophosphamide, busulfan, carmustine, fludarabine, melphalan, antithymocyte globulin, and campath. However, because many of the children who receive BMT for chemotherapy-resistant LCH are young at the time of transplantation, TBI-containing conditioning programs should be used only with great caution. From the available literature, about 60% of patients treated with BMT may be expected to be long-term survivors (33,53,64,135–139).

RADIOTHERAPEUTIC MANAGEMENT

Dosage

There is no clear relationship between the dosage of irradiation and local control of LCH. Childs and Kennedy (80) reported 12 patients treated with radiotherapy. Their series began with an infant treated in 1927–1928 with a radium source. They thought that a dosage of approximately 600 roentgens was necessary to control individual lesions. Smith et al. (114) reported on 89 courses of irradiation administered with 250-kV x-rays or cobalt-60. Less than 1000 cGy was administered in 92% of the cases, and the local success rate was 87%. Three of five sites treated with less than 450 cGy had a

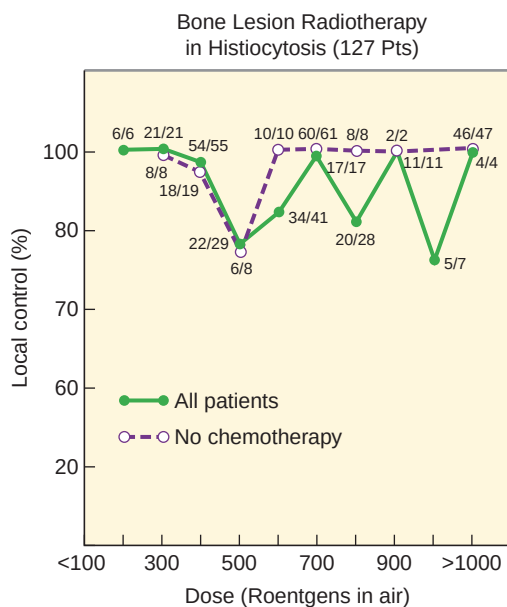


Figure 17.6 Local control of bone lesions as a function of dosage delivered. (From Greenberger JS, Cassady JR, Jaffe N, et al. Radiation therapy in patients with histiocytosis: management of diabetes insipidus and bone lesions. *Int J Radiat Oncol Biol Phys.* 1979;5:1749–1755, with permission.)



Figure 17.7 A 4-month-old boy developed a seborrheic skin rash with focal areas of ulceration. Skin biopsy showed Langerhans cell histiocytosis (LCH). No other organ systems were involved. At 6 months of age, proptosis was noted, and orbital computed tomography scan demonstrated erosion of the lateral wall of the right orbit by a destructive lesion. Surgery was felt to be ill-advised because of concern over damage to the lateral rectus muscle and an unacceptable cosmetic result. Vinblastine and prednisone were administered. Proptosis improved but then subsequently worsened. A total dosage of 6 Gy in four fractions was administered with a right anterior oblique half-beam-blocked 4-MV photon field with shielding of the lens and two thirds of the globe in 1984. Vinblastine was continued for 15 months after radiotherapy. The bone lesion healed within 2 months after irradiation. There is no evidence of LCH 25 years after the initial diagnosis. The adult is now being treated for attention deficit disorder.

local failure but were salvaged with additional irradiation. Dosages greater than 1000 cGy did not appear to be more effective than dosages of 450–1000 cGy.

Greenberger et al. (79) described 89 patients receiving RT to 380 fields for control of bone lesions. Between 100 and 2000 cGy, local control was obtained in 75% of courses (Fig. 17.6). In a study of 56 irradiated sites, Selch and Parker (26) found no difference in median dosage between controlled and relapsed bony sites (9 vs. 10 Gy) or soft tissue sites (median dosage 15 Gy for either controlled or relapsed sites). Overall local control was 82% (Fig. 17.7). Reviews describe the use of total dosages of 5–35 Gy, with 5–10 Gy in three to five fractions being the favored range (Fig. 17.8) (44,74,77). Cassady (140) advised using a total dosage of 15–20 Gy in patients older than 18 years because of a perceived higher risk of local failure and a lower risk of bone damage by radiation.

For DI, Smith et al. (114) reported no relief in seven patients treated with 500–1830 cGy. Greenberger et al. (79) administered 345–1600 cGy to 21 patients and, as discussed previously, observed a complete response in four patients and a partial response in another four patients. Minehan et al. (43) reported three of the five patients (60%) with DI responding when treated with more than 15 Gy, compared with 7 of 23 (30%) treated with less than 15 Gy. Saliba et al. (109) irradiated one of two DI patients with success.

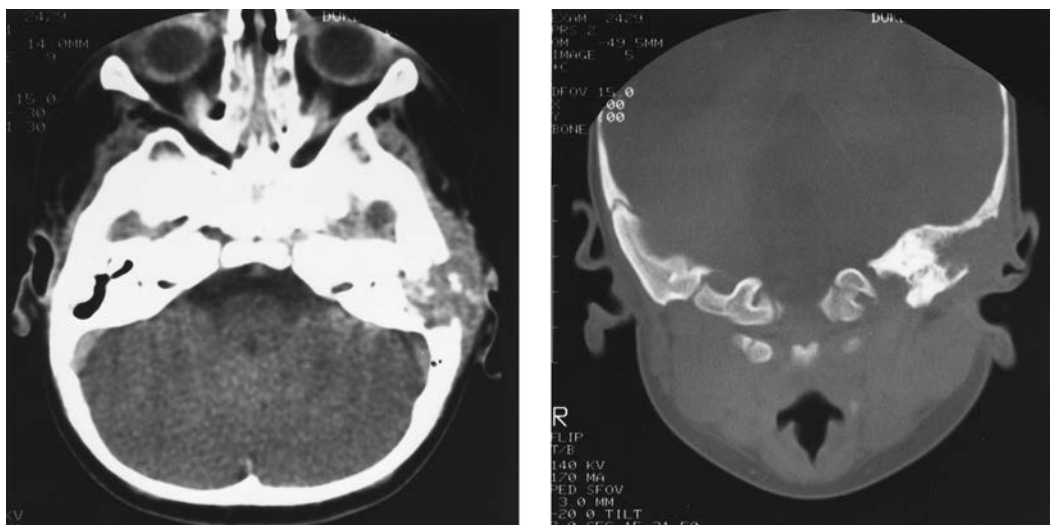


Figure 17.8 An 11-month-old boy presented to medical attention with protrusion of the superior aspect of the left ear. Computed tomographic scan showed a left mastoid soft tissue mass with erosion into the temporal bone. Open biopsy made the diagnosis of Langerhans cell histiocytosis (LCH). In 1987, the child received local irradiation with 12-MEV electrons to a total dosage of 6 Gy in three fractions. After irradiation he was treated with Vinblastine and Prednisone. He remains without evidence of persistent or recurrent LCH.

Volume

To treat DI, one uses a 5×5 to 7×7 cm set of parallel opposed fields, arcs, a three-field technique, or conformally planned fields to cover the hypothalamic–pituitary axis. Bone lesions should be treated with a field designed to cover the radiographic abnormality with a small margin. In the treatment of skull lesions, we attempt to minimize the dosage to the underlying brain by treating with electrons or orthovoltage equipment. If electrons are used, an adjustment for attenuation by compact bone infiltrated by LCH should be made. This is best done by taking density measurements of the involved bone with a cranial CT scan.

LONG-TERM SEQUELAE OF LCH AND ITS TREATMENT

Because of the low dosage of irradiation used, acute side effects of radiotherapy for LCH are rare. However, it is common to see late sequelae of LCH, most of which may be attributable to the disease and some of which may be attributable to the treatment (141,142).

Long-term disabilities are common in survivors of LCH. The French Langerhans Cell Histiocytosis Group reported 320 living patients followed for a median of 39.5 months. The most common sequelae were DI (18%), GH deficiency and short stature (5%), hypothyroidism (2.5%), deafness (2.5%), and vertebra plana and orthopedic sequelae (2.5%) (19). The most common sequelae in the University of California, San Francisco, series were DI (26%), growth failure (20%), sex hormone deficiency (16%), and hearing loss (16%) (24). The 90 children followed by the Italian Cooperative Group had an overall incidence of disease-related disabilities of approximately 48%. These included DI, orthopedic abnormalities, growth defects, tooth loss, chronic hepatitis, exophthalmus, and hearing loss (113,123,133). McLelland et al. (22,144) described orthopedic abnormalities, endocrine dysfunction,

and liver fibrosis as well as DI. The incidence of DI in conservatively treated patients with multisystem disease, for whom treatment was reserved only for exacerbations, was 36% compared with a 15% incidence in the DAL series and 20% in the Italian trial, both of which used intensive chemotherapy. However, the McLelland series is from a single institution, and referral may be accounted for the difference. In a study of 15 long-term survivors of LCH, Ransom et al. (142) found that 7 had an IQ lower than 89. In a large study of the Histiocyte Society, DI (24%), orthopedic abnormalities (20%), hearing loss (13%), and neurologic consequences (11%) were most frequent (144).

Growth and endocrine disorders are common in multisystem LCH. A study of 144 patients with multisystem LCH evaluated at the Great Ormond Street Hospital for Sick Children in London showed that 50 had endocrinopathy, 49 of whom had DI. GH insufficiency was present in 21 patients. GH therapy was able to significantly improve growth in these patients. It was not clear that RT to the head increased the incidence of GH insufficiency. It is clear that children with LCH should be investigated for hormone insufficiency, especially those who have DI or growth failure. It appears that GH insufficiency is secondary to direct hypothalamic–pituitary involvement by the disease. Thickening of the pituitary stalk on MRI scan provides additional evidence of GH insufficiency (145).

The frequency of secondary malignancy after therapy for LCH is uncertain (6,52,129). In a report describing the association between LCH and other malignancies (91 patients), 39 had LCH and lymphoma (Hodgkin or non-Hodgkin), 22 had LCH and leukemia, and 30 had LCH and a solid tumor, most commonly lung cancer. Although the leukemias and nonlung solid tumors most commonly occurred years after LCH, most of the lymphomas and lung cancers preceded LCH or were diagnosed concurrently, in an unexplained association (146). Affected patients had initially received irradiation and chemotherapy, irradiation only, or chlorambucil only (54,147). One case of leukemia was seen among 90 patients

followed in the Italian Cooperative Group Study (123). One case of leukemia was seen in 51 patients followed more than 3 years at the University of California, San Francisco (24). There were no second malignancies in 106 patients with LCH treated in the Dutch–German–Austrian DAL-HX83 trial (25,56,124).

Haupt et al. (148) evaluated children with LCH enrolled in three protocols of the Italian Association of Pediatric Hematology/Oncology. These patients received a variety of chemotherapy programs including vinblastine, adriamycin, etoposide, vincristine, cyclophosphamide, and prednisone. The median follow-up after entry into the study cohort was 5 years and 5 months. There were three cases of ANLL, all in children who had received etoposide. Two had received etoposide alone, and one had received etoposide in combination with alkylating agent chemotherapy and other chemotherapy or RT.

RESULTS

In patients presenting with solitary LCH of bone, close to 100% survival has been reported (20,24,35,36,38). In the presence of organ dysfunction with multisystem disease, survival ranges from 33% to 54%. In its absence, survival ranges from 82% to 96% (20,29–3154,116). In the 348 patients reported from 32 French centers treated from 1983 to 1993, the 6-year actuarial survival according to the DAL-HX staging system was as follows: localized disease, isolated unifocal or bifocal bone involvement, 100%; soft tissue involvement with or without bone involvement, no organ dysfunction, 90%; liver, lung, or bone marrow dysfunction, 49% (19). In the

DAL-HX83 trial, the probability of survival, using the DAL-HX83 staging system for disseminated disease described earlier in this chapter, was 100% for group A, 96% for group B, and 62% for group C. The 15-year survival rates in the series of Willis et al., by type of initial presentation, were skin disease only, 83%; monostotic disease, 100%; polyostotic disease, 100%; and multisystem disease, 76% (25,41,124).

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Hemangioma, Lymphangioma, and Skin Cancer

Edward C. Halperin, L. Claude, and John P. Kirkpatrick

HEMANGIOMAS

Hemangiomas are common developmental vascular abnormalities. These benign blood vessel tumors may be encountered in any portion of the body (1–7). In this chapter, we consider cutaneous, ocular, and vertebral body hemangiomas. Subglottic hemangiomas are discussed in Chapter 16.

Historically, hemangiomas were divided into three clinical types. Nevus flammeus (port-wine stains) is usually located on the head and neck, varying in size and color. Sturge–Weber syndrome (SWS) is a neurocutaneous syndrome consisting of port-wine stain in the cutaneous distribution of cranial nerve V, congenital glaucoma, and leptomeningeal angiomas (8,9). Nevus vasculosus (strawberry mark) is red and elevated. Angiocavernosum (cavernous hemangioma) was considered a lesion of the deep vasculature, especially the veins. Kasabach–Merritt phenomenon (KMP) is a rare thrombocytopenic consumption coagulopathy associated with an enlarging cavernous hemangioma or Kaposiform hemangioendothelioma (10). It may be complicated by a life-threatening situation due to thrombocytopenia, hemolytic anemia, and consumptive coagulopathy caused by platelet sequestration and high shear stresses within the lesion (Kasabach–Merritt syndrome) (10,11).

Modern classification divides vascular birthmarks into two broad categories—vascular tumors and vascular malformations—based on vasculogenesis, histopathology, and clinical features (6,12–14). Vascular tumors are dynamic lesions characterized by a growth phase, marked by endothelial proliferation and hypercellularity, followed by involution (6,12–14). This category includes the common hemangioma of infancy and rarer entities such as Kaposiform hemangioendothelioma, which is associated with Kasabach–Merritt syndrome (15,16). In contrast, vascular malformations are essentially stable, demonstrating little or no growth over time. These structural malformations include capillary (port-wine stain), venous, lymphatic, and arteriovenous malformations (Table 18.1). Hemangiomas often can be diagnosed by a thorough history and physical examination. If the natural history or appearance suggests a more aggressive neoplasm, imaging studies may prove useful in establishing a diagnosis. Doppler ultrasonography offers a rapid and inexpensive method of differentiating hemangiomas from vascular malformations (17). Tumor-specific vascularization pattern in contrast-enhanced ultrasound has a high diagnostic impact for the differential diagnosis of tumors in clinical practice, especially in hepatic localizations (18). Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI)

Table 18.1

Classification of Congenital Vascular Abnormalities

Vascular Tumors	Vascular Malformations
<i>Types</i>	
Hemangioma of infancy	Simple
Kaposiform hemangioendothelioma	Capillary (port-wine stain)
Tufted angioma	Venous
Pyogenic granuloma	Arterial
Hemangiopericytoma	Lymphatic
	Complex
	Arterial–venous, capillary–venous, capillary–arterial–venous, etc.
<i>Characteristics</i>	
Usually absent at birth	Present at birth
Appear during first weeks of life	
Dynamic: proliferation	Adynamic, stable
stabilization slow, spontaneous involution	

Adapted from Refs. 1, 13, and 14.

scans provide detailed anatomic information of greater utility in planning therapy (17,19,20). The MRI appearance of a hemangioma differs according to evolutionary stage. During the proliferative phase, hemangiomas appear as well-circumscribed lobulated lesions that are hypo- to isointense relative to muscle on T1-weighted images, are hyperintense on T2-weighted images, and demonstrate early and homogeneous enhancement after gadolinium-based contrast material administration (21,22). During the involuting phase, as increasing amounts of fat replace the tumor, foci of increased signal intensity are noted within the lesion on T1-weighted images, associated with less avid contrast enhancement (22,23). The choice of imaging modality depends on the specific anatomic location of the lesion. For example, contrasted T1-weighted and T2-weighted MRI are particularly effective at distinguishing vascular tumors of the head and neck from other soft tissue structures. MRI has also been well described and has shown an important role in the detection and diagnosis of pure spinal epidural cavernous hemangioma. It shows a characteristic lobulated contour, which encircled the spinal cord. T1-weighted images on the MRI presented as isointense and T2-weighted images presented as hyperintense and a homogeneously

strong enhancement (24). The differential diagnosis for these vascular tumors, apart from vascular malformations, includes mainly infantile fibrosarcoma and dermatofibrosarcoma protuberans (25).

Only 20% of hemangiomas are present at birth. The other 80% arise within the first 8 weeks of life. The natural history of the common hemangioma of infancy is one of the rapid growth during the first 6–9 months of life and then a period of more slowly increasing size that parallels the infant's growth. Involution generally follows at a rate of about 10% per year, with complete disappearance of 50% of the lesions by 4 or 5 years of age and 90% by 9 years (6,14,26). Hemangiomas are most commonly seen on the face and neck (60% of cases), followed by the trunk (25%) and extremities (15%) (27), and are multiple in about 20% of cases (15). At pathologic analysis, common hemangiomas of infancy express a unique immunophenotype known as glucose transporter protein-1, which is not seen in vascular malformations, other vascular tumors, or the vasculature of malignant tumors (28). In most cases, hemangiomas of infancy are best managed by observation (29). A prospective, randomized controlled trial on 121 infants aged 1–14 weeks with early hemangiomas was recently published (30). The aim was to compare treatment with pulsed dye lasers with a wait-and-see policy. The number of children whose lesions showed complete clearance or minimum residual signs at 1 year was not significantly different in the treated and observation groups (42% vs. 44%; $p = 0.92$).

However, there are some indications for treatment, including rapid progression of the lesion producing unacceptable symptoms (e.g., an eyelid hemangioma, obstructing vision and producing deprivation amblyopia); progressive ulceration and infection (perineal lesions are at particular risk); progression of a lesion causing unacceptable deformity from compression, or overgrowth of an extremity from increased blood flow in a hemangioma (hemangiomatous gigantism); growth of a lesion in an intertriginous area, where it is subject to trauma and secondary infection; facial lesions producing severe cosmetic deformity; high-output cardiac failure; and life-threatening Kasabach–Merritt syndrome (3,5–7,29, 31–34). When the decision is made to treat a hemangioma, options available include topical, intralesional, and systemic steroids in first-line approach (29). In the treatment of hemangiomas, 30–80% of lesions respond to steroids (2,6,35). In second line, interferon, laser therapy, and surgical resection are the options. Interferon is often effective, although there have been reports of severe neurotoxicity, including spastic diplegia (36–39). Embolization, vasoligation, chemotherapy (cyclophosphamide, vincristine ...), and angiogenesis inhibitors can also be discussed (6,31–35, 36,38,40–44). Resection or arterial ligation is indicated for small lesions for which excision would produce significant cosmetic deformity. Surgery is also appropriate for treatment of uncontrolled ulceration, bleeding or infection, arteriovenous shunts with high-output cardiac failure, or visual obstruction (3,5–7).

Radiotherapy should be considered only for lesions that have failed to respond to steroids or interferon and are not appropriate for treatment with other modalities. Significant late effects have been attributed to irradiation of hemangiomas, which include scarring, bone growth abnormalities with dental and periodontal long-term effects (42,45), and

secondary neoplasms (33,46–51). The incidence of cancer after radiotherapy for skin hemangiomas has been studied extensively in a series of articles from Sweden. These reports describe a total of 14,633 children below 18 months irradiated at the Radiumhemmet in Stockholm from 1909 to 1959 and 12,055 treated at Sahlgrenska Hospital, Göteborg, from 1930 to 1965 (46–51). At the Radiumhemmet, treatment was most commonly by ^{226}Ra applicators (81%) or contact x-ray therapy (60 kVp or less, 16%). At Göteborg, ^{226}Ra was used for 99% of the treatments. The median age of treatment was 6 months at Radiumhemmet and 5 months at Göteborg. There is a higher-than-expected incidence of cancer in these irradiated children. Significantly higher levels of breast cancer were detected in the pooled studies (hazard ratio 1.2, 95% confidence interval (CI): 1.06–1.36), and there was an approximate twofold increase in the expected incidence thyroid cancer. Recalculation of the dosages from the ^{226}Ra applicators suggests a linear dose–response relationship. Conceivably, the use of electron therapy in lieu of ^{226}Ra might mitigate the long-term effects of radiotherapy in these patients. Another large French report on 8307 patients treated for 4767 hemangiomas was included in an incidence study, among whom 3795 had received radiotherapy (52). External radiotherapy, radium 226, strontium 90, yttrium 90, and phosphorus 32 were used. The mean estimated radiation dose received by the thyroid during radiotherapy was 41 mGy. This study confirms that radiation treatment performed in the past for hemangioma during infancy increased the risk of thyroid carcinoma and adenoma. A significant dose–response relationship was found between the radiation dose received by thyroid and the risk of thyroid cancer (excess relative risk per Gy, ERR/Gy: 14.7, 95% CI: 1.6–62.9). These studies strongly argue against the routine use of radiotherapy to treat hemangiomas of infancy and indicate that irradiation of the thyroid, breast buds, and gonads should be avoided (46–52). The response of cutaneous hemangiomas of infancy to irradiation can be dramatic. In 1940, Kasabach and Merritt originally reported a combination of external irradiation with superficial x-rays and interstitial irradiation with radium needles as a successful primary treatment (53). Furst et al. reported good results in 88% of treated cases (41,48). In treating patients with Kasabach–Merritt syndrome, the objectives are both regression of the hemangioma and control of the thrombocytopenia and coagulopathy. Ogino et al. demonstrated regression of the lesion and an increase in platelet count to more than $10^5/\text{mm}^3$ within 40 days of radiotherapy (43). The rise in platelet count appears to parallel corresponding clinical evaluations. It has been suggested that a platelet count response may predict tumor regression following radiotherapy (54). When radiotherapy is used, gross tumor volumes should ideally be defined clinically, with the aid of CT or MRI to determine the optimal field sizes (32). Minimal margins should be used to yield the least morbidity. Fraction sizes vary from 1 to 2.5 Gy and schedules commonly apply daily treatments (43). The majority of lesions respond to two or three fractions for a total dosage of 300–750 cGy. Occasionally, higher dosages may be indicated, but the total dosage should not exceed 10 Gy (43,54). If these guidelines are observed, regressions generally will occur rapidly, and scarring should be minimal.

On rare occasions, the radiation oncologist is consulted on cases of hemangiomas that began in infancy and continued

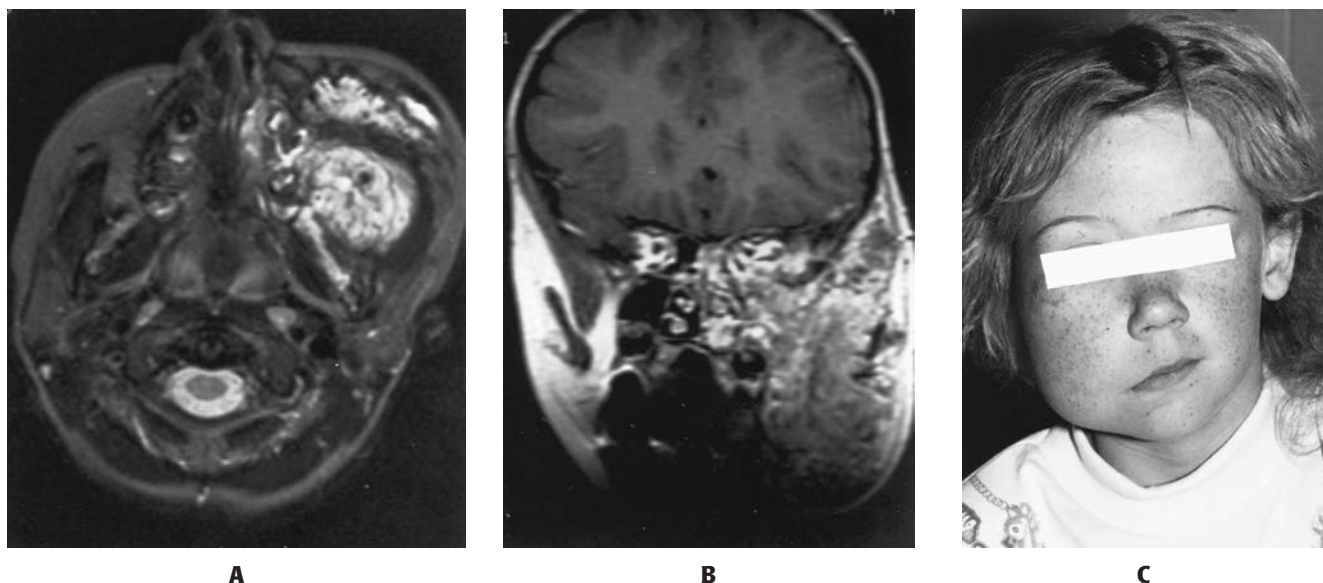


Figure 18.1 A,B: This hemangioma grew from birth until the age of 8 years. There was significant facial deformity and bleeding from the intraoral component of the lesion. There was a moderate response after a split course of irradiation to a total dosage of 45 Gy. C. Disease remains stable 11 years after irradiation. At last follow-up contact, the patient was 3 months pregnant.

to enlarge slowly rather than regress. These older children or young adults present with severe deformity and rarely hemodynamic compromise, anemia, or coagulopathy (55). A host of other treatments fail before radiotherapy is considered for these patients. The response of these large, symptomatic lesions often is substantial (32,34,56). Before treatment, the lesion should be evaluated by careful physical examination and by imaging, preferably by MRI as described earlier. The lesion is irradiated with tight margins using fractionated radiotherapy in 150–200 cGy daily fractions, typically to a total dosage of 30–40 Gy (56). (See Figure 18.1)

Orbital hemangiomas are another special treatment case (57,58). When irradiation of the lid is needed, the eye is protected by a lead shield placed behind the lid and over the lens of the eye. Superficial x-rays or electrons are then used for treatment. Posterior orbit hemangiomas may be successfully treated to a total dosage of 12–18 Gy using techniques similar to the commonly used lateral beam approach for retinoblastoma (see Chapter 5) (32). Gamma knife radiosurgery may be an effective treatment option for selected orbital hemangiomas, while increasing the possibility of visual function preservation in selected cases in which the lesion is adjacent to the optic apparatus (59).

Hemangiomas of the bone are benign, slow-growing tumors that can exhibit cavernous or capillary architecture. The majority of these lesions are asymptomatic and are detected on routine radiographs. The hemangioma produces replacement of the normal cancellous bone with thick bony trabeculae. On plain radiographs and CT scan, a honeycomb or polka-dot appearance is characteristic (60). The incidence increases with age, and less than 10% occur in the first two decades of life (61). Hemangiomas of the vertebrae may give rise to neurologic signs and symptoms ranging from pain to severe spinal cord compression. The pathophysiology of these lesions includes ballooning of the vertebrae with narrowing and deformation of the spinal canal, extension of the hemangioma into the epidural space, and, rarely, vertebral body compression fracture. Although

asymptomatic vertebral bodies do not warrant treatment, intervention is needed for paresis, paraplegia, or severe pain. Laminectomy is recommended by some in the setting of rapid-onset cord compression but is hazardous because of the chance of severe hemorrhage. Catheter embolization of feeder vessels has been successful but runs the risk of vascular catastrophe (60).

Rades et al. (62) analyzed the results from University Hospital Eppendorf and published reports on the outcome after radiation therapy in the treatment of symptomatic vertebral hemangiomas (60–65). A total of 117 patients were evaluable, ranging in age from 12 to 78 years (median age 47 years). To identify a dose–effect relationship, patients were divided into two groups based on the total radiation dosage of 20 Gy ($n = 62$, median total dose 30 Gy) or 36 Gy ($n = 55$, median dose 40 Gy). Total radiation dosages were calculated based on a 2-Gy per fraction equivalent dosage using a ratio of 3 Gy. Complete pain relief was achieved in 82% of the higher dose group and 39% of the lower dose group ($p = 0.003$). Complete or partial pain relief was obtained in 100% and 87% of the higher and lower dose patients, respectively. This analysis suggests that a total of 40 Gy delivered in 2 Gy per fraction can provide effective palliation of symptomatic vertebral hemangiomas (62).

LYMPHANGIOMAS

Lymphangiomas usually are first noted in the neonate and can produce symptoms at any age. They can occur throughout the body but predominate in the neck. They may infiltrate the tongue or the floor of the mouth, causing deformity, pain associated with frequent infections, and obstruction of the aerodigestive passages. Spontaneous regression of these lesions is rare (66).

Lymphangiomas are composed of dilated lymph vessels, the walls of which consist of endothelial cells and connective tissues (67). Four distinct forms have been described. These include capillary lymphangiomas, an uncommon lesion that

may have the appearance of an ordinary wart or group of small vesicles. These lesions consist of a network of lymphatic spaces formed by small- and medium-sized vessels. Cavernous lymphangiomas occur in the skin and subcutaneous tissue, salivary glands, and lips. These are diffuse spongy masses, often with indistinct margins. They consist of multiple dilated lymph channels that are lined with either single or multiple layers of endothelial cells. Cystic hygromas are the most common lymphangiomas. They are composed of cysts ranging from a few millimeters to several centimeters in diameter. The cysts compress surrounding tissues, and small vessels course over their walls. Finally, lymphangial hemangiomas consist of a combination of blood- and lymph-containing channels. Although these lesions are quite similar to cavernous lymphangiomas, some spaces in these lesions also contain erythrocytes and are therefore presumed to be in direct communication with blood vessels (67,68).

Although surgical excision is the preferred therapy for lymphangiomas, this may be difficult in certain situations and entail repeated operations (68–70). Various sclerotherapy agents have been shown to have minimal effects on lymphangiomas. In addition, the results have been problematic because of poor cosmetic outcome (71) and fistula formation. Bleomycin fat emulsions and, more recently, OK-432 (Picibanil), an immunostimulant composed of group A *Streptococcus pyogenes*, have been advocated for the treatment of unresectable lymphangiomas (68,72–77). An intracystic injection of OK-432 produces a local inflammatory reaction, which can lead to resolution of the lesion. On 11 pediatric lymphangioma patients with OK-432, complete regression was obtained in 6, marked regression in 4, and no response in 1 case. However, the authors recommend to anticipate local swelling, especially when treating lesions near the upper airway (74). Another recent case of clinically regressed microcystic lymphangioma by sclerotherapy with OK-432 after intralesional excision was reported, and this method was presented as an alternative effective method in the treatment of microcystic lymphangioma (78). A systematic review of the published literature regarding the efficacy of nonsurgical therapies in the treatment of head and neck lymphatic malformations in children was published in 2008 (79). Random-effects modeling revealed that 43% of patients undergoing sclerotherapy with OK-432 achieved a complete/excellent response, 23.5% achieved a good response, 16.9% achieved a fair/poor response, and 15.4% observed no response. In the bleomycin group, the results were: 35.2% excellent, 37.1% good, 18.4% fair/poor, and 11.6% no response. Of note, seven major complications were noted out of 289 patients in the series, including two mortalities. The efficacy of this agent in treating large lesions in children has been questioned elsewhere (67).

Radiation therapy is rarely used. Dosage inhomogeneity and the risk of infection have discouraged radiation oncologists from using interstitial brachytherapy. Some dramatic responses of neck, chest (80), vulva (81), and mesenteric lymphangiomas to external beam radiotherapy have been reported in the literature (80,82–84). However, one must be cautious because physicians are more likely to report their therapeutic successes than their failures (67).

Fractionated radiotherapy to a total dosage of 15–30 Gy has been used to treat lymphangiomas of the head and neck. However, the known risks of radiation to this region, including inhibition of bone growth and soft tissue development and the increased risk of thyroid cancer, should be considered in the decision to treat.

BASAL AND SQUAMOUS CELL CARCINOMAS

Basal and squamous cell skin cancers are rarely diagnosed in children (85,86). When they do occur in childhood, there is usually a predisposition to skin cancer, that is, basal cell nevus syndrome (BCNS) or xeroderma pigmentosa (XP). They are very rarely isolated (87). A computerized review of the literature was performed by Alcalay et al. One hundred eight children were reported with idiopathic basal cell skin cancers *de novo*. Most of the tumors were nodular and located on the head in children, the same as in adults (88). They have also been reported as arising in a nevus sebaceous (89), after thorium X treatment of a hemangioma (90) after cranial irradiation for acute lymphoblastic leukemia (91). The Childhood Cancer Survivor Study (CCSS) reported that among the 13,132 5-year survivors of childhood and adolescent, 213 have reported nonmelanoma skin cancers. Ninety percent of patients had previously received radiation therapy; 90% of tumors occurred within the radiotherapy field. Radiotherapy was associated with a 6.3-fold increase in risk (92). Another study of 6306 patients who received high-dose chemotherapy at ages 0–65 years after conditioning regimens with ($n = 3870$) or without ($n = 2436$) total body irradiation, followed from 100 days to 36.2 years after high-dose chemotherapy was recently published. The additional risk associated with radiation exposure was higher for the young ones, with relative risks exceeding 20 for those transplanted at ages below 10 years, and decreased with increasing age at exposure until age 40 years. Relative risk in the irradiated population did not vary significantly with age, dose fractionation, or race (93).

BCNS may provide a unique example of the genetic-environmental interaction in the production of malignancies. BCNS (also known as nevoid basal cell carcinoma syndrome or Gorlin syndrome) is characterized by the occurrence of multiple basal cell epitheliomas, a positive family history for the syndrome, keratocysts of the jaw, epidermal cyst and hamartoma formation, palmar and plantar pits, skeletal abnormalities, and oculoneurologic abnormalities (94). Intellectual deficit is present in up to 5% of cases (94). Nevoid basal cell carcinoma syndrome is caused by mutations in the *PTCH1* gene and is transmitted as an autosomal dominant trait with complete penetrance and variable expressivity (95). The basal cell epitheliomas that warrant treatment develop on the face, neck, and trunk. Patients may be treated with chemotherapy, immunotherapy, electrodesiccation, cryotherapy, Mohs' chemosurgery, or primary surgery with reconstruction of the defect (95). Some children have been treated with radiotherapy, although this treatment is generally reserved for adults. About 5–10% of BCNS patients develop the brain malignancy medulloblastoma (96). In many survivors, multiple basal cell epitheliomas have developed within 6 months to 3 years of craniospinal irradiation. These skin cancers develop at an age distinctly earlier and in a distribution unlike that of family members with BCNS. The distribution of basal cell epitheliomas corresponds to the radiotherapy ports. The development of multiple cutaneous skin cancers has not been generally reported in the general population of long-term survivors in medulloblastoma (97). This unusual illustration of multistep mutagenesis may suggest that radiotherapy for skin epitheliomas is relatively contraindicated in young children with BCNS.

XP is an autosomally dominant inherited disease. The clinical manifestations occur primarily on sun-exposed skin that develops abnormal pigmentation and multiple malignant tumors. Areflexia, mental retardation, and other neurologic abnormalities are associated with XP. The biochemical defect appears to be a poor ability to repair ultraviolet-induced DNA damage. Basal cell and squamous cell carcinomas of the skin may develop in patients with XP. These carcinomas usually are treated with the standard techniques of electrodesiccation, curettage, surgery, cryosurgery, or chemosurgery. Because ionizing radiation damage to XP cells is repaired normally, there is no theoretical objection to radiotherapy treatment of tumors if indicated. However, situations in which radiotherapy is appropriate are quite rare (98).

At St. Jude Children's Research Hospital (SJCRH), eight children with skin carcinomas were seen from 1962 to 1986. In four patients, basal cell epitheliomas developed in previously irradiated fields (acute lymphoblastic leukemia, Hodgkin disease, neuroblastoma). There was a fifth patient with BCNS. The three patients treated for squamous cell carcinoma had a prior diagnosis of XP (99). From 1971 to 1991, seven cases of basal cell carcinoma and three cases of squamous cell carcinoma were encountered at the National Institute of Pediatrics in Mexico City (85). Five of the seven children with basal cell carcinoma had XP, one had BCNS, and one developed in a previous radiotherapy field. One of the three patients with squamous cell carcinoma also had XP.

MALIGNANT MELANOMA

The incidence of malignant melanoma before the age of 15 years is estimated at 1–2 per million population in the United States and United Kingdom and approximately 4 per million in Australia. Fewer than 2% of malignant melanomas are seen in children and adolescents (86,100). Childhood melanoma in Australia is higher than that reported in other series, accounting for 3.3% of all pediatric neoplasms. Melanoma is the most common cancer diagnosed in females between the ages of 25 and 29 years (101). This high incidence is attributed to excessive exposure to sunlight (86,102). In the United States, the reported incidence of cutaneous melanoma rose approximately twofold between 1974 and 1994, with the increase observed across all age groups (103–105).

Pediatric melanoma is often classified by the mode of occurrence as well as the histological subtype (106).

1. *Transplacental melanoma, transmitted from the mother with melanoma to the fetus in utero.* There are rare reports of transplacental transmission of metastatic melanoma from mother to child (107). The infant usually has disseminated disease at birth, and the prognosis is poor.
2. *Transformation from giant congenital melanocytic nevus.* Large congenital nevocytic nevi (LCNN) are defined as congenital nevi 20 cm in diameter or larger. They may occur anywhere on the body and include the so-called "bathing trunks" nevi. There is a controversy in the literature regarding the relative risk of malignant melanoma arising in LCNN, with lifetime risks ranging from 2% to 31% (106–109).
3. *In association with congenital predisposing conditions such as xeroderma pigmentosum, dysplastic nevus syndrome, and albinism.* Familial dysplastic nevus syndrome is an autosomal

dominant trait characterized by unusual nevi at risk for developing melanoma. Patients with XP are at significant risk for developing melanoma, as described earlier.

4. *Development from healthy skin.*
5. *Development from a pre-existing nevus.* The total number of melanocytic nevi strongly influences the risk of developing melanoma later in life (102–107). In turn, the number of melanocytic nevi in children is closely associated with the degree of sun exposure and the nevus counts in the parents (110).

The risk of malignant melanoma is also higher in congenital immunodeficiency syndromes and iatrogenic immunosuppression, suggesting that immunoincompetence adversely influences melanoma development.

Sun exposure is a critical epidemiological factor in the development of malignant melanoma (100,110–113). Although there is a debate about the timing of sun exposure, particularly severe sunburns, and the eventual development of malignant melanoma, the data strongly support the concept that the lifetime total exposure to sunlight is directly related to the incidence of malignant melanoma. Thus, medical practitioners, including radiation oncologists, should counsel parents to protect children from excessive sun exposure.

Malignant melanoma is categorized histologically into four types: lentigo maligna melanoma, superficial spreading melanoma, acral lentiginous melanoma, and nodular melanoma. Childhood melanoma may be staged with the following system: stage I, localized disease; stage II, regional lymph node involvement; and stage III, distant metastatic disease (114). Three important factors should be considered in evaluating stage I patient: the presence of local ulceration, Clark's level of invasion, and Breslow's depth of invasion (Table 18.2). All three have been shown to be important prognostic indicators in childhood melanoma (118). In children, metastatic disease is rare in lesions less than 1.5 mm thick (114). In the SJCRH series of 33 children treated from 1967 to 1988, there were no tumor-related deaths in children with thin melanomas (Clark's level I–II, Breslow thickness less than 1.5 mm). Twenty-four patients 16 years of age or younger with malignant melanoma were reviewed at St. Thomas' Hospital, London, from 1981 to 1993. All the three patients with tumors 1.2 mm or smaller were alive without tumor. In contrast, of the 19 children with tumors 1.6 mm or larger, 15 were disease-free, 3 were alive but suffered locoregional relapse, and 1 died of disease (107). As in adult patients, brain metastases often occur and convey a poor prognosis (119).

To genetically characterize childhood melanoma, 21 pediatric patients were studied by germ-line analysis of *CDKN2A*, *CDK4*, and *MC1R* genes. Cutaneous melanoma in childhood and adolescence shows frequent loss of *INK4A* and gain of *KIT* (120).

It is important to distinguish malignant melanoma from juvenile melanoma or nevi of large spindle or epithelioid cells or Spitz nevi. In 1948, Sophie Spitz, a pathologist at New York's Memorial Hospital, described 12 of 13 children who were long-term survivors of this peculiar "benign" childhood melanoma (121). Spitz nevi usually are symmetric and small, exhibit epithelial hyperplasia, contain clefts between nests of melanocytes and epidermis, exhibit mature melanocytes, and contain dull, pink epidermal globules called Kamino bodies (122–124). The histologic differentiation of Spitz nevi and

Table 18.2
Classification of the Primary Lesion in Malignant Melanoma

Clark et al.'s "Levels" (115)	Breslow's "Thickness" (116)	American Joint Committee on Cancer T Category (117)
Level I: All tumor cells above the basement membrane	Using an ocular micrometer, measure maximal thickness of lesion from granular cell layer to deepest point of lesion. If the lesion is ulcerated, measure from the ulcer base over the deepest point of the lesion (i.e., 0.76 mm, 0.76–0.50 mm, 1.50 mm).	T ₀ : No evidence of primary tumor
Level II: tumor cells into the papillary but not reticular dermis		T _{is} : Melanoma in situ
Level III: tumor of the papillary–reticular dermis interface		T ₁ : Melanoma 1.0 mm thick, with or without ulceration
Level IV: neoplastic cells into the collagen bundles of the reticular dermis		T ₂ : Melanoma 1.01 mm thick, with or without ulceration
Level V: invasion of subcutaneous tissue		T ₃ : Melanoma 2.01–4 mm thick, with or without ulceration
		T ₄ : Melanoma >4 mm thick, with or without ulceration

malignant melanoma is difficult, even among expert dermatopathologists (125).

The inclusion of benign Spitz nevi cases in pediatric malignant melanoma series results in an overdiagnosis of malignant melanoma and an underestimate of mortality rate (126–128). Analysis of pediatric malignant melanoma series that exclude the benign Spitz tumors indicates that survival rates in children are similar to those of adults. Among the 8635 patients registered with the Duke Melanoma Clinic, only 85 (less than 1%) were under age 18 (107,129). Fifty-nine percent of the patients had the superficial spreading histologic type, and 20% of the remaining patients were Clark's level III or IV. There was no difference in the actuarial survival rates between adult and juvenile stage I patients (Fig. 18.2). Overall, on a stage-by-stage basis, survival in children and adults appears comparable (128). Conti and colleagues reported a series of 212 European children (age less than 15 years) with melanoma identified through the EURO CARE database over an 11-year time period and attempted to evaluate the population-based survival for this disease in different national populations (126). The overall 5-year survival for all children diagnosed with any type of melanoma was 79%, similar to 77% for the whole population. Five-year survival was best for children diagnosed with cutaneous melanoma (87%) and worst for patients with melanoma not of the skin or eye (57%). Within the cutaneous melanoma population, survival was negatively impacted by having a primary lesion on the trunk (76%) (126).

The standard treatment for localized malignant melanoma is wide local excision (126–128,130–132). Once a diagnosis of melanoma has been made, the focus turns to adequately staging the disease. Re-excision of the lesion is the first step in treatment, and prospective, randomized trials have determined the necessary margin to minimize local recurrence related to the lesion depth (133,134). In certain

situations, a skin graft may be used to close the resulting defect. The role of elective node dissection of clinically uninvolved regional lymph nodes has been a subject of debate. It is clear that not all patients are candidates for elective lymph node dissection. However, for patients with melanoma more than 0.75 mm thick, the proper initial extent of surgery is debatable. The arguments in favor of elective node dissection

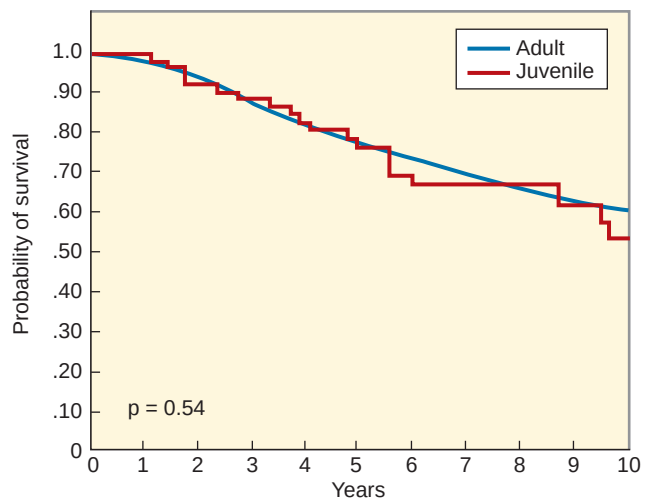


Figure 18.2 Actual survival rates of the adult and juvenile stage I patients registered at the Duke University Melanoma Clinic. Of 18 pediatric patients who were disease-free for more than 7 years, 12 (67%) ultimately developed recurrent disease, including 5 patients whose disease recurred more than 13 years after the initial diagnosis. Late recurrences indicate that patients must be followed for life. (Adapted from Reintgen DS, Vollmer R, Seigler HF: Juvenile malignant melanoma. *Surg Gynecol Obstet.* 1989;168(3):249–253, with permission).

include staging, detecting microscopic disease, and treating occult metastatic disease if present, thereby reducing tumor burden and removing a potential source of future metastases (130,132).

Sentinel lymph node biopsy is emerging as the standard method of staging metastasis to regional lymph nodes. To identify the sentinel node (i.e., the first node draining an anatomical site), a colloidal dye or radioactive isotope is injected at the tumor bed. During surgery, the sentinel node is identified by visual inspection or by a handheld gamma probe, and the node is excised for sectioning and immunohistochemical staining. In adults, this low-morbidity procedure offers an accurate and sensitive method of determining nodal involvement (135). In turn, the regional lymph node status has been found to be the strongest prognostic factor in early-stage melanoma (135–138). Although data on the utility of sentinel lymph node biopsy in malignant melanoma for the pediatric population are limited because of the rarity of this disease, the similarities between malignant melanoma in the adult and child suggest that sentinel lymph node biopsy should be considered in staging pediatric patients (139–142). It is quite well proven now that sentinel lymph node biopsy allows for an accurate biopsy in children. However, some younger patients may require sedation, and it may be more challenging to isolate the sentinel node (143). Patients with positive sentinel nodes usually undergo completion lymphadenectomy and may be candidates for clinical trials.

There is some published evidence supporting the use of chemotherapy or immunotherapy to treat metastatic or relapsed disease in adults. Unfortunately, pediatric patients are not included in most trials of adjuvant therapy for melanoma, and therefore treatment plans for children must be extrapolated from adult studies. Chemotherapy regimens have usually a poor activity against melanoma. However, SJCRH has reported a complete or partial response in 8 of 18 patients (44%) receiving cyclophosphamide, vincristine, and dacarbazine (144). Responses have also been observed with single-agent dacarbazine and melphalan with hyperthermic isolated limb perfusion. In adults, an improvement in relapse-free survival and overall survival using high-dose interferon alfa-2b was proven in patients with high-risk melanoma when compared with observation (145). Vaccination against defined melanoma antigens for patients with high-risk melanoma has not proved to be more effective than interferon alfa-2b in adult trials till now (146). Given the favorable results with the use of interferon alfa-2b in adults, 15 patients less than 18 years of age with stage III melanoma, defined as having a primary tumor thickness >4 mm or having lymph node or in-transit metastases, were included in a SJCRH feasibility study (147). They concluded that interferon alfa-2b could be used in pediatric melanoma patients with acceptable toxicity, without data on efficiency. Another recent report from Toronto proposed the use of high-dose interferon in 6 children with metastatic disease on sentinel lymph node biopsy, on 10 patients with melanoma (148). All patients in their series who had positive sentinel lymph nodes then underwent completion lymph node dissection. Five of them received high-dose interferon therapy, and one patient refused therapy. Most of the patients did complete their therapy, almost all required alterations in

dosage due to toxicity. With a median follow-up of 26 months, 10 out of 11 patients survived.

Radiotherapy is reasonably effective for the symptomatic palliation of metastases. Radiobiologic interest had been focused on the possibility that at a cellular level, malignant melanoma is truly radioresistant (149). A survey of Dq values (width of the shoulder of the cell survival curve in response to ionizing radiation) of various mammalian cell lines suggests that a typical value for Dq is about 90 cGy. However, observations from several investigators suggest that malignant melanoma in vitro has a particularly broad-shouldered survival curve, with a Dq greater than 200 cGy. These data reinforced the belief that malignant melanoma, though intrinsically radioresistant, might be more responsive to high dosages per fraction. A review of several retrospective studies of the effect of fraction size on disease response in malignant melanoma in adults suggested that the probability of a complete response was 34% for dosages less than 400 cGy but 59% for dosages 400 cGy or greater (150). This analysis excluded bone metastases, which showed equal responses for small and large fractions (151).

Subsequently, a prospective clinical trial of patients at least 15 years old, with measurable melanoma lesions, randomized 126 patients to either 4 weekly fractions of 8 Gy per fraction or 20 fractions of 2.5 Gy per fraction 5 days per week (152). In both the large and conventional fraction arms, equivalent complete and partial clinical responses were observed. Stratification by tumor size (greater than or less than 5 cm) or tumor site (soft tissue or skin, nodal, other) also failed to show any difference between the 8- and 2.5-Gy fractionation schemes (130). Based on the retrospective results, it seems reasonable to use high-dose-per-fraction radiotherapy for palliation of metastatic melanoma when late effects are not an issue. The prospective trial suggests that conventional fraction is equally reasonable when there is a significant probability of long-term survival.

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Late Effects of Cancer Treatment

Debra L. Friedman and Louis S. Constine

With advances in multimodality therapy and supportive care, the cure rate for childhood cancer continues to improve and now approaches 80% (1). However, the therapy associated with this improved survival, chemotherapy and radiotherapy (RT), can lead to adverse long-term health-related outcomes that manifest months to years after completion of cancer treatment, commonly called *late effects*. Late effects include organ dysfunction, subsequent malignant and benign neoplasms, and adverse psychosocial sequelae, placing survivors at risk for chronic health conditions as they

enter their adult years. In a report from the Childhood Cancer Survivor Study (CCSS), the 30-year cumulative incidence for severe, disabling, or life-threatening conditions or death due to a chronic condition was 42% (2), and in another report from this same cohort study, the 30-year cumulative mortality was 18% among survivors compared to the general population, and RT increased risk 2.2-fold (3). From the CCSS, where survivors all now have over 20 years of follow-up since childhood cancer diagnosis, Figure 19.1 shows the cumulative incidence of chronic health conditions. Figure 19.2

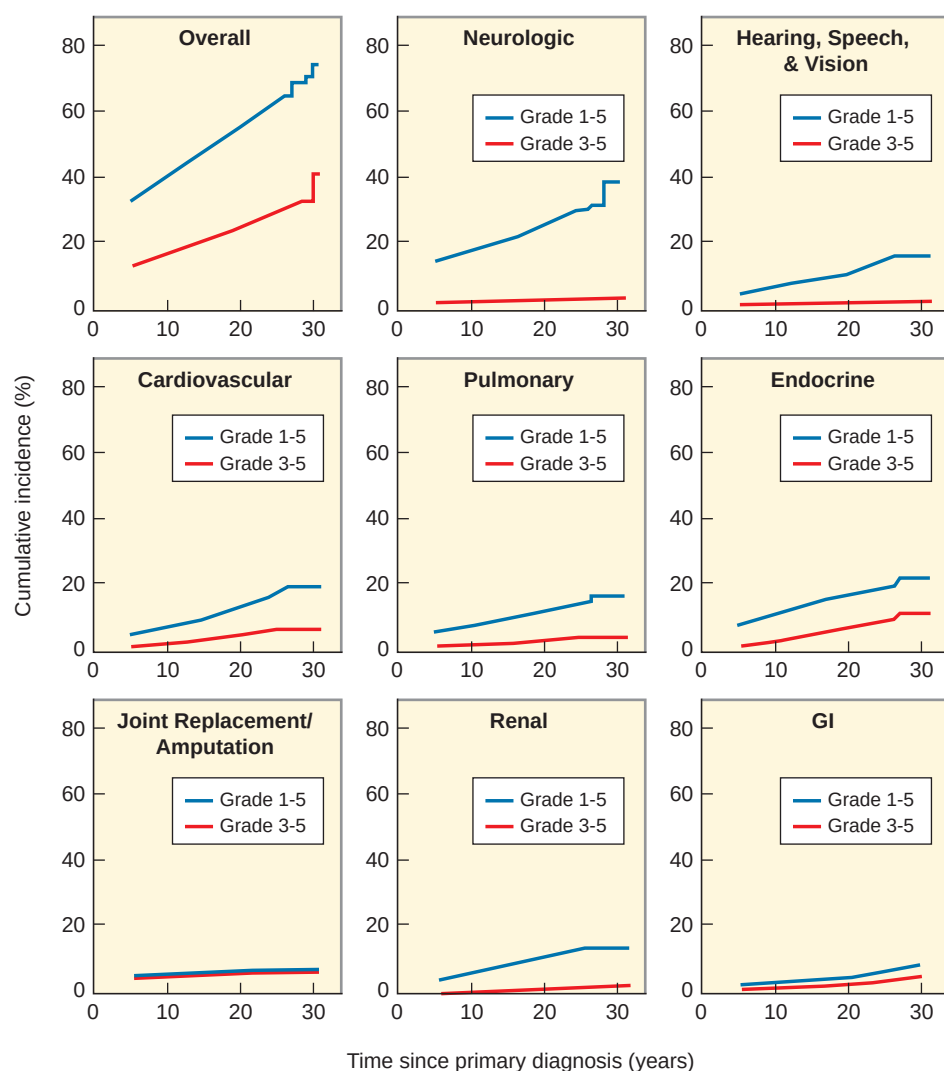


Figure 19.1 Cumulative incidence of chronic health conditions of adult survivors of childhood cancer by primary childhood cancer diagnosis and severity of condition (From Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355:1572–1582, with permission.)

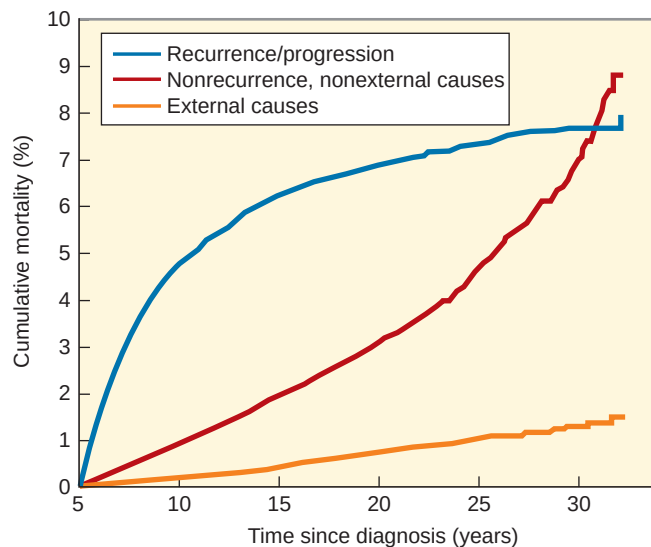


Figure 19.2 Cumulative cause-specific mortality. (From Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2009;27:2328–2338, with permission.)

shows the cause-specific cumulative late mortality. Risk of death remains highest for recurrence of original disease, but 14% of deaths from this cohort are now from subsequent malignancies (4).

To prevent or ameliorate late effects related to RT exposure requires an understanding of tissue tolerance to therapy and are affected by the total and fractional dosage of irradiation, dosage rate, overall treatment time, machine energy, treatment volume (5), and dosage distribution. Radiation damage is produced by some combination of parenchymal cell loss and injury to the underlying vasculature. Initial tissue recovery results mainly from parenchymal cell repopulation. The progressive component of damage is the arteriopathy fibrosis, which predominates in the late irreparable injury and accentuates the cellular depletion of the parenchyma. It is the vascular changes that follow irradiation, but not chemotherapy, that partially account for the differences in late effects of the two modes of treatment. The distribution of late radiation damage reflects primarily vascular injury and cannot be explained simply as an indirect effect of parenchymal cell loss. Devastating late effects of RT $\pm$ chemotherapy can occur in both rapidly and slowly proliferating normal tissues without a clinically recognizable acute phase because of this vascular injury.

Advances in molecular biophysiology have provided insights into the responses of normal tissues to chemotherapeutic and radiation injury. The acute and late phases of adverse effects are actually manifestations of an ongoing sequence of events caused by autocrine, paracrine, and endocrine messages that occur immediately after injury to a variety of cells: epithelial, endothelial, fibroblastic, and inflammatory. A variety of growth and inhibitory factors are released, specific cell receptors are altered, and the resulting signals received by these receptors are translated into postreceptor cytoplasmic, nuclear, and interstitial events. A combination of cell death,

the production of reactive oxygen species, alterations in gene expression, and the expression of both proinflammatory and profibrotic cytokines are viewed as integral in the pathogenesis of late effects.

EFFECTS OF CHEMOTHERAPY AND RADIOTHERAPY ON NORMAL TISSUE

Late effects have been reported in patients who received dosages of chemotherapy and RT below the generally accepted threshold levels for either of the two when used alone. Therefore, one must be circumspect in accepting “tolerance dosages” for normal tissues and organs in the combined-treatment modality era. Untoward reactions can occur at unexpected times and in unpredictable ways. In rapid renewal systems, the same stem cell population is affected, and one can usually reduce the increase in acute toxicity of both modes by applying them sequentially. In slow renewal tissues, the additive ill effects of drugs and radiation often are related to entirely different target cell populations in the same organ system. Late effects may not be avoidable because chemotherapy, whenever applied, can result in additional stem cell kill and lead to expression of subclinical radiation effects. Therefore, the tolerance dosages of fractionated RT, listed in Table 19.1, might be lower in the setting of chemotherapy and in younger children. Table 19.2 lists some of the common adverse effects of chemotherapy, which may act synergistically with RT.

INFLUENCE OF THE DEVELOPMENTAL STAGE OF THE TARGET ORGAN ON ITS SENSITIVITY TO THERAPY

The potential for the development of debilitating effects in normal tissues is related to the cellular activity and maturation in the tissue under consideration. In children, a mosaic of different tissues are developing at different rates and in different temporal sequences. In many (but not all) tissues, organ development goes hand-in-hand with cell growth, and cellular proliferation starts during the prenatal period. During the developmental period of each tissue, stem cells within the embryo will move beyond the pluripotent stage and, under the influence of intrinsic and extrinsic factors, will follow one of two paths: (a) toward self-renewal, that is, generation of more stem cells (multipotency), or (b) toward differentiation, thereby giving rise to a more specialized cell type or tissue (unipotency). Achieving a delicate balance between these two processes is critical for an organ to achieve homeostasis. Thus, both pathways are involved in growth as well as the repair and regeneration of tissues. It can be simplistically assumed that the downstream consequences from an injury, such as radiation, may be predicted from the response of the respective stem cell populations since stem cells and their progeny proliferate to ensure both organ growth and regeneration of injured and dying cells. However, as adulthood/full maturation is reached, each organ will be made up of a mosaic of both dividing and nondividing cells, not just within the tissue as a whole, but also within each of the representative cell

Table 19.1**Tolerance Dosages, TD₅–TD₅₀ (Fractionated Dosage, Whole or Partial Organ)**

Target Cell	Complication Endpoint	Dosage Range (Gy), TD ₅ –TD ₅₀ *
Range: 2–10 Gy		
Lymphoid and lymphocytes	Lymphopenia	2–10
Testes spermatogonia	Sterility	1–2
Ovarian oocytes	Sterility	6–10
Diseased bone marrow (CLL or multiple myeloma)	Severe leukopenia and thrombocytopenia	3–5
Range: 10–20 Gy		
Lens	Cataract	6–12
Bone marrow stem cell	Acute aplasia	15–20
Range: 20–30 Gy		
Kidney: renal glomeruli	Arterionephrosclerosis	23–28
Lung: type II vasculoconnective tissue systems	Pneumonitis or fibrosis	20–30
Range: 30–40 Gy		
Liver central veins	Hepatopathy	35–40
Bone marrow	Hypoplasia	25–35
Range: 40–50 Gy		
Heart, whole organ	Pericarditis and pancarditis	40–45
Bone marrow microenviron- ments, sinusitis	Permanent aplasia	45–50
Range: 50–75 Gy		
Gastrointestinal	Infarction necrosis	50–55
Heart, partial organ	Cardiomyopathy	50–55
Spinal cord	Myelopathy	50–60
Brain	Encephalopathy	54–70
Mucosa (upper aerodigestive tract)	Ulcer	65–75
Rectum	Ulcer	65–75
Bladder	Ulcer	65–75
Mature bones	Fracture	65–70

*Severe to life-threatening complications occurring in 5% to 50% of patients within 5 years.

CLL, Chronic lymphoblastic leukemia.

Modified from Rubin P, Constine L, Williams J. Late effects of cancer treatment: radiation and drug toxicity. In: Perez C, Brady L, eds. *Principles and Practice of Radiation Oncology*. Philadelphia: Lippincott-Raven; 1998:155–211, with permission.

populations. Nondividing cells exist in several compartments: for example, some may be found resting in G₀ phase, although not all of these are fully quiescent since some populations appear to be capable of re-entering cell cycle if the tissue is challenged or stimulated (6). Clinically, it is clear that the greater potential for growth in pediatric tissues will mirror many of the adverse effects of radiation therapy since insult will absolutely compromise growth potential and manifest as impaired development. In fact, the injury that can occur in a pediatric tissue may not become manifest until that tissue rapidly develops. An example of this is the impairment of bone growth seen during adolescence but due to radiation many years before.

Traditionally, radiation dosages in children are modified by age, but without specific recognition of the periods of active proliferation, differentiation, and eventual maturation of one organ or tissue as it differs from another. When does a pediatric tissue or organ become similar to an adult tissue or organ? This is a major question that must be addressed in order to predict the sensitivity to late effects (6).

The growth of any given tissue follows one of four general developmental patterns (Fig. 19.3). The first is commonly recognized skeletal pattern with peak growth rates in the early postnatal period and during puberty. The organs of circulation and digestion also follow this pattern. The second is the neural type, characterized by a rapid postnatal growth that slows in late infancy and ceases in adolescence. The respiratory and renal organs tend to follow this pattern. The third is the genital pattern, which shows little change during early life but shows rapid development just before and coincident with puberty. The sequence is followed by breast tissue, testes, and ovaries. The fourth pattern is the lymphoid type, characterized by a gradual evolution and involution to the time of puberty. Identifying these different rates and ages at which each tissue matures is necessary for determining its radiosensitivity (7). In addition, recognizing the mechanism of organ growth—that is, an increase in the size of cells (hypertrophy) as opposed to the number of cells (proliferation)—allows better identification of relative radiosensitivity because organs that only hypertrophy are less vulnerable to functional disturbance by irradiation.

Table 19.2

Common Chemotherapy Late Effects

System	Agents	Potential Effects	Monitoring Guidelines
Central nervous system	Intrathecal chemotherapy High-dose methotrexate	Cognitive dysfunction Leukoencephalopathy (risk increases with increased dosage)	Neurocognitive evaluation Neurologic evaluation
Cardiac	Cytarabine Doxorubicin Daunomycin Idarubicin Epirubicin	Cerebellar dysfunction Cardiomyopathy Arrhythmias	Electrocardiogram, echocardiogram, Holter, or cardiac stress dependent on dosage, age at the time of treatment, symptoms, or radiation exposure
Hearing Vision Dentition	Cisplatin > carboplatin Corticosteroids Vincristine	Hearing loss Cataracts Dental enamel, bone, and root abnormalities	Audiology evaluation Ophthalmologic evaluation Dental evaluation
Pulmonary	Bleomycin Lomustine Carmustine Busulfan	Pulmonary fibrosis Abnormal pulmonary diffusion Restrictive or obstructive disease	Pulmonary function tests
Urologic	Cyclophosphamide Ifosfamide	Chronic hemorrhagic cystitis Second bladder cancers	Urinalysis
Hepatic	Methotrexate Thioguanine Mercaptopurine Dactinomycin Busulfan	Hepatic dysfunction Veno-occlusive disease (dactinomycin D, busulfan, thioguanine)	Liver function tests Doppler ultrasound
Renal	Cisplatin > carboplatin High-dose methotrexate	Renal insufficiency or failure Renal electrolyte wasting or insufficiency	Urinalysis Renal function tests Creatinine clearance
Gonadal	Ifosfamide Mechlorethamine Cyclophosphamide Procarbazine Dacarbazine Ifosfamide Busulfan Melfalan Lomustine Carmustine	Ovarian failure, early menopause Testicular failure, Leydig cell dysfunction	Leuteinizing hormone, follicle-stimulating hormone Estradiol or testosterone Reproductive counseling or endocrinology evaluation Gynecologic evaluation Sperm analysis Tanner staging Menstrual history
Second malignancies	Mechlorethamine > other alkylating agents Etoposide Doxorubicin Cisplatin Cyclophosphamide	Leukemia Transitional bladder carcinoma	Complete blood count Urinalysis

LATE EFFECTS BY ORGAN SYSTEM

Central Nervous System

Pathophysiology

The brain develops rapidly in the first 3 years of life and very little after age 6. This growth is caused by an increase in the

size but not the number of neurons. Axonal growth, dendritic arborization, and synaptogenesis are most active at this time. If maturation is judged by the degree of myelination, then most regions are well developed by the second year but are not complete until puberty (8). Radiation injury would be expected to be profound during the early years. The essential

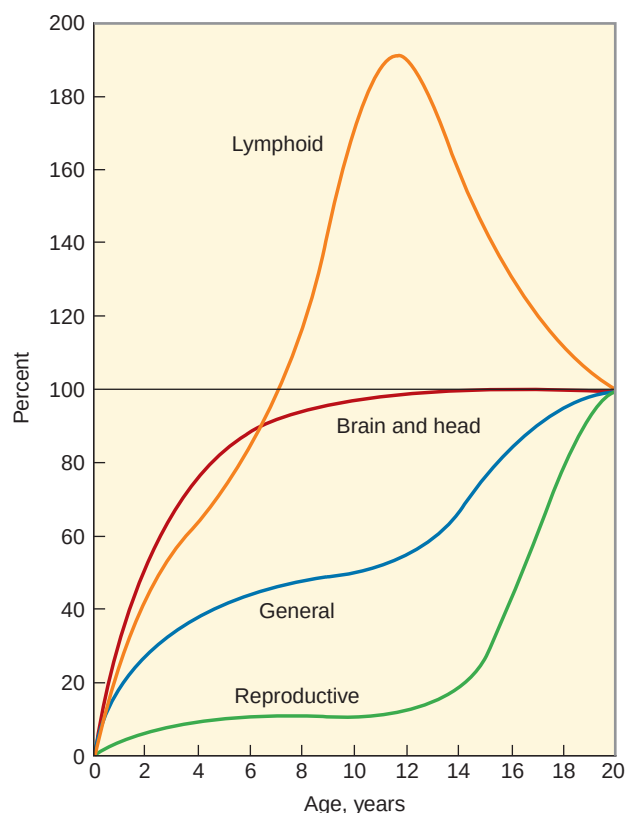


Figure 19.3 Growth curves of different tissues. (From Tanner JM. *Growth at Adolescence*. Oxford: Blackwell Scientific, 1962, with permission.)

radiation insult in radiation injury to the central nervous system (CNS) is a demyelinating lesion with focal or diffuse areas of white matter necrosis (9).

The basic mechanisms underlying the pathologic changes are not precisely known for any particular syndrome of irradiation damage. The three most commonly proposed mechanisms may act alone or in combination. The vascular mechanism acknowledges that the endothelial cell is essential for patency of the microcirculation. This cell is radiosensitive, and damage is expressed as cell death or endothelial hyperplasia. Because endothelial cell turnover is slow, injury based on these cells occurs over a prolonged time interval. The evolution of hyalin degeneration and obliterating sclerosis of the arterioles produces areas of complete and incomplete necrosis. The clonogenic death of glial cells mechanism postulates a radiation-induced reproductive death of the slowly reproducing oligodendrocyte. The oligodendrocyte maintains myelin. These cells show a decrease in numbers within weeks after irradiation. Damage in individual nerve fibers can be demonstrated quantitatively by electron microscopy as early as 2 weeks after irradiation and before vascular damage. Effects on myelin synthesis and maintenance may be especially important in childhood because myelogenesis is most active in the first year of life. The ultimate result is demyelination. Radiation-induced endothelial cell death followed by vascular occlusion also promotes necrosis. The allergic mechanism of pathologic change in the

brain after irradiation argues that the lesions of delayed radiation necrosis sometimes consist of disseminated plaques of demyelination with central necrosis and occasional petechial hemorrhage. In the patent blood vessels that remain, there may be perivascular cuffing with lymphocytes and plasma cells. The postulated autoimmune mechanism is that an antigen is produced by the reaction of ionizing irradiation with the oligodendromyelin complex. This antigen would stimulate the accumulation of inflammatory cells.

The classic findings of radiation-induced necrosis of the CNS are large areas of confluent, coagulative necrosis of the white matter and deep layers of the cortex; the vascular changes of fibrinoid necrosis or fibrin incontinence; atypia or absence of endothelial cells; vascular thickening; telangiectasis; and vascular proliferation.

Clinical Manifestations

Necrosis. The incidence of radiation necrosis after therapeutic dosages is uncertain. Quoted incidence data range from 0.1% to 5% after dosages of 50–60 Gy fractionated over 5–6 weeks (9,10). The variability in the data is the result of the uncertainty, in some studies, concerning the denominator; the long time delay until the occurrence of necrosis; the lack of histologic confirmation in many surviving patients; and the absence of postmortem data in patients who succumb. The clinical signs and symptoms of radiation necrosis are headache and mass effect. Surgical debulking is performed when possible and is often therapeutic (10). Corticosteroids may offer transient relief. Anecdotal reports of the benefits of anticoagulation with heparin or warfarin compounds exist (11,12).

Necrotizing Leukoencephalopathy and Mineralizing Microangiopathy. Leukoencephalopathy is a late complication of cranial irradiation and systemic methotrexate (MTX). The histologic appearance is of multifocal white matter destruction, especially in the centrum semiovale and periventricular regions, with loss of myelin and oligodendrocytes. Hypodense areas emerge in the white matter, and there is cerebral atrophy, an increase in the sulcal width, and enlargement of the ventricles. Mineralizing microangiopathy can occur and is visualized on computed tomography (CT) scanning as intracerebral calcification (11). The clinical features include lethargy, seizures, spasticity, paresis, and ataxia. The multifactorial origin and risk of leukoencephalopathy have been studied in acute lymphoblastic leukemia (ALL) survivors. Radiation and MTX appear to be contributing factors (Fig. 19.4) (13). Of interest is a report from the German Late Effects Working Group, which documented CT and magnetic resonance imaging (MRI) evidence of atrophy, leukoencephalopathy, calcification, or gray matter changes in approximately 50% of children treated for ALL (14). The frequency and severity of abnormalities were greater in children treated with cranial RT and MTX than in those treated with MTX alone. It is worth emphasizing that the situation is decidedly worse in children who have CNS involvement with ALL. In these cases, the presence of leukemia can alter the cerebrospinal clearance of MTX and increase the risk of injury.

Neuropsychologic and Intellectual Deficits. Cranial irradiation of children may have significant adverse effects on intelligence, learning, and social and emotional adjustment

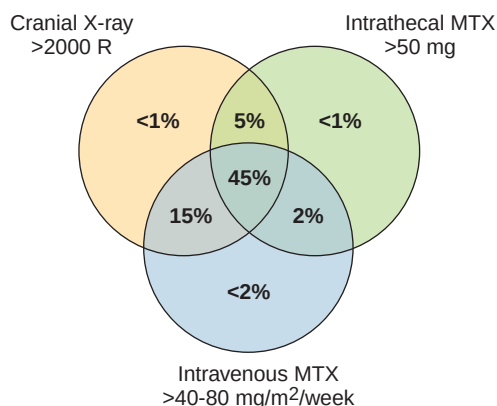


Figure 19.4 Approximate risks of leukocephalopathy (From Griffin TW. White matter necrosis, microangiopathy, and intellectual abilities in survivors of childhood leukemia. Association with central nervous system irradiation and methotrexate therapy. In: Gilbert HA, Kagan AR, eds. *Radiation Damage to the Nervous System*. New York: Raven Press; 1980:155–174, with permission).

(11,12,15–17). Neurocognitive late effects most commonly follow treatment of malignancies that necessitate CNS-directed therapies, such as cranial radiation, intraventricular or IT or high dose systemic (CNS penetrating) chemotherapy. Thus, children with CNS tumors, head and neck sarcomas, and ALL are most commonly affected. Studies of patients with brain tumors must account for the confounding variables of CNS injury by the tumor, seizures and their therapy, elevated intracranial pressure, and surgery. In patients with leukemia and brain tumors, the use of chemotherapy and the impact of the illness on body image and school attendance may complicate the issue.

Deficits occur in a variety of areas, which include general intelligence, age-appropriate developmental progress, academic achievement (especially in reading language and mathematics), visual and perceptual motor skills, nonverbal and verbal memory, receptive and expressive language, and attention (11,12,15–17). Younger age at the time of treatment is associated with a greater neurocognitive deficit (18).

The effects of cranial RT on subsequent intellectual function have been studied in detail, most comprehensively in survivors of CNS tumors and leukemia. However, the effects of radiation on the brain are difficult to define, especially when cranial radiation is often routinely a part of multimodality therapy that may also include surgery and systemic or IT chemotherapy. Moreover, tumor-related deficits caused by direct invasion of the brain, seizures, and hydrocephalus must be recognized.

With detailed assessment of IQ, achievement tests, learning ability, and school performance, it is clear that cranial RT can result in significant neurocognitive dysfunction. With changes in the dosage, fields, and volumes of cranial and craniospinal RT, changes in the incidence and spectrum of these adverse effects of therapy are expected. More recent studies using lower dosages and more targeted volumes have demonstrated better results (19–21). Ris et al. (19) evaluated the intellectual outcome of 43 children treated on Children's Cancer Group study 9892 for posterior fossa medulloblastoma or primitive neuroectodermal tumor (PNET). The study used a reduced craniospinal RT regimen of 23.4 Gy to the neuraxis and 32.4-Gy boost to the posterior fossa with adjuvant

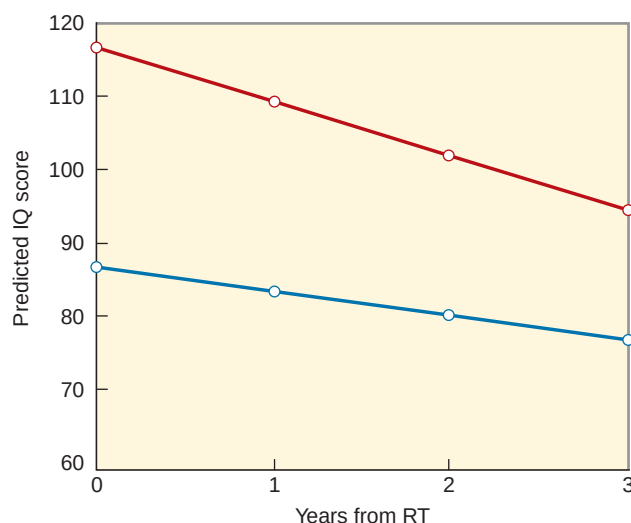


Figure 19.5 Full-scale IQ change by baseline intelligence. Blue, baseline IQ < 100; Red, baseline IQ > 100. (From Ris MD, Packer R, Goldwein J, et al. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. *J Clin Oncol*. 2001;19:3470–3476, with permission.)

chemotherapy. The mean age at the time of treatment was 6 years, with a range of 3–15 years. The estimated rate of change of FSIQ was 4.3 points/year, for VIQ 4.2 points/year, and for nonverbal IQ (NVIQ) 4.0 points/year. In examining host-related factors, a more significant decline was seen for girls (–8 points/year) than boys (–3 points/year) for VIQ and for children less than 7 years old (–5.2 points/year) as opposed to children 7 years and older (–0.8 points/year) for NVIQ. This latter observation was noteworthy in that the older children's baseline was lower, with little decline over time, as compared with the younger children, who had a much higher baseline followed by a steep decline. The effect of baseline intelligence was examined for the whole group, and the same phenomenon was seen. Children who had a baseline IQ of 100 or higher had a much steeper decline in FSIQ, VIQ, and NVIQ than children who had a baseline under 100. The effect on FSIQ is shown in Figure 19.5.

Another recent study supports the hypothesis that patients with medulloblastoma demonstrate a decline in IQ values because of an inability to acquire new skills and information at a rate comparable to that of their healthy same-age peers rather than a loss of previously acquired information and skills (15). In a Danish study of 133 children treated for brain tumors, younger age at diagnosis, tumor site in the cerebral hemisphere, hydrocephalus treatment with shunt, and radiation therapy predicted lower cognitive functions (22). Finally, a reduction in the volume of normal-appearing white matter has been observed in some survivors of childhood brain tumors, and this was associated with decreased attentional abilities, which led to an IQ deficit and impaired academic achievement (16).

For ALL, older studies again show significant neurocognitive impairment (23). Even when combined with IT chemotherapy, reduction in the cranial radiation dosage has resulted in less neurocognitive impairment (18,24,25). Studies on CNS prophylaxis for ALL comparing cran-

iospinal RT with cranial RT combined with IT MTX showed that children who were less than 5 years old at the time of treatment and had received RT and IT chemotherapy had lower IQ scores than those who received craniospinal RT alone. Meadows et al. (23) found a significant IQ deficit in children treated with 24-Gy cranial RT combined with IT MTX, as compared with childhood cancer survivors who received no CNS-directed therapy, with the effect greatest among those less than 5 years old. A similar effect on cognition with the addition of IT MTX has been found in children treated for medulloblastoma (26).

Controversy regarding the role of RT in impairing neurocognition will continue, largely because of differences in the radiation dosages and drugs used in various protocols and different endpoints. Prophylactic cranial irradiation of 24 Gy at 2 Gy per fraction in the treatment of ALL can lower IQ and achievement test scores. IQ loss may be on the order of 8–10 points (i.e., median of normals of 100 down to 90–92). Some studies suggest that the undesirable consequences of 18 Gy are less than 24 Gy, and that 12 Gy (commonly used in current protocols) does not cause identifiable deficits, but the data on this point are not definitive (23).

The deleterious effects of systemic MTX, especially at dosages greater than 1 g/m², may be no different from those of 18-Gy cranial RT (27,28). At lower MTX dosages, there does not appear to be a consistent pattern of neurocognitive deficits (29). A recent long-term study of infants who received high-dose systemic MTX combined with IT cytarabine and MTX for CNS leukemia prophylaxis and were tested 3–9 years after treatment showed that cognitive function was in the average range (30).

In a small study from Italy, cognitive outcome was evaluated in 21 children who received both cranial RT and IT MTX. Mean total IQ was within normal limits, but there was a large discrepancy between the VIQ and PIQ, with the former being significantly higher than the latter. In addition, intracerebral calcifications on MRI were associated with the number of intrathecal MTX dosages and with low scores on IQ, attention, and visual integration tests. Age at treatment and RT dosage were not associated with neuropsychiatric outcomes (31).

Chemotherapy without RT for ALL may result in cognitive dysfunction, but study results vary significantly. Some studies have demonstrated impairment in tasks of higher-order cognitive functioning, mathematics (27), and mild visual and verbal short-term memory deficits (32) in leukemia survivors treated with intrathecal chemotherapy. Yet, others have demonstrated no significant problems (24,33,34). The substitution of dexamethasone for prednisone in the treatment of ALL has been implicated in increasing cognitive dysfunction (25), but a recent study examining differences between children treated for ALL on a study, where there was a randomization between prednisone and dexamethasone, found no significant differences in neurocognitive performance (Kadan-Lottick) (34).

Somnolence Syndrome. Irradiation of the brain of children can result in the somnolence syndrome. The syndrome has its onset 4–8 weeks after irradiation and is characterized by drowsiness, nausea, irritability, anorexia, apathy, and dizziness. The majority of children reported to have developed this syndrome were irradiated for ALL, although it can occur after treatment of a brain tumor. The

somnolence syndrome resolves spontaneously, but corticosteroids hasten recovery.

Arterial vasculopathy is an uncommon occurrence, almost always described after irradiation to the parasellar region, primarily in children. Single- or multiple-vessel narrowing or obliteration results in typical stroke deficits (35).

Myelopathy. The spectrum of radiation injuries to the spinal cord includes transient and irreversible syndromes. A rare, rapidly evolving permanent paralysis is presumed to result from an acute infarction of the cord. A more common form of radiation injury is manifested by the Lhermitte sign or Lhermitte symptom, which consists of an electric shock-like sensation that radiates down the spine and often into the limbs (36). The location of the sensation can change with time. The symptoms may be precipitated by flexion of the neck, walking on a hard surface, sitting on a hard surface, or other forms of physical exertion. The syndrome generally occurs a few months after spinal irradiation. The mechanism is thought to be transient demyelination, although detailed human pathologic studies are lacking. There are no known CT or MRI correlations. It is also reported in association with cisplatin administration, where the results may be long-lasting (37).

Chronic progressive radiation myelitis (CPRM) is rare. The initial symptoms, generally subtle, are usually paresthesias and sensory changes (including diminished temperature sensation or proprioception), which start 9–15 months after therapy and progress over the subsequent year (38). Much longer intervals to initial symptoms are seen occasionally. The neurologic lesion must be within the irradiated volume. Recurrent or metastatic tumor must be ruled out. Cerebrospinal fluid (CSF) protein may be elevated, and myelography can demonstrate cord swelling or atrophy. MRI and CT provide additional supportive information.

The incidence of CPRM and the radiation dosage causing this event are poorly defined because of the diagnostic difficulties and the variety of radiation techniques (with uncertain dosimetries). A review by Wara et al. (39) suggests that 42 Gy in 25 fractions carries a 1% risk, 45 Gy a 5% risk, and 61 Gy a 50% risk. Data from Marcus and William (40) suggest that the cervical cord may be more tolerant to radiation than previously presumed when 1.8- to 1.9-Gy fractional doses are used; in 324 patients treated to dosages of 55 Gy or less, no cases of myelitis were seen. A higher risk of myelopathy is associated with higher individual fraction sizes, shorter overall treatment time, higher total dosages, and long lengths of the cord treated (especially more than 10 cm). Children may be more susceptible to CPRM, developing it after lower radiation dosages and with shorter latency periods (38).

Table 19.3 reviews several CNS late effects with respect to causative treatments, signs and symptoms, screening and diagnostic tests, and management and intervention (41).

Psychosocial

Psychological Effects. Due to the lack of systematic screening for patients with and without evident psychosocial difficulties, the prevalence of psychological distress among survivors is poorly characterized. It is clear, however, that a meaningful minority of childhood cancer survivors and their parents demonstrate symptoms of uncertainty, distress and posttraumatic stress, with some meeting full criteria for posttraumatic stress disorder (PTSD). Because avoidance of

Table 19.3

Evaluation of Patients at Risk for Late Effects: Central Nervous System

Late Effects	Causative Treatment		Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention	
	Chemotherapy	Radiation				
Neurocognitive deficit	High-dose IV MTX, IT MTX	>18 Gy	Resection of central nervous system tumor	Difficulty with reading, language, verbal and nonverbal memory, arithmetic, receptive and expressive language, decreased speed of mental processing, attention deficit, decreased IQ, behavior problems, poor school attendance, poor hand-eye coordination	Neurocognitive testing: Psychoeducational Neuropsychologic	Psychoeducation assistance
Leukoencephalopathy	IT or IV MTX IT cytosine arabinoside	>18 Gy (with MTX)		Seizures, neurologic impairment; compare with premorbid status	CT and MRI for baseline and symptoms	Symptom management: muscle relaxants, anticonvulsants, physical therapy, occupational therapy
Focal necrosis	IT or high-dose IV MTX Carmustine, cisplatin	>50 Gy (especially with >2 Gy daily fraction)	Tumor resection	Headaches; nausea; seizures; papilledema hemiparesis or other focal findings; speech, learning, and memory deficits	CT and MRI for baseline, PRN Positron emission tomography or single-photon emission computed tomography	Steroid therapy Debulking of necrotic tissue
Large-vessel stroke		>35 Gy		Headache, seizures, hemiparesis, aphasia, focal neurologic findings	CT and MRI Arteriogram	Determined by specific neurologic impairment
Vision loss	Intra-arterial carmustine, cisplatin	>50 Gy (optic nerve chiasm, occipital lobe)	Tumor resection	Progressive visual loss	Ophthalmic evaluation Visual-evoked response	Visual aids
Ototoxicity	Cisplatin, carboplatin	>35 Gy (middle and inner ear)	Surgery, CSF shunting	Abnormal speech development Hearing	Audiogram for baseline, PRN	Speech therapy Hearing aid
Myelitis		45–50 Gy	Spinal cord surgery	Paresis, spasticity, altered sensation, loss of sphincter control	MRI	Steroids Physical therapy Occupational therapy

IT, intrathecal; MTX, methotrexate; IV, intravenous; CT, computed tomography; MRI, magnetic resonance imaging; PRN, as needed; CSF, cerebrospinal fluid.

From Constine LS, Hobbie W, Schwartz C. Facilitated assessment of chronic treatment by symptom and organ systems. In: Schwartz C, Hobbie W, Constine L, et al., eds. *Survivors of Child and Adolescent Cancer: A Multi-Disciplinary Approach*. Berlin: Springer-Verlag; 2005:17–34, with permission.

places and people associated with the cancer is part of PTSD, the syndrome may interfere with appropriate access to health care. Risk factors include perception of threat to life and severity of treatment, poor family functioning and decreased social support (42–47).

A combined analysis of symptoms of somatic distress and depression has been completed from the Childhood Cancer Survivor Study (CCSS) cohort. This included 1834 survivors of HL who were compared with sibling controls. Eighty-seven had scores on the brief symptom index that were symptomatic for depression, and 237 for somatic distress. Risk factors included female sex, low socioeconomic status, lack of a complete high school education, lack of employment, intensive chemotherapy, and elapsed time since therapy (48). In a subsequent analysis of the entire CCSS cohort, Mulrooney et al. (49) evaluated risk factors for fatigue or sleep impairment. In univariate analysis, compared with other diagnostic groups, a diagnosis of HL or sarcoma was associated with higher risks of fatigue, depression, and sleep impairment. In multivariate analysis of the fatigue risk factors, hypothyroidism and depression were independent risk factors, and radiation therapy had a marginal association.

Neuroendocrine

Hypothalamic–pituitary (HP) irradiation may produce a spectrum of neuroendocrine abnormalities.

Growth Hormone

The effects of cranial irradiation on growth hormone (GH) production and release are most common. GH is secreted episodically by the anterior pituitary gland. Growth hormone–releasing hormone (GHRH), produced in the hypothalamus, stimulates GH production, whereas the hypothalamic neuropeptide somatostatin exerts an inhibitory effect. In the liver and other tissues, circulating GH stimulates the production of insulin-like growth factor 1 (IGF-1, also called somatomedin-C), which promotes cell proliferation and protein synthesis. The anatomic site of the radiation injury that produces GH deficiency is the hypothalamus.

Clinical Manifestations

The potential for neuroendocrine damage is likely to decrease with the use of more focused RT and a decrease in dosage in some settings such as medulloblastoma. Approximately 60–80% of irradiated pediatric brain tumor patients who have received dosages greater than 30 Gy have impaired serum GH response to provocative stimulation. This usually occurs within 5 years of treatment. The dose–response relationship has a threshold of 18–20 Gy, and the higher the radiation dosage, the earlier the GH deficiency will occur after treatment. A study of conformal RT in children with CNS tumors indicates that GH insufficiency usually can be demonstrated within 12 months of RT depending on hypothalamic dose–volume effects (50). Children treated with CNS irradiation for leukemia are also at greater risk of GH deficiency. Sklar et al. (51) evaluated 127 patients with ALL treated with 24 Gy, 18 Gy, or no cranial irradiation. The change in height standard deviation score (SDS) was significant for all three groups, with a dose–response relationship noted: 0.49–0.14 for no RT group, 0.65–0.15 for the 18-Gy RT group, and 1.38–0.16 for the 24-Gy group. In the CCSS, Chow demonstrated that risk for adult short stature is highest among

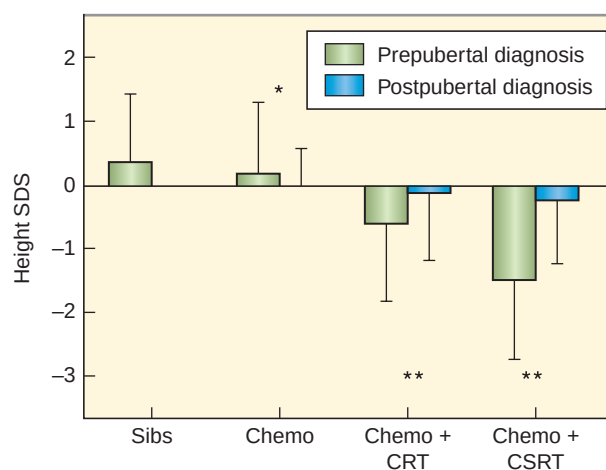


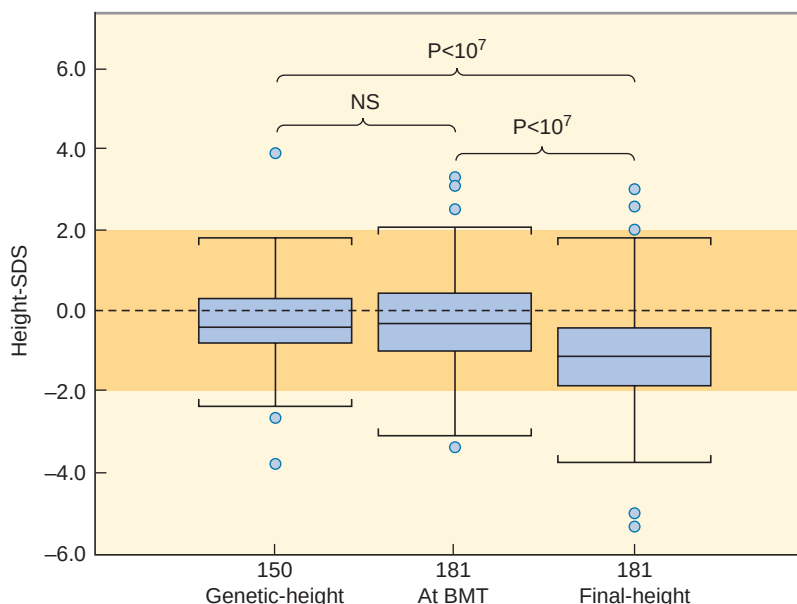
Figure 19.6 Height standard deviation scores (SDS) for ALL survivors, treated pre- or postpubertally with chemotherapy alone, cranial or craniospinal RT. (From Chow EJ, Friedman DL, Yasui Y, et al. Decreased adult height in survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *J Pediatr*. 2007;150:370–375, with permission)

patients treated with cranial or craniospinal RT, but is also elevated among those treated with chemotherapy alone (52). Figure 19.6 shows the height SDS for ALL survivors, treated pre- or postpubertally with chemotherapy alone, cranial or craniospinal RT as compared with siblings.

Children who receive bone marrow transplantation (BMT) with total body irradiation (TBI) have a significant risk of GH deficiency. Risk is higher with single-dose as opposed to fractionated radiation, pretransplant cranial irradiation, female sex, and posttreatment complications such as graft-versus-host disease (GVHD) (53,54). Regimens with busulfan and cyclophosphamide also increase risk (54). Hyperfractionation of the TBI dosage markedly reduces risk in the absence of pretransplant cranial radiation (55). In a review, Socie et al. (56) discuss this risk at length. The mean loss of height is estimated to be approximately 1 SDS (6 cm) compared with the mean height at the time of stem cell transplantation and mean genetic height. In a report from the European Group for Blood and Marrow Transplantation, among 181 patients with aplastic anemia, leukemias, and lymphomas who underwent stem cell transplantation before puberty, an overall decrease in final height SDS value was found compared with the height at transplant and with the genetic height. The type of transplantation, GVHD, GH, or steroid treatment did not influence final height. TBI (single greater than fractionated dosage), male sex, and young age at transplant were found to be major factors for long-term height loss. The majority of patients (140 of 181) reached adult height within the normal range of the general population. Data from this study demonstrating the changes in SDS by type of RT are shown in Figure 19.7 (57).

GH deficiency should be treated with replacement therapy. There has been some controversy surrounding this therapy, with a concern over increased risk of recurrence and second malignant neoplasms (SMNs). However, most studies are limited by selection bias and small sample size. Sklar et al. (58) studied 361 GH-treated cancer survivors enrolled in the

Figure 19.7 Correlation between the genetic height, height standard deviation score (SDS) at bone marrow transplantation, and final height SDS. Numerals indicate the number of cases studied in each group. The dotted area indicates the height SDS distribution for the normal general population. The lower line in the box plot indicates the 25th percentile, the upper line indicates the 75th percentile, and the horizontal lines above and below the boxes represent the 3rd and the 97th percentile, respectively. Statistical analyses: paired Student's *t* test. (From Cohen A, Rovelli A, Bakker B, et al. Final height of patients who underwent bone marrow transplantation for hematological disorders during childhood: a study by the Working Party for Late Effects-EBMT. *Blood*. 1999;93:4109–4115, with permission.)



CCSS and compared risk of recurrence, risk of SMN, and risk of death between survivors who did and did not receive treatment with GH. The relative risk of disease recurrence was 0.83 (95% CI 0.37–1.86) for GH-treated survivors. GH-treated subjects were diagnosed with 15 SMNs, all solid tumors, for an overall relative risk of 3.21 (95% CI 1.88–5.46), mainly because of a small excess number of SMNs observed in survivors of acute leukemia. Two other studies have shown no increased risk of relapse or SMN (59,60). The data surrounding SMNs must be interpreted with caution given the small number of events.

Non-Growth Hormone Tropins

Pubertal growth can also be adversely affected by cranial radiation. Dosages greater than 50 Gy may result in gonadotropin deficiency, and dosages of 18–47 Gy can result in precocious puberty. Precocious puberty has occurred mostly in girls who received dosages of at least 24 Gy cranial radiation. However, earlier puberty and earlier peak height velocity are seen in girls treated with 18 Gy cranial radiation (61).

Shalet et al. (62) showed that the age of pubertal onset is positively correlated with the age at the time of cranial irradiation. The impact of early puberty in a child with radiation-associated GH deficiency is significant, and the timing of GH is especially important for GH-deficient girls also at risk of precocious puberty. With higher dosages of cranial irradiation (more than 35 Gy), deficiencies in the gonadotropins can be seen, with a cumulative incidence of 10–20% at 5–10 years (63).

Constine et al. (64) documented non-GH abnormalities in 20 children treated with irradiation for brain tumors not involving the HP region, including low free T4 levels caused by hypothalamic or pituitary injury and low luteinizing hormone (LH) and estradiol with oligomenorrhea. The frequency of central hypothyroidism after cranial irradiation relates to the dosage to the HP axis, with a greater likelihood after dosages greater than 40 Gy. Although some reports suggest that the incidence is as low as 6%, the radiation dosages to the HP axis in those reports were not specifically determined (65,66). In

Constine et al.'s series (67), 65% of patients treated in the higher dosage range had evidence of subclinical or clinical hypothyroidism. In a report by Paulino (68) on children treated for medulloblastoma, and thus with somewhat lower HP dosages, 19% of children developed central hypothyroidism.

Adrenocorticotropin deficiencies and hyperprolactinemia are rare in children because dosages greater than 50 Gy are needed for their development (64,69). Samaan et al. (70) described 110 patients treated for nasopharyngeal or paranasal sinus carcinoma, in whom more than 60 Gy was typically administered. They found deficiencies in 83%. Twenty-seven percent had thyroid abnormalities, attributed to hypothalamic injury in one third of the patients and pituitary injury in the remainder. Cortisol deficiency attributable to hypothalamic injury also occurred in 27% of patients. Abnormalities of prolactin and LH were noted in 39% and 30%, respectively. A summary of neuroendocrine complications of therapy, the relationship to dosage, diagnostic studies, and interventions are provided in Table 19.4 (41).

Thyroid

Radiation-induced thyroid neoplasms are considered in Chapter 20. In this section, we will review the effects of therapeutic irradiation on the endocrine function of the thyroid. The thyroid may be directly irradiated in the treatment of childhood head and neck cancers such as rhabdomyosarcoma, nasopharyngeal lymphoepithelioma, and squamous cell carcinoma, a variety of other aerodigestive tract tumors, and HL. A photon spinal field used during craniospinal irradiation for brain and spinal tumors and for leukemia will deliver radiation to the thyroid.

Pathophysiology

The thyroid gland consists of follicles filled with colloid and lined by follicular cells, which trap iodide. The glycoprotein thyroglobulin is a major component of the colloid and participates in the formation and storage of thyroid hormones. The primary, hormonally active iodothyronines,

Table 19.4

Evaluation of Patients at Risk for Late Effects: Neuroendocrine

Late Effects	Causative Treatment		Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
	Chemotherapy	Radiation			
GH deficiency		>18 Gy to HP axis	Tumor in region of HP axis Falling off of growth curve Inadequate growth velocity Inadequate pubertal growth spurt	Annual stadiometer height (q6 months at age 9–12 years) Growth curve Bone age at 9 years, then yearly until puberty is reached Insulin stimulation test and pulsatile GH analysis Cortisol (a.m.) for baseline, PRN Insulin—hypoglycemia; metapyrone stimulation tests	GH therapy Delay puberty with GnRH agonist
Adrenocorticotrophic hormone deficiency		>40 Gy to HP axis	Tumor in region of HP axis Muscular weakness, anorexia, nausea, weight loss, dehydration hypotension, abdominal pain, increased pigmentation (skin, buccal mucosa)		Hydrocortisone
Thyrotropin-releasing hormone deficiency		>40 Gy HP axis	Tumor in region of HP axis Hoarseness, fatigue, weight gain, dry skin, cold intolerance, dry brittle hair, alopecia, constipation, lethargy, poor linear growth, menstrual irregularities, pubertal delay, bradycardia, hypotension	Free T4, T3, TSH baseline, q1 year	Hormone replacement with thyroxine Anticipatory guidance regarding symptoms of hypothyroidism
Precocious puberty (especially girls)		>20 Gy to HP axis	Tumor in region of HP axis Early growth spurt False catch-up Premature sexual maturation: Female: Breast development and pubic hair before 8 years and menses before 9 years Male: testicular and penile growth and pubic hair before 9.5 years	Height, growth curve q yr Bone age q2 years until mature LH, FSH, estradiol, or testosterone Pelvic ultrasound, GnRH stimulation testing	GnRH agonist
Male gonadotropin deficiency		>40 Gy to hypothalamic region	Tumor in region of hypothalamus Delayed, arrested, or absent pubertal development: lack of or diminished pubic and axillary hair, penile and testicular enlargement, voice change, body odor, acne	LH, testosterone q1–2 years GnRH testing	Testosterone replacement

(continued)

Table 19.4

Evaluation of Patients at Risk for Late Effects: Neuroendocrine(Continued)

Management Late Effects	Causative Treatment		Symptoms	Signs and Diagnostic Tests	Screening and Intervention
	Chemotherapy	Radiation			
Female gonadotro- pin deficiency		>40 Gy to hypothal- amic region	Tumor in region of hypothal- amus	Testicular atrophy (softer and smaller) Failure to impregnate Delayed, arrested, or absent pubertal development, including breasts, female escutcheon, female habitus, vaginal estrogen effect, body odor Acne Changes in duration, frequency, and character of menstruation (less cramping) Estrogen deficiency: hot flashes, vaginal dryness, dyspareunia, low libido Infertility If on birth control pills, then adjust dose	Anticipatory guidance regarding symptoms of estrogen deficiency
Hyperprolact- inemia		>40 Gy HP axis	Tumor in region of hypothal- amus	LH, FSH, estradiol q1–2 years GnRH stimulation tests	Hormone replacement Early intervention may prevent osteoporosis, atherosclerosis
Metabolic syndrome	Steroids	? ≥18 Gy (dosage not well established)	Obesity, hypertension, hyperlipidemia, hyperglycemia, insulin resistance with hyperinsulinemia	Prolactin level baseline, then PRN Fasting lipids, glucose, insulin levels, body mass index evaluation	Dopamine agonist (bromocriptine) Refer to endocrinology

GH, growth hormone; HP, hypothalamic–pituitary; GnRH, gonadotropin-releasing hormone; PRN, as needed; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid stimulating hormone.

From Constine LS, Hobbie W, Schwartz C. Facilitated assessment of chronic treatment by symptom and organ systems. In: Schwartz C, Hobbie W, Constine L, et al., eds. *Survivors of Child and Adolescent Cancer: A Multi-Disciplinary Approach*. Berlin: Springer-Verlag; 2005:17–34, with permission.

triiodothyronine (T3) and thyroxine (T4), are largely bound to plasma proteins when released by the gland. Thyroxine-binding globulin is the major transport protein, and only a small percentage of unbound T3 and T4 is available for activity. The pituitary hormone thyroid-stimulating hormone (TSH) regulates synthesis and release of T3 and T4. TSH secretion is stimulated by the hypothalamic hormone thyrotropin-releasing hormone (TRH) and inhibited by the circulating free thyroid hormones. The pathophysiology of radiation-induced thyroid dysfunction is not precisely defined. Direct radiation damage to the thyroid follicular cells, the thyroid vasculature, or the supporting stroma may occur. Less likely mechanisms that could contribute include the induction by RT of an immunologic reaction or damage from the iodine load administered for lymphangiography. Histopathologic changes in an irradiated thyroid gland include progressive obliteration of the fine vasculature, degeneration of follicular cells and follicles, atrophy of the stroma, and, less commonly, lymphocytic infiltration. Because radiation damage depends on the degree of mitotic activity and the thyroid of a developing child grows in parallel with body growth, this gland might be expected to show an age-related degree of injury and repair.

Hypothyroidism

Of children treated with radiation therapy, most develop hypothyroidism within the first 2–5 years posttreatment, but new cases can occur later. Reports of thyroid dysfunction differ depending on the dose of radiation, the length of follow-up, and the biochemical criteria utilized to make the diagnosis. The most frequently reported abnormalities include elevated TSH, depressed thyroxine (T4), or both (71–74). Compensated hypothyroidism includes an elevated TSH with a normal T4 and is asymptomatic. Uncompensated hypothyroidism includes both an elevated TSH and a depressed T4.

The incidence of hypothyroidism should decrease with lower cumulative doses of radiation therapy employed in newer protocols. In a study of Hodgkin lymphoma (HL) patients treated between 1962 and 1979, hypothyroidism occurred in 4 of 24 patients who received mantle doses less than 26 Gy but in 74 of 95 patients who received greater than 26 Gy. The peak incidence occurred at 3–5 years post treatment, with a median of 4.6 years (67). A cohort of childhood HL survivors treated between 1970 and 1986 were evaluated for thyroid disease by use of a self-report questionnaire in the CCSS. Among 1791 survivors, 34% reported that they had been diagnosed with at least one thyroid abnormality. For hypothyroidism, there was a clear dose response, with a 20-year risk of 20% for those who received less than 35 Gy, 30% for those who received 35–44.9 Gy, and 50% for those who received greater than 45 Gy to the thyroid gland. The RR for hypothyroidism was 17.1. Elapsed time since diagnosis was a risk factor, where the risk increased in the first 3–5 years after diagnosis (71). The cumulative incidence of hypothyroidism among survivors 15 years following leukemia diagnosis has also been evaluated in the CCSS and was 1.6%. In multivariate analysis, survivors who received ≥ 20 Gy cranial RT plus any spinal RT had the highest risk of subsequent hypothyroidism (HR 8.3) compared with those treated with chemotherapy alone. In radiation dosimetry analysis, pituitary doses ≥ 20 Gy combined with thyroid doses ≥ 10 Gy were associated with hypothyroidism (75). Figure 19.8 shows

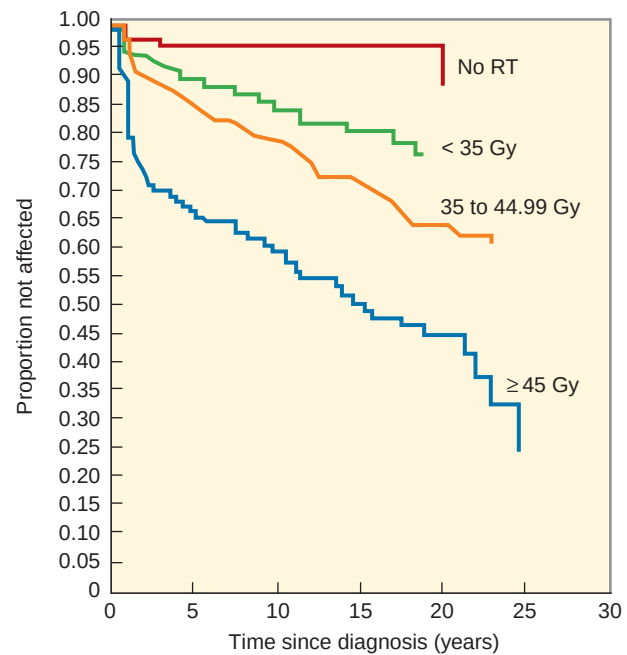


Figure 19.8 Probability of developing an underactive thyroid after diagnosis of the Hodgkin disease. (From Diller L, Chow EJ, Gurney JG, et al. Chronic disease in the Childhood Cancer Survivor Study Cohort: a review of published findings. *J Clin Oncol*. 2009;27:2339–2355.)

the cumulative incidence of hypothyroidism respectively after treatment for HL.

Survivors of pediatric hematopoietic stem cell transplantation (HSCT) are at increased risk of thyroid dysfunction, with the risk being much lower (15–16%) after fractionated TBI, as opposed to single-dose TBI (46–48%). While mildly elevated TSH is common, it is usually accompanied by normal thyroxine concentration (76). Non-TBI-containing regimens historically were not associated with an increased risk. However, in a recent report from the Fred Hutchinson Cancer Research Center, the increased risk for thyroid dysfunction was not different between children receiving a TBI or busulfan-based regimen compared with cyclophosphamide conditioning alone.

Hyperthyroidism

Thyrotoxicosis may occur after mantle or cervical irradiation for HL. In Hancock et al.'s report (77), approximately 2% of patients ($n = 34$) developed Graves disease. Almost all had a diffuse goiter, high free T4, low TSH, and elevated thyroid uptake of radioiodine. One half of these patients developed infiltrative ophthalmopathy, as did an additional four patients who did not have overt hyperthyroidism. The relative risk for Graves disease was 7.2–20.4. Six patients developed silent thyroiditis characterized by transient mild symptoms of thyrotoxicosis, elevated serum-free T4 and low TSH, no thyroid enlargement or tenderness, and low thyroid uptake of radioiodine (78). All of these patients subsequently developed hypothyroidism.

In the CCSS study of HL survivors by Sklar et al. (71), the relative risk for hyperthyroidism compared with sibling control subjects was 8.0, with cases becoming manifest

3–5 years after diagnosis. In the study of ALL survivors from the CCSS, the 15-year cumulative incidence was 0.6%. Craniospinal RT was associated with an increased risk of subsequent hyperthyroidism (HR 6.1) compared with chemotherapy alone. In radiation dosimetry analysis, pituitary doses ≥ 20 Gy combined with thyroid doses ≥ 15 Gy were associated with hyperthyroidism (75).

Detection and Screening

Laboratory screening evaluations for asymptomatic patients should include serum concentrations of TSH and free thyroxine. Because the latent interval to the development of abnormality can be prolonged, systematic clinical and laboratory evaluation should be performed yearly.

Management

Patients with uncompensated hypothyroidism (low serum concentration of thyroxine) clearly need thyroid replacement therapy. Patients with elevated serum concentrations of TSH but normal thyroxine are treated with thyroid replacement therapy in most institutions. The rationale for this approach is that subclinical hypothyroidism may evolve into overt hypothyroidism, and prolonged TSH stimulation of an irradiated thyroid gland may increase the risk of carcinoma (67,77).

Table 19.5 reviews several thyroid late effects with respect to causative treatments, signs and symptoms, screening and diagnostic tests, and management and intervention (80).

Bone and Body Composition

Pathophysiology

It has long been established that bone growth can be impaired by radiation. The pathophysiology of radiation injury to growing bone probably is attributable to damage to the chondroblasts. Single doses of 2–20 Gy inhibit proliferation of cartilage cells, thereby decreasing cellularity and causing disarray of the cellular columns within the growth plate. The resulting retarded bone growth is attributed to this loss of proliferating cells in the growth plate, the decreased ability of surviving cells to synthesize matrix, or the production of an abnormal matrix that fails to calcify.

The effects of radiation on growing bone have been summarized by Rubin et al (6). Epiphyseal irradiation, to a sufficient dosage, causes an arrest of chondrogenesis; metaphyseal irradiation results in a failure of absorptive processes in calcified bone and cartilage; and diaphyseal irradiation produces an alteration in periosteal activity, which causes abnormal bone modeling. Therefore, the location of an RT field on a long bone can significantly influence the nature and severity of the subsequent deformity.

Clinical Manifestations

Bone Growth Retardation. Chondroblasts and chondrocytes are affected by radiation therapy in growing children, and this can result in soft tissue hypoplasia and diminution of bone growth. These effects are associated with the total and fractional radiation dosage and the inclusion of the epiphyses in the radiation field.

Clinically, radiation's effects on growing bone may be most simply characterized as shortening of long bones (i.e., femur, tibia, humerus) or hypoplasia of flat bones (i.e., ilium). The crucial factors influencing the ultimate height of

the patient may be inferred from the data previously presented: the radiation total dosage and dosage per fraction; the energy, dosage distribution, and absorptive properties of the beams; the bones that are irradiated and the epiphyseal plates that are encompassed; the age at the time of irradiation (implying that the amount of growth already obtained is important in judging ultimate outcome); the influence of other toxins on growth, such as exogenous steroids and cytotoxic chemotherapy; and the patient's genetic constitution.

A large body of knowledge has been developed concerning loss of height after childhood irradiation. Much of the data published in the 1970s and 1980s reflect treatment with higher dosages of RT than those currently used. However, several recent reports indicate that stature loss must still be considered in the late effects of RT. For children treated with craniospinal RT for ALL or CNS tumors, the cranial dosage can result in decreased growth by causing growth hormone deficiency, and the spinal dosage can result in stature loss through its effect on the vertebral bodies (52).

Determining final adult height is not clear. Silber et al. (79) have attempted to address this problem with a mathematical model to predict adult stature after treatment of cancer in childhood. However, the model was based on data from only 49 patients. Donaldson (80) was unable to confirm the model's efficacy in two of three cases.

Patients who receive radiation therapy for the Wilms tumor are an ideal population for study of the effect of RT and age at the time of treatment on stature. As a result of earlier studies showing a higher risk of spinal curvature with asymmetric radiation to the vertebral bodies, standard flank radiation now includes the affected side and extends across the spinal column but excludes the contralateral kidney. Radiation dosages have decreased over successive National Wilms Tumor Study Group (NWTSG) protocols. Hogeboom et al. (81) evaluated stature loss in 2778 children treated on NWTSG 1–4. Repeated height measurements were collected during long-term follow-up. The effects of radiation dosage, age at treatment, and chemotherapy on stature were analyzed using statistical models that accounted for the normal variation in height with sex and advancing age. Predictions from the model were validated by descriptive analysis of heights measured at the age of 17–18 years for 205 patients. For those under 12 months of age at diagnosis who received more than 10 Gy, the estimated adult height deficit was 7.7 cm when contrasted with the nonradiation group. For those who received 10 Gy the estimated trunk shortening was 2.8 cm or less. Among those whose height measurements in the teenage years were available, patients who received more than 15 Gy of RT were 4–7 cm shorter on average than their nonirradiated counterparts, with a dose-response relationship evident. Chemotherapy did not confer additional risk.

Scoliosis and Kyphosis. Scoliosis and kyphosis are common consequences of spinal or flank irradiation. Asymmetric spinal growth has been seen most often after irradiation for the Wilms tumor and neuroblastoma, where there has been flank surgery (e.g., nephrectomy) and radiation (82). The types of deformities observed included a lateral flexion curve, concave to the side of the primary tumor, and a rotary scoliosis. However, with current dosages and fields of RT used to treat the Wilms tumor, scoliosis and kyphosis are less common. In a

Table 19.5

Evaluation of Patients at Risk for Late Effects: Thyroid

Late Effects	Causative Treatment		Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
	Chemotherapy	Radiation			
Overt hypothyroidism (elevated TSH, decreased T4)		>20 Gy to the neck, cervical spine >7.5 Gy total body irradiation	Hoarseness, fatigue, weight gain, dry skin, cold intolerance, dry brittle hair, alopecia, constipation, lethargy, poor linear growth, menstrual irregularities, pubertal delay, bradycardia, hypotension	Free T4, TSH annually up to 10 year postirradiation or if symptomatic Plot on growth chart	Refer to endocrinologist Thyroxine replacement Anticipatory guidance regarding symptoms of hyperthyroidism and hypothyroidism
Compensated hypothyroidism (elevated TSH, normal T4)		Same as for overt hypothyroidism	Asymptomatic	Same as for overt hypothyroidism	Refer to endocrinologist Thyroxine to suppress gland activity
Thyroid nodules		Any dosage	Same as for overt hypothyroidism	Same as for overt hypothyroidism Physical exam Ultrasound for technetium-99m scan for baseline and then PRN	Refer to endocrinologist Thyroid scan Biopsy or resection
Hyperthyroidism (low TSH, elevated T4)		Same as for overt hypothyroidism	Nervousness, for tremors, heat intolerance, weight loss, insomnia, increased appetite, diarrhea, moist skin, tachycardia, exophthalmus, goiter	Same as thyroid nodules T3, antithyroglobulin, antimicrosomal antibody baseline, then PRN	Refer to endocrinologist PTU, propranolol ¹³¹ I Thyroidectomy

TSH, thyroid-stimulating hormone; PRN, as needed; PTU, propothiouracil.

From Constine LS, Hobbie W, Schwartz C. Facilitated assessment of chronic treatment by symptom and organ systems. In: Schwartz C, Hobbie W, Constine L, et al., eds. *Survivors of Child and Adolescent Cancer: A Multi-Disciplinary Approach*. Berlin: Springer-Verlag; 2005:17–34, with permission.

series by Paulino et al. (83), in a group of 42 children treated for the Wilms tumor from 1968 to 1994, 7 developed muscular hypoplasia, 5 were found to have limb length inequality, 3 had kyphosis, and another 3 had iliac wing hypoplasia. Scoliosis was seen in 18, with only 1 patient needing orthopedic intervention. Median time to development of scoliosis was 102 months (range 16–146). A clear dose–response relationship was seen, with children treated with lower dosages (less than 24 Gy) having a significantly lower incidence of scoliosis than those who received more than 24 Gy. There was also a suggestion that the incidence was lower in patients who received 10–12 Gy, the dosages currently used for the Wilms tumor, although the sample size was small.

Asymmetric irradiation of the vertebrae seemed to promote the development of rotary scoliosis and lateral flexion curvature. Some clinicians believe that it is better to arrest a growth plate than partially irradiate it and cause a curvature. It is for this reason that some clinicians prefer true anteroposterior portals. Lateral and tangential ports may give sufficient variation in intensity of radiation to the epiphyseal plates of the spine to produce scoliosis by the irregular advance of the epiphyses. This led to the change in RT fields now used to treat unilateral intra-abdominal tumors of childhood. If therapy is limited to one half of the abdomen, it is advisable to bring the ports slightly beyond the midline so that the entire transverse diameter of the spine is included, receiving irradiation of fairly uniform intensity. If the entire abdomen needs treatment and it must be subdivided into quadrants, caution should be exercised in avoiding quadruple cross-firing of the spine, producing a “hot spot” in the region of the first or second lumbar vertebrae.

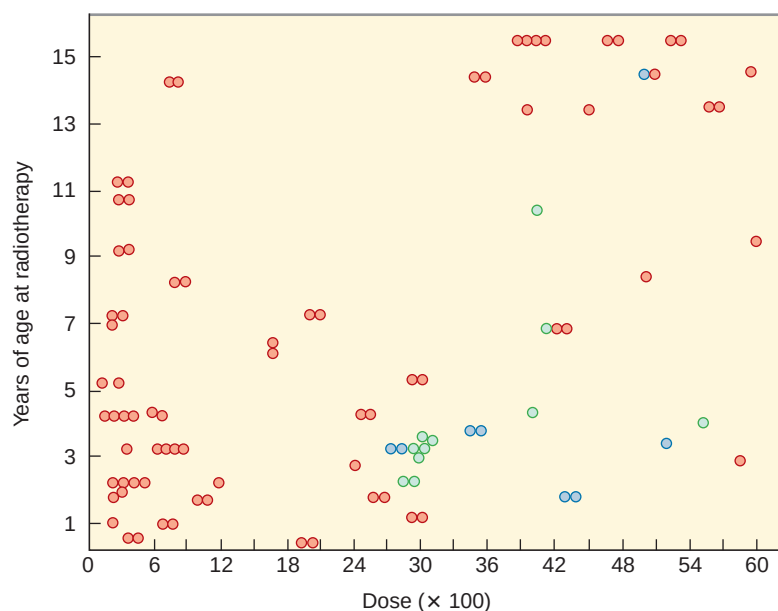
Slipped Femoral Capital Epiphysis. Slipped femoral capital epiphysis is a clinically significant adverse effect observed in patients after irradiation of the femoral head (84). There is a threshold dosage of 25 Gy for this complication. It occurred in about 50% of children irradiated before 4 years of age (7 of 15), compared with only one of twenty-one 5- to 15-year-olds (Fig. 19.9). A similar age effect is seen with TBI for HSCT. Fletcher et al. (85) examined 10 children with skeletal

surveys 7–9 years after transplant with TBI and found more significant metaphyseal and epiphyseal abnormalities in those treated before 8 years of age than in those treated between 12 and 19 years of age, supporting the effect of radiation on growing tissue. The mechanism of femoral capital epiphyseal plate slippage is postulated to be a radiation-induced delay in maturation of the epiphyseal plate with disruption of normal calcification and bone matrix deposition. This renders the plate weak and prone to slippage through shearing stress at the tilted femoral line. When the femoral heads are shielded during irradiation, the frequency of this complication is small.

Avascular Necrosis (Osteonecrosis). Avascular necrosis (osteonecrosis [ON]) is reported now with increased frequency following not only RT, but also following treatment with corticosteroid (Fig. 19.10). The rate of self-reported avascular necrosis was evaluated in the CCSS. Fifty-two cancer survivors reported ON in 78 joints, yielding 20-year cumulative incidence of 0.43% and a rate ratio (RR) of 6.2 (95% CI, 2.3–17.2) compared with sibling and 44% developed ON in a previous radiation field. Risk was greatest among survivors of stem-cell transplantation for leukemia. Nontransplantation patients with leukemia and bone sarcoma were at higher risk for ON. Older age at diagnosis, shorter elapsed time, older treatment era, exposure to dexamethasone ($\pm$ prednisone), and gonadal and nongonadal radiation were independently associated with ON (86).

Even among patients treated with more contemporary therapy for ALL or NHL without RT, there is increasing information on the occurrence of ON, where the affected number is unclear, due to lack of systematic methods of detection. However, as many as 1 of 3 may be affected, likely reflecting the cumulative exposure to glucocorticosteroid therapy. The pathogenesis includes suppression of bone formation, expansion of the intramedullary lipocyte compartment and a direct effect on nutrient arteries. Children 10 years of age and older are at particular risk and the disorder is substantially more common in Caucasians than African Americans, and risk is higher in newer protocols with higher cumulative and more

Figure 19.9 The relationship of radiation dosage and age in the production of slipped capital femoral plates (blue circles). The green circles are other reported cases. Refer to Fig. 2 of Ref. 84 from which data were obtained. Normal epiphyseal plates are represented by orange circles. (From Silverman CL, Thomas PR, McAlister WH, et al. Slipped femoral capital epiphysis in irradiated children: dose, volume, and age relationships. *Int J Radiat Oncol Biol Phys.* 1981;7:1357–1363, with permission).



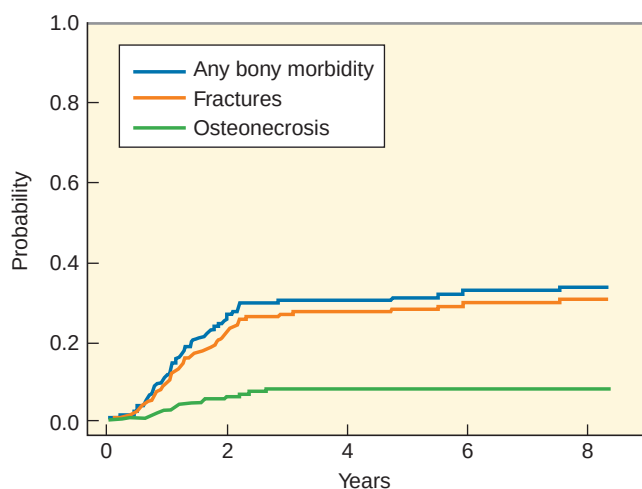


Figure 19.10 Cumulative incidence (CI) of bony morbidity for 176 children treated for ALL between 1987 and 1991. With 7.6 years of median follow-up, the overall 5-year CI ($\pm$ SE) was 30% $\pm$ 4%. The 5-year CI of fracture was 28% $\pm$ 3%, and of osteonecrosis, 7% $\pm$ 2%. (From Strauss AJ, Su JT, Dalton VM, et al. Bony morbidity in children treated for acute lymphoblastic leukemia. *J Clin Oncol.* 2001;19:3066–3072, with permission.)

continuous use of dexamethasone. Genetic predisposition may play a role. In an analysis from the Children's Oncology Group, a PAI-1 polymorphism (rs6092) was associated with risk of osteonecrosis in univariate and multivariate analyses (adjusting for gender, age, and treatment arm) (87). Osteonecrosis is often multiarticular and bilateral, affecting weight-bearing joints predominantly (88–91).

Other Skeletal Abnormalities

A variety of other skeletal abnormalities can be seen after irradiation. These include sternal deformity (hypoplasia, asymmetry, pectus excavatum, pectus carinatum) (92); hypoplasia of the iliac bones or lower ribs; cartilaginous exostoses; (93) osteochondromata (94); hypoplasia of the mandible; deformity of orbital, maxillary, nasal, or temporal bone (94,95); and lower extremity abnormalities such as acetabular dysplasia, coxa vara, hip dislocation, and leg shortening (96).

Table 19.6 reviews several musculoskeletal late effects with respect to causative treatments, signs and symptoms, screening and diagnostic tests, and management and intervention (41).

Osteopenia. Bone mineral density in childhood cancer survivors may be reduced, especially in children treated for ALL, or with HSCT, where it has been best studied. Risk factors include increased age at the time of exposure, estrogen deficiency, female sex, corticosteroid use and type, GH deficiency, and cranial radiation. Prevalence, chronicity, and severity are not consistent across studies, so the risk remains poorly defined (97–100). Further research into the pathophysiology, the contribution of the various risk factors, the type and frequency of screening, the populations at highest risk, and interventions are clearly indicated.

Body Composition. Similarly of concern, but not yet rigorously studied, is abnormal body composition, which is

reported in survivors of pediatric ALL. Oeffinger (101) evaluated obesity in 1764 ALL survivors followed in the CCSS and compared them with a cohort of 2565 siblings. The odds ratio for being obese was 2.6 for female survivors and 1.9 for male survivors who received dosages greater than 20 Gy. The highest risk was for girls treated at 0–4 years of age and with cranial radiation dosages greater than 20 Gy (Fig. 19.11). Risk of obesity was not higher among ALL survivors treated with chemotherapy alone or with cranial radiation dosages of 10–19 Gy. Similar findings were reported by Warner et al. (102), where body mass index Z-score, skinfold thickness, percentage fat by dual-energy x-ray absorptiometry, and ratio of central to peripheral fat was higher in girls treated for ALL than in siblings or patients treated for other malignancies. Reilly et al. (103) found higher obesity rates in survivors of childhood ALL, with higher risk in younger children and those thinner at the time of diagnosis, and associated with premature adiposity. However, there are also data that children treated for ALL in the absence of cranial RT are still at increased risk of obesity and hypertension, which may persist for years after therapy ends, as reported in a retrospective series by Chow (104). A follow-up study in the CCSS, where the use of cranial RT was common, also reveals continued risk of obesity among adult survivors (105). Increased body mass index is a component of the metabolic syndrome, which includes insulin resistance, hyperglycemia, hyperinsulinemia, hypertension, hyperlipidemia, and obesity. Long-term risk for cardiovascular disease from metabolic syndrome is of concern (102,104,106).

Cardiac

The functional and structural complexity of the heart places it at risk for a spectrum of RT and chemotherapy injuries that can occur. The radiation-associated sequelae include acute pericarditis during radiation (rare and associated with juxtapericardial cancer); delayed pericarditis, which can present abruptly or as chronic pericardial effusion; pancarditis, which includes pericardial and myocardial fibrosis with or without endocardial fibroelastosis (only after large dosages); myopathy in the absence of significant pericardial disease; coronary artery disease (uncommon), usually involving the left anterior descending artery; functionally valvular injury; and conduction defects (107–109). The hallmark of these injuries histologically is fibrosis in the interstitium with normal-appearing myocytes and capillary and arterial narrowing.

Several parameters must be considered in the evaluation of these radiation-associated injuries, including the relative weighting of the radiation portals and, therefore, the amount of radiation delivered to different depths of the heart; the presence of juxtapericardial tumor; the volume and specific areas of the heart irradiated; the total and fractional irradiation dosage; the presence of other risk factors in each patient such as age, weight, blood pressure, family history, lipoprotein levels, and habits such as smoking; and the use of specific chemotherapeutic agents.

The effects of thoracic RT are difficult to separate from those of anthracyclines because few children are exposed to thoracic RT in the absence of anthracyclines. The pathogenesis of injury differs, however, with radiation affecting primarily the fine vasculature of the heart and anthracyclines directly damaging myocytes. However, with current techniques and reduced dosages of RT, these effects are unlikely after

Table 19.6

Evaluation of Patients at Risk for Late Effects: Musculoskeletal

Late Effects	Causative Treatment		Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
	Chemotherapy	Radiation			
Muscular hypoplasia		>20 Gy (growing child) Younger children more sensitive	Asymmetry of muscle mass when compared with untreated area Decreased range of motion Stiffness and pain in affected area (uncommon)	Careful comparison and measurement of irradiated and unirradiated areas Range of motion	Prevention: good exercise program, range of motion, muscle strengthening
Spinal abnormalities: scoliosis, kyphosis, lordosis Decreased sitting height Length discrepancy		For young children, RT to hemiabd-omen or spine (especially hemivertebral) 10 Gy (minimal effect) >20 Gy (clinically notable defect) >20 Gy	Back pain Hip pain Uneven shoulder height Rib humps or flares Deviation from vertical curve Gait abnormalities Lower back pain, limp, hip pain, discrepancy in muscle mass and length when compared with untreated extremity, scoliosis	Standing and sitting height at each visit and plot on chart (stadiometer). During puberty examine spine q3–6 months until growth is completed and then q1–2 years Spinal films for baseline during puberty, then PRN curvature (Lippman–Cobb technique to measure curvature) Annual measurement of treated and untreated limb (completely undressed patient to ensure accurate measurements) Radiograph baseline to assess remaining epiphyseal growth Radiographs annually during periods of rapid growth Baseline radiograph of treated area to assess bone integrity, then PRN	Refer to orthopedist if any curvature is noted, especially during a period of rapid growth Contralateral epiphysiodesis Limb-shortening procedures
Pathological fracture		>40 Gy	Pain, edema, ecchymosis	Baseline radiograph of treated area to assess bone integrity, then PRN	Prevention: consider limitation of activities (e.g., contact sports) Surgical repair of fracture; may need internal fixation Symptomatic care Joint replacement
Osteonecrosis	Steroids	40–50 Gy (more common in adults) RT	Pain in affected joint, limp	Radiograph, CT scan PRN	
Osteocartilaginous exostoses			Painless lump or mass noted in the field of radiation	Radiograph for baseline and PRN with growth of lesion	Resection for cosmetic or functional reasons, counsel regarding 10% incidence of malignant degeneration
Osteopenia and osteoporosis	Steroids	>18 Gy cranial RT	Fractures; pain	Dual-energy x-ray ab : sorpitiometry intervals of testing unclear Pediatric norms not well established. Best data are in adults	Calcium supplementation Increase weight-bearing exercise Refer to endocrinology for possible bis-phosphonate therapy
Slipped capital-moral	High-dose steroids	>25 Gy (at young age)	Pain in effected hip, limp, abnormal gait	Radiograph baseline to assess integrity of the treated joints, then PRN	Refer to orthopedist for surgical intervention

RT, radiotherapy; PRN, as needed; CT, computed tomography.

From Constine LS, Hobbie W, Schwartz C. Facilitated assessment of chronic treatment by symptom and organ systems. In: Schwartz C, Hobbie W, Constine L, et al., eds. *Survivors of Child and Adolescent Cancer: A Multi-Disciplinary Approach*. Berlin: Springer-Verlag; 2005:17–34, with permission.

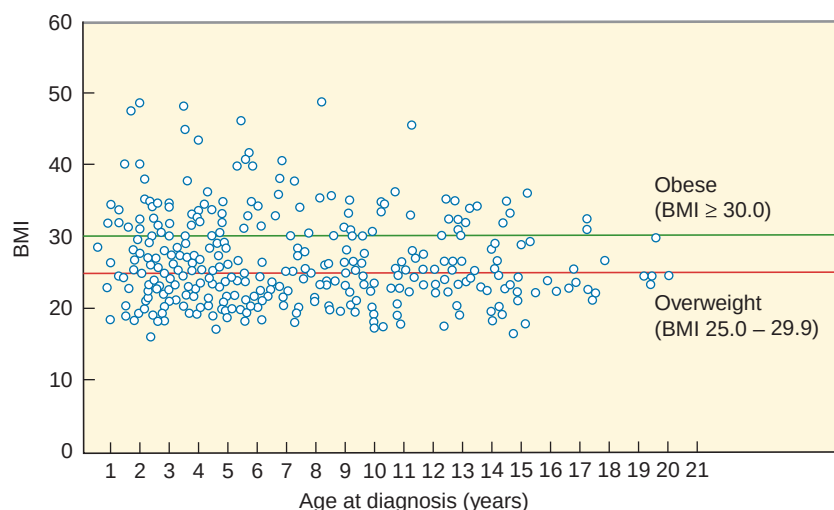


Figure 19.11 Scatterplot for unadjusted body mass index (BMI) by age at diagnosis of acute lymphoblastic leukemia for females treated with >20 Gy cranial radiotherapy. (From Oeffinger KC, Mertens AC, Sklar CA, et al. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2003;21:1359–1365, with permission.)

treatment for childhood cancer. Review of data from the CCSS shows significant cardiovascular morbidity across a number of childhood cancer survivor diagnostic groups, with the caveat that the data are based on self-report. Gurney et al (105) identified that 18% of childhood brain tumor survivors reported a heart or circulatory late effect. Risk was highest among those treated with surgery, RT, and chemotherapy compared to surgery and RT alone, suggesting a potential additive vascular injury from chemotherapy. Among ALL survivors in the CCSS cohort reporting a chronic medical condition, the risk of reporting a cardiac condition was nearly sevenfold higher compared to the siblings. No significant association was identified based on radiation exposure. A similar analysis among acute myeloid leukemia (AML) survivors in the cohort found the 20-year cumulative incidence of cardiac disease to be 4.7. Twenty-one percent of rhabdomyosarcoma survivors reported ≥ 1 cardiac sequelae compared to siblings. Among survivors of non-Hodgkin lymphoma (NHL), the standardized mortality ratio (SMR) for cardiac disease was 6.9 (110). A recent follow-up study of Wilms tumor survivors reported a cumulative risk of congestive heart failure of 4.4% at 20 years for those who received doxorubicin as part of their initial therapy, and 17.4% at 20 years where doxorubicin was received as part of therapy for relapsed disease. Risk factors for congestive heart failure in this cohort included female sex, lung irradiation with dosages 20 Gy or higher, left-sided abdominal irradiation, and doxorubicin dosage of 300 mg/m² or more (111). Finally, cardiac complications after BMT may occur, with arrhythmias, pericarditis, and myopathies predominating. High-dose cyclophosphamide is clearly a causative agent. TBI is a secondary contributing factor.

Pericarditis

Delayed acute pericarditis can be symptomatically occult or present suddenly with fever, dyspnea, pleuritic chest pain, friction rub, ST and T wave changes, and decreased QRS voltage. Up to 30% of patients treated for HL with a mean midplane heart dosage of 46 Gy are affected (112). With equally weighted anterior and posterior fields and the use of subcardinal blocking, the frequency decreases to 2.5% (113). The onset of delayed acute pericarditis averages 6 months, and 92% of effusions occur within 12 months. Although the effusion usually

resolves in 1–10 months, it may persist for years. Pericardiectomy is a high-risk procedure in this setting because of the coexistence of other types of radiation-induced damage such as fibrosis of the myocardium and lung, coronary artery and valvular disease, impaired chest wall healing, and the patient's general condition. However, Hancock et al. (114) noted a 4% (at 17 years) actuarial risk of pericardiectomy (occurring only in children treated with higher radiation dosages), and most patients improved after surgery.

Myocardiopathy

Myocardiopathy is highly potentiated by doxorubicin and other anthracyclines (idarubicin, epirubicin, daunomycin) but occurs in its absence (113,114). With modern radiation techniques and appropriate cardiac blocking, measures of cardiac function including left ventricular ejection fraction (LVEF) and peak filling rate (PFR) in patients irradiated to portions of the heart are commonly preserved. This was demonstrated by Constine et al. (116), who assessed 50 asymptomatic survivors of HL treated with mean central cardiac RT dosages of 35.1 Gy (range 18.5–47.5 Gy). The mean LVEF and PFR were normal, and two (4%) and eight (16%) patients, respectively, had low test results.

Although an in-depth discussion of the late cardiotoxic effects of anthracycline administration will not be presented, its importance and frequency must be emphasized. This is especially important because more contemporary HL treatment protocols are using lower dosages of RT but continue to use doxorubicin in the 200–300-mg/m² range. Doxorubicin has been the most extensively studied of the anthracyclines, and its cardiotoxicity is often progressive and disabling. Increased risk of doxorubicin-related cardiomyopathy is associated with female sex, cumulative dosages greater than 200–300 mg/m², younger age at the time of exposure, and increased time from exposure (117–122). The effects of anthracyclines on long-term cardiac outcomes are shown in Figure 19.12.

Prevention or amelioration of anthracycline-induced cardiomyopathy is of utmost importance due to the use of anthracyclines in cancer therapy (123). Dexrazoxane (DZR) is a bis-dioxopiperazine compound that readily enters cells and is subsequently hydrolyzed to form a chelating agent. DZR has been shown to prevent cardiac toxicity in adults and children

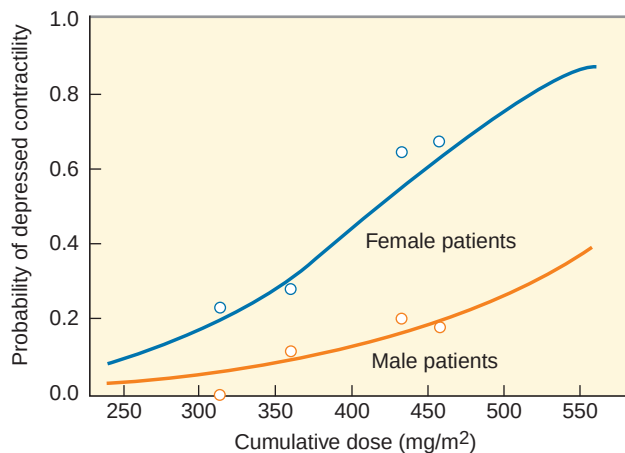


Figure 19.12 Probability of depressed cardiac contractility as a function of the cumulative dosage of doxorubicin in female and male patients. (From Lipshultz S, Lipsitz S, Sallan S. Chronic progressive left ventricular systolic dysfunction and afterload excess years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *Proc Am Soc Clin Oncol*. 2000;19:580a, with permission.)

treated with anthracyclines (123–127). An unexpected finding of increased risk of SMN following DZR use has been reported in a single study of its use in HL, where it was administered within hours of not only doxorubicin, but etoposide, another topoisomerase II inhibitor (128). This has not been found to date in other studies where DZR is used as a cardioprotectant (129).

Children who need HSCT are at especially high risk of cardiac toxicity. They may have received anthracyclines or RT with the heart in the field as part of their initial cancer therapy, and they are subsequently exposed to conditioning regimens that may include high-dose cyclophosphamide and TBI (130,131). Assessment of the cardiovascular complications of BMT will assume greater importance with the increasing number of children undergoing this therapy. In a report from the University of Minnesota on 63 transplanted children, 74% of children old enough to undergo treadmill exercise testing had a borderline or abnormal response to exercise, and 12.7% of patients had symptomatic cardiovascular abnormalities (130). The preparative regimen included TBI in slightly more than half of the patients, but this was independently associated with outcome.

Valvular Disease

Fibrous valvular endocardial thickening occurs in 80% of autopsied patients treated with high radiation dosages. The mitral, aortic, and tricuspid valves are most often affected (132). Although such valvular lesions are common, they rarely evolve into symptomatic valvular disease. In addition, they have not been reported in patients treated with the more commonly used low dosages of RT. In some patients, the radiation-induced cellular injury to the valvular endocardium, combined with chronic pressure-related trauma, may eventually lead to valvular deformation, resulting in stenosis or insufficiency. In a report by Hancock et al. (114) on 635 children treated for HL, 2 patients died of valvular disease, and 3 others have undergone aortic (2 patients) or mitral (1 patient) valve replacement. A contribution of mediastinal irradiation to significant or accelerated valvular disease could not be

clearly determined. Unfortunately, in another report, valve replacement in such patients was infrequently successful and operative mortality was high (66%) (133).

Arrhythmia

High-degree atrioventricular (AV) conduction abnormalities are rarely seen and have been attributed to fibrosis of the AV node conducting branches (134). In one series, all patients with radiation-associated AV block had received more than 40 Gy to the chest, with a median time to development of the block of 14 years (135). Again, as with myocardiopathy, the effect of doxorubicin should be considered.

Coronary Artery Disease

As the population of cured childhood cancer patients ages and becomes exposed to the risk factors for coronary artery disease (CAD) such as smoking, obesity, hypertension, diabetes, and elevated cholesterol, it is possible that excess morbidity and mortality from ischemic heart disease may occur if RT or chemotherapy accelerates atherosclerosis. RT can lead to ischemic heart disease via endothelial damage and obliteration of the microvasculature and via accelerated atherosclerosis of large vessels.

The manner in which thoracic irradiation is administered may significantly affect the incidence of radiation-associated CAD. Mantle irradiation using only a single anterior beam or an anteriorly weighted pair of opposed beams, or treating only one field per day, may significantly increase the cardiac dosage. The cardiac dosage and the risk of CAD may also be influenced by the extent of cardiac blocking via left ventricle and subcarinal blocks, the radiation dosage per fraction, and the total dosage. However, it is important to note that the proximal coronary arteries, which are commonly the site of obstruction, are not shielded with routine cardiac blocking (Fig. 19.13) (108). Data from the University of Rochester demonstrated that the site of coronary artery stenosis in patients irradiated for HL was most commonly in the proximal coronary arteries, and this was no different than that which

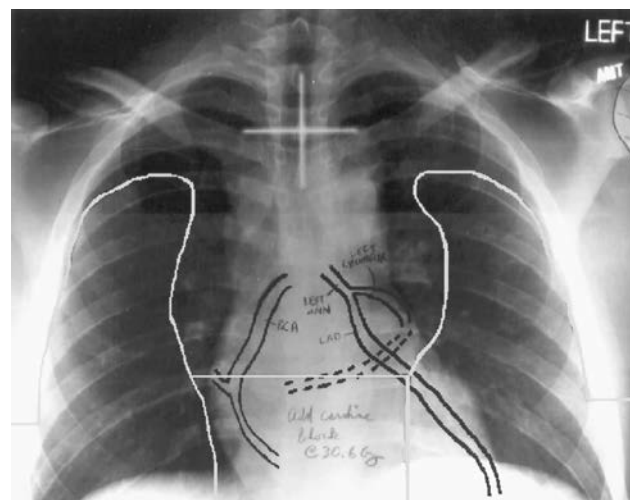


Figure 19.13 Location of the coronary vessels (dark lines) on a standard mantle field is illustrated. The blocks are outlined in white. (From King V, Constine LS, Clark D, et al. Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease. *Int J Radiat Oncol Biol Phys*. 1996;36:881–889, with permission.)

would be found in the general population. More specifically, the left main and the proximal portions of the left anterior descending and right coronary arteries are most commonly involved (108). Retrospective reviews that indicate an association between chest irradiation and CAD may reflect the dangers of older forms of RT and therefore be of only historical interest to the modern pediatric radiation oncologist (136).

The risk of myocardial infarction (MI), cardiac failure, and death are clearly related to RT dosage and field, although host factors may modify this risk. The Institut Gustave-Roussy reported 13 MIs in 499 mantle-irradiated patients (10-year cumulative incidence of 30%) but observed no MIs in 138 patients who received no irradiation. Among the retrospective series evaluating the incidence of CAD after heart irradiation of adults and adolescents, one can readily find data indicating that moderate- to low-dose irradiation does not increase the risk of MI or cardiac death. Hancock et al. (137) at Stanford found that in patients with HL irradiated with more modern radiotherapeutic techniques, there was no significant difference in MI mortality when compared with that in age- and sex-matched control subjects. Of interest are data from the University of Rochester that assessed the risk of CAD in survivors of HL and also the prevalence of cardiac risk factors. Although the risk of cardiac death was elevated at 2.8 (3.1 for males and 1.8 for females), other risk factors were more common than in the general population; among patients with HL, 72% smoked, 72% were male, 78% had hypercholesterolemia, 61% were obese, 28% had a positive family history, 33% had hypertension, and 6% had diabetes (108). This suggests that RT is one of several risk factors for CAD in patients treated for HL.

Table 19.7 reviews several cardiac late effects with respect to causative treatments, signs and symptoms, screening and diagnostic tests, and management and intervention (41).

Lungs

The target cells for pulmonary injury are type I and II pneumocytes, fibrocytes, endothelial cells, and macrophages (6,138). Several pulmonary radiation syndromes occur in the child. Acute pneumonitis and chronic fibrosis result from injury to the type II pneumocytes and endothelial cells. Chronic respiratory limitations result from impairment in the development of new alveoli or from growth impairment of the established ones. Limitations of a different character result from a reduction in growth of the muscle, cartilage, and bone that form the thoracic cage.

Pathophysiology

The acute reactions of radiation pulmonary injury, known as the exudative phase, can be detected within 24 hours of irradiation. It is signified by intra-alveolar edema and exudation of proteinaceous material into the alveoli, impairing gas exchange. Infiltration by inflammatory cells and desquamation of epithelial cells from the alveolar walls occur. A proliferative phase occurs between 2 and 6 months with accumulation of type II alveolar cells and protein leakage into the alveolar spaces. Interstitial edema organizes into collagen fibrils, leading to the thickening of the alveolar septa and a clinical pneumonitis. Injury to the type II pneumocyte, with resultant changes in the surfactant system (and thus alveolar surface tension and compliance) and in the endothelial cell and capillary permeability, causes these changes (139). After 6 months the fibrotic phase

occurs. Alveolar septa become fibrotic and thickened by bundles of elastic fibers, forming the basis for chronic respiratory injury. Eventually, the alveoli collapse and are obliterated by connective tissue. Capillaries are lost, replaced, and then recanalized. The target cells that trigger this process are less clearly established but include the septal fibrocyte and endothelial cell.

Clinical Manifestations

Acute pneumonitis usually occurs 3–6 months after the start of irradiation. The symptoms include fever, congestion, a hacking but eventually productive cough, dyspnea, chest tightness, and pleuritic pain. Signs are initially absent, but consolidation and pleural fluid or a friction rub may be detected. If a large enough volume (greater than 75%) of lung is treated at dosages greater than 45 Gy, then cor pulmonale and death can occur. Surviving patients experience a protracted phase that slowly resolves. Lung function abnormalities are generally not detected for 4–8 weeks after completion of irradiation. Restrictive changes with volume loss occur, accompanied by a fall in diffusion capacity with mild arterial hypoxemia. Hypoperfusion of the irradiated area and decreased lung compliance can be demonstrated. The earliest radiographic changes (1–3 months after therapy) are a diffuse infiltrate corresponding to the radiation field with volume loss.

Chronic fibrosis is seen months to years after therapy, but most changes are apparent by 1–2 years. Most patients are asymptomatic, but chronic respiratory impairment with dyspnea, orthopnea, cyanosis, or cor pulmonale may occur. Maximum breathing capacity and tidal volume decrease. Chest radiographs show linear streaking that may extend outside the irradiated field. Regional contraction, pleural thickening, and tenting of the diaphragm occur.

Radiation and Chemotherapy Effects on the Lung

In the modern management of pediatric malignancies, RT is often given in combination with chemotherapy. It is important to recognize that many chemotherapeutic agents either induce lung damage on their own or potentiate the damaging effects of radiation on the lung. In the CCSS, both RT and chemotherapy increased risk of chronic lung problems. Statistically significant associations were present between thoracic irradiation and lung fibrosis, need for supplemental oxygen, chronic cough, and pleurisy. Chemotherapy agents associated with the same self-reported pulmonary problems included carmustine, lomustine, bleomycin, and cyclophosphamide. With ongoing follow-up of the cohort, the cumulative incidence continues to increase for lung fibrosis up to 15–25 years after diagnosis for those who received chest RT both with and without pulmonary-toxic chemotherapy (110,140). Figure 19.14 shows the cumulative incidence of pulmonary toxicity with ongoing follow-up. Changes in lung function in children treated to the whole lung for metastatic Wilms tumor have been reported. A dosage of 12–14 Gy reduced total lung capacity and vital capacity to about 70% of predicted values, and even lower if the patient had undergone thoracotomy. Fractionation of dosage decreases this risk (141,142). Chemotherapeutic agents such as doxorubicin, dactinomycin, and busulfan are radiomimetic agents and can reactivate latent radiation damage (141,143). The development of bleomycin-associated pulmonary fibrosis with permanent restrictive disease is dose dependent, usually

Table 19.7
Evaluation of Patients at Risk for Late Effects: Cardiac

Late Effects	Causative Treatment		Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
	Chemotherapy	Radiation			
Cardiomyopathy	Anthracycline >300 mg/m ² >200 mg/m ² and radiotherapy to mediastinum High-dose CTX Bone marrow transplantation Possibly ifosfamide	>35 Gy >20 Gy and anthracyclines	Fatigue, cough, dyspnea on exertion, peripheral edema, hypertension, tachypnea and rales, tachycardia, cardiomegaly (S3/S4), hepatomegaly, syncope, palpitations, arrhythmias	ECG, stress ECHO, radionuclide, and CXR baselines, q1–5 years (depending on risk factors) Holter monitor and exercise testing for baseline, PRN, and after high cumulative anthracycline dosage (>300 mg/m ²)	Diuretics, digoxin, afterload reduction, antiarrhythmics, cardiac transplant, education regarding risks of: isometric exercises, alcohol consumption, drug use, smoking, pregnancy, anesthesia
Valvular damage (mitral and tricuspid aortic)		>30 Gy	Weakness, cough, dyspnea on exertion, new murmur, pulsating liver	ECHO and CXR (baseline), q3–5 years then PRN	Penicillin prophylaxis for surgery or dental procedures Pericardial stripping
Pericardial damage		>35 Gy	Fatigue, dyspnea on exertion, chest pain, cyanosis, ascites, peripheral edema, hypotension, friction rub, muffled heart sounds, venous distension, pulsus paradoxus	ECG (ST–T changes, decreased voltage), ECHO, CXR baseline, q3–5 years	
Coronary artery disease		>30 Gy	Chest pain on exertion (radiates to arm and neck), dyspnea, diaphoresis, pallor, hypotension, arrhythmias	ECG, stress ECHO, or radionuclide baseline, q3–5 years Lipid profile, q1–3 years regimens	Diuretics, cardiac medications (e.g. statins, aspirin) Low-sodium, low-fat diet, conditioning

ECG, electrocardiogram; ECHO, echocardiogram; CXR, chest radiograph; PRN, as needed; CTX, cyclophosphamide.

From Mertens AC, Yasui Y, Neglia JP, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *J Clin Oncol*. 2001;19:3163–3172, with permission.

occurring at dosages greater than 200 U/m², higher than those used in pediatric malignancies (143,144). While symptomatic pulmonary disease is uncommon with lower doses (15–25 Gy) of RT in combination with bleomycin therapy, pulmonary function tests may reveal abnormal diffusing capacity (145,146).

Patients who are treated with HSCT are at greater risk of pulmonary toxicity, related to preexisting pulmonary dysfunction, the preparative regimen, which may include cyclophosphamide, busulfan, carmustine, and TBI and to the presence of GVHD (147–150). Although most transplant survivors are not clinically compromised, restrictive lung disease may occur. Obstructive disease is less common, as is the recently described late-onset pulmonary syndrome, which includes the spectrum of restrictive and obstructive

disease. Bronchiolitis obliterans, with or without organizing pneumonia, diffuse alveolar damage, and interstitial pneumonia may occur as a component of this syndrome, generally 6–12 months after transplant. Cough, dyspnea, or wheezing may occur with either normal chest radiograph or diffuse or patchy infiltrates; however, most patients are symptom free (148,150).

Cerveri et al. (147) evaluated pulmonary function tests in survivors of pediatric HSCT at baseline, and at 3–6, 12, and 24 months after transplant. Before transplant, at 3–6 months after transplant, and at 24 months after transplant, 44%, 85%, and 62% of children, respectively, had abnormal pulmonary function tests. A restrictive abnormality was most common at 3–6 months after transplant. Data on type of abnormality by follow-up period are shown in Figure 19.15 (147).

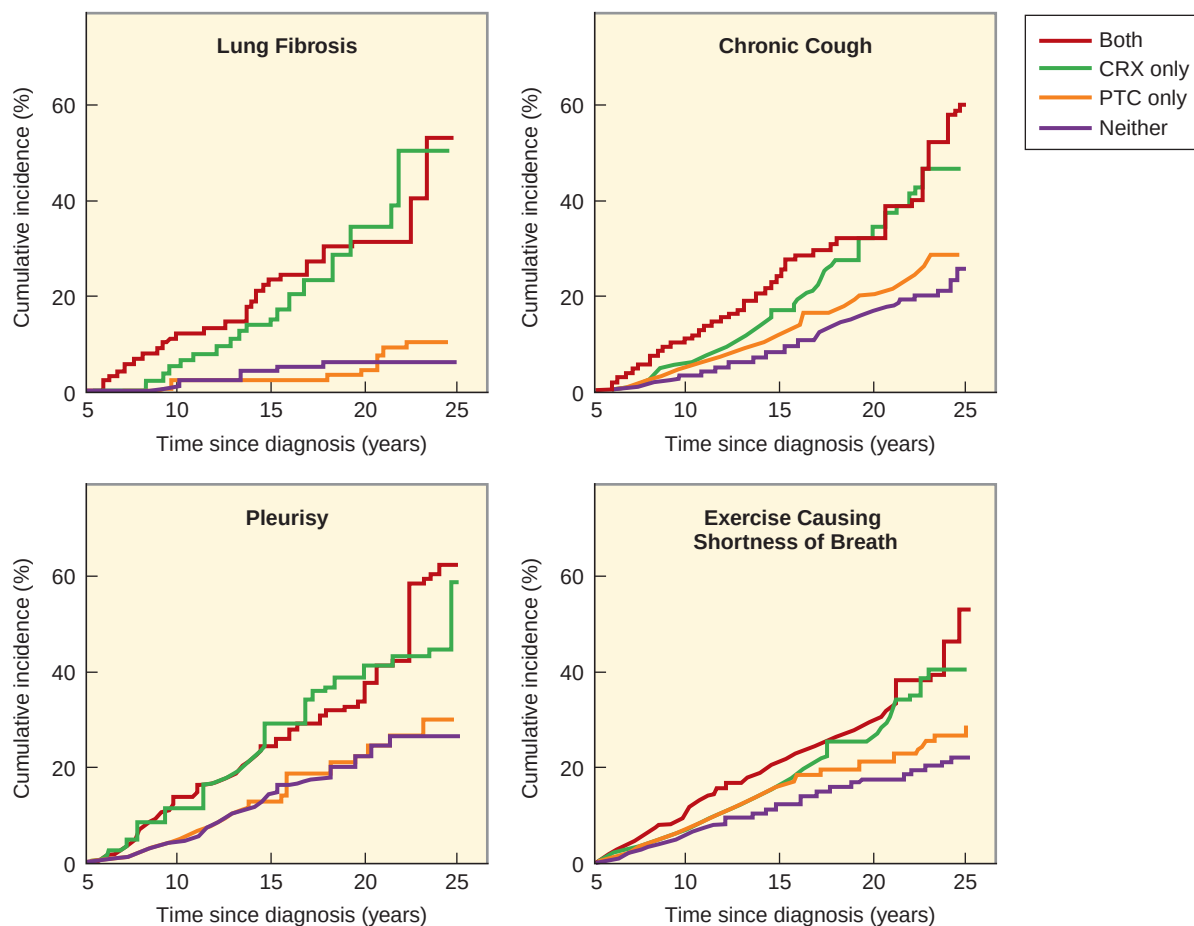


Figure 19.14 Cumulative incidence of chronic pulmonary conditions by type of therapy. (From Diller L, Chow EJ, Gurney JG, et al. Chronic disease in the Childhood Cancer Survivor Study cohort: a review of published findings. *J Clin Oncol.* 2009;27:2339–2355, with permission.)

Fryer et al. (139) and Keane et al. (151) analyzed the relationship between single doses of irradiation to the whole lung and the resulting fatal pneumonitis. After correction for an increased lung transmission of 15–20%, a dose–response relationship was generated. Lethal pneumonitis was seen in 5% of patients after 8.2 Gy, 50% after 9.3 Gy, and 90% after

11 Gy. Thus, a difference of 2 Gy could change mortality from 0% to 50%, which emphasizes the importance of correcting for lung density. Increasing the dose rate from 0.1 to 0.5 Gy per minute increased the frequency of injury from 50% to 90%. TBI for BMT is associated with acute and sometimes fatal pneumonitis and with chronic pulmonary compromise.

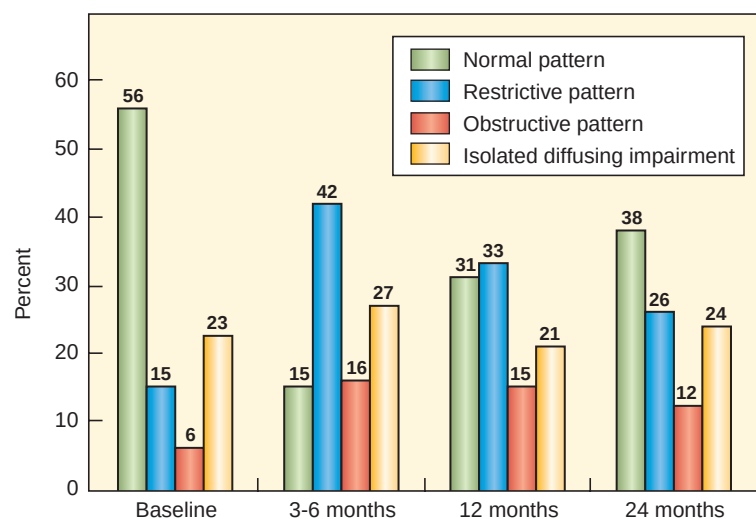


Figure 19.15 Distribution of different respiratory function patterns in patients before bone marrow transplant and 3–6 months, 12 months, and 24 months after transplant. (From Cerveri I, Fulgoni P, Giorgiani G. Lung function abnormalities after bone marrow transplantation in children: has the trend recently changed? *Chest.* 2001;120:1900–1906, with permission.)

Table 19.8**Evaluation of Patients at Risk for Late Effects: Pulmonary**

Late Effects	Causative Treatment		Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
	Chemotherapy	Radiation			
Pulmonary fibrosis	Bleomycin, lomustine, carmustine, CPM, methotrexate, mitomycin, vinca alkaloids	Pulmonary radiotherapy 15–20 Gy Risk increases with dosage, larger volume irradiated, and younger age	Fatigue, cough, dyspnea on exertion, reduced exercise tolerance, orthopnea, cyanosis, finger clubbing, rales, cor pulmonale	Baseline chest radiograph and O ₂ saturation, pulmonary function test including diffusing capacity of lung for carbon monoxide, then q3–5 years if symptomatic	Consider pulmonary evaluation, steroid therapy Prevention: avoidance of smoking Avoidance of infections: influenza vaccine, Pneumovax After bleomycin: avoid FiO ₂ > 30% intraoperatively and postoperatively Avoid excessive hydration

CPM, cyclophosphamide.

From Constine LS, Hobbie W, Schwartz C. Facilitated assessment of chronic treatment by symptom and organ systems. In: Schwartz C, Hobbie W, Constine L, et al., eds. *Survivors of Child and Adolescent Cancer: A Multi-Disciplinary Approach*. Berlin: Springer-Verlag; 2005:17–34, with permission.

The risk of acute pneumonitis increases from 5% after autologous transplantation to 20% after allogeneic. The use of fractionated and low-dose rate regimens may decrease the risk.

Table 19.8 reviews several pulmonary late effects with respect to causative treatments, signs and symptoms, screening and diagnostic tests, and management and intervention (41).

Ovary

Radiation and chemotherapy can cause transitory or permanent effects on reproductive capacity, endocrine integrity, and sexual function. The complexity of defining these sequelae stems from the dose-dependent effects caused by different chemotherapy agents, RT, and their combination. Injury to the ovaries can cause both sterilization and suppressed hormone production because of the relationship of the latter to the presence of ova and maturation of the primary follicle. Therefore, affected patients can have impaired development of secondary sexual characteristics, menstrual irregularities including amenorrhea, and symptoms associated with menopause such as hot flashes, loss of libido, and osteoporosis.

Pathophysiology

The ovary produces oocytes and secretes steroid hormones. Active mitosis of oogonia occurs during fetal life. The cortices of the ovaries harbor the follicles within connective tissue. The follicles arise from the germinal epithelium, which covers the free surface of the ovary. Through involution, atresia, and, to a much lesser extent, ovulation, the follicles disappear entirely at menopause. Hypothalamic gonadotropin-releasing hormone (GnRH) surges in late childhood to initiate puberty. GnRH stimulates release of the pituitary gonadotrophs, which orchestrate follicular maturation (follicle-stimulating hormone, FSH) and ovarian luteinization (LH). With sexual maturity comes the 28-day cycle with an estrogen-dependent midcycle surge of FSH and LH. After ovulation, the corpus

luteum forms and produces progesterone, estradiol, and 17-hydroxyprogesterone, and the resultant endometrial changes. Without chorionic gonadotropin from a conceptus, the corpus luteum is exhausted and progesterone and estrogen fall. As FSH increases, the endometrium sloughs (menstruation). Ovarian hormones have critical physiologic effects on other organs, including maturation and maintenance of the breasts and vagina, bone mineralization, integrity of the cardiovascular system, and libido. With depletion of oocytes by radiation, chemotherapy, or aging, the ovaries undergo atresia, and menstruation and estrogen production cease.

Radiation causes a decrease in the number of small follicles, impaired follicular maturation, cortical fibrosis and atrophy, generalized hypoplasia, and hyalinization of the capsule. Alkylating chemotherapeutic agents affect the resting oocyte in a dose-dependent, cell cycle-independent manner. Thecal cells and ova are depleted, as are the primordial follicles, resulting in arrest of follicular maturation and decreased estrogen secretion. Because girls treated before puberty have a greater complement of ova than do older women, ovarian function is more resistant to the effects of chemotherapy RT in younger girls.

Clinical Manifestations

Effect on ovarian function by RT depends not only on dose and fraction, but also on the patient's age, sexual developmental stage. Data from Ash (152) summarized the effect of fractionated RT on ovarian function in women of reproductive age (Table 19.9). Ovaries in younger girls are more resistant to the effects of RT than those of adolescents. When one considers dosages to the ovary, after single fractions, temporary sterility can occur with ovarian dosages of 1.7–6.4 Gy and permanent sterility after 3.2–10 Gy (153). Wallace et al. reviewed data to estimate an LD₅₀ of 600 cGy for the oocyte. Whole abdomen dosages of 20–30 Gy are associated with primary or premature secondary ovarian failure (154).

Table 19.9
Effect of Fractionated Irradiation on Ovarian Function in Women of Reproductive Age

Minimum Ovarian Dosage (Gy) ^a	Effect
0.6	No deleterious effect
1.5	No deleterious effect in most young women. Some risk of sterilization especially in women age >40
2.5–5.0	Variable. Age 15–40 years: about 60% sterilized permanently. Aged >40: 100% sterilized permanently
5–8	Variable. Age 15–40 years: about 70% sterilized permanently, temporary amenorrhea in some of remainder
>8	100% permanently sterilized

^aNo attempt has been made to allow for variation in mode of fractionation.

Modified from Ash P. The influence of radiation on fertility in man. *Br J Radiol.* 1980;53:271–278, with permission.

Stillman et al. (155) studied girls less than 17 years old who were treated with 12–15 Gy, and they confirmed the relationship between ovarian failure and radiation dosage. Ovarian failure occurred in 17 of 25 girls (68%) whose ovaries received the full irradiation dosage. Five of 35 girls (14%) with at least one ovary at the edge of the abdominal treatment volume (estimated dosage 0.9–10 Gy with a mean of 2.9 Gy) experienced ovarian failure. None of 34 girls who received an estimated ovarian dosage of 0.5–1.5 Gy (mean 0.54 Gy), by having at least one ovary outside the treatment volume, had ovarian failure. It is possible that direct or scattered irradiation from the spinal component of craniospinal irradiation may produce ovarian damage (154,156).

To shield the ovaries from direct irradiation during, for example, pelvic irradiation from HL, an oophoropexy may be performed, where the ovaries are moved to a midline position in front of or behind the uterus or laterally to the iliac wings. The ovaries should be marked by the surgeon with clips that can later be identified by a simulator film. Central pelvic blocking at the time of “inverted Y” field will prevent direct irradiation, although scatter dose and transmitted dose will be inevitable. Medial or lateral transposition of the ovaries results in ovarian dosages of 8–10% and 4–5%, respectively, of the pelvic dosage (157). For most patients this is compatible with preservation of fertility, although there may be temporary amenorrhea.

Because RT is no longer used as a single modality to treat most forms of childhood cancer, the effects of chemotherapy must also be considered. Cyclophosphamide, nitrogen mustard (mechlorethamine), busulfan, procarbazine, and other alkylating agents and nitrosoureas are capable of causing ovarian dysfunction. In a study of 2498 survivors and 3509 siblings treated between 1945 and 1975, there was a 7% fertility deficit among female survivors as compared with their siblings. Forty-two percent of those with alkylating agent exposure and abdominal radiation experienced menopause by

the age of 31 years (158). In another study of 719 survivors treated between 1964 and 1988, there was a 15.5% failure to conceive (159). Mechlorethamine and procarbazine together are perhaps the most damaging of the agents. Substitution of cyclophosphamide for mechlorethamine appears to have significantly reduced the risk of ovarian dysfunction, which is further lessened by reduction in total dosage of both agents. In the CCSS, acute ovarian failure occurred in 8.3% of eligible survivors and premature nonsurgical menopause occurred in 8% of survivors as compared with 0.8% of siblings. Risk factors included attained age, exposure to increasing doses of RT to the ovaries, increasing alkylating agent score, and a primary diagnosis of HL. In a multivariable regression, the rate ratio for premature menopause was 4.3 for ovarian RT doses <1.0 Gy, 5.7 for doses 1.0 to <10 Gy, and 110 for doses of ≥10 Gy. Rate ratio related to alkylating agent score increased from 2.3 for low doses, to 5.8 for higher doses (160). Figure 19.16 shows the cumulative incidence of nonsurgical premature menopause (161).

In transplant recipients, TBI is associated with ovarian failure. Sklar et al. (162) documented amenorrhea and the failure to develop secondary sexual characteristics in prepubertal girls who received 10 Gy TBI and ovarian failure in all pubertal women, of whom 50% had menopausal symptoms. Sanders et al. (163) evaluated gonadal function in HSCT survivors 1–11 years after marrow transplantation. All 15 women less than 26 years old and 3 of 9 more than 26 years old who were treated with 200 mg/kg cyclophosphamide recovered normal gonadotropin levels and menstruation. Of 38 women who were prepared with 120 mg/kg cyclophosphamide and 920–1200 cGy TBI, 3 had normal gonadotropin levels and menstruation.

Table 19.10 reviews several ovarian late effects with respect to causative treatments, signs and symptoms, screening and diagnostic tests, and management and intervention (41).

Testes

Germ cell integrity, Leydig and Sertoli cell functioning, and the neuromuscular control of ejaculation are vulnerable to cancer therapy. Although fertility and hormone production are closely related in the ovary because of their dependence on the

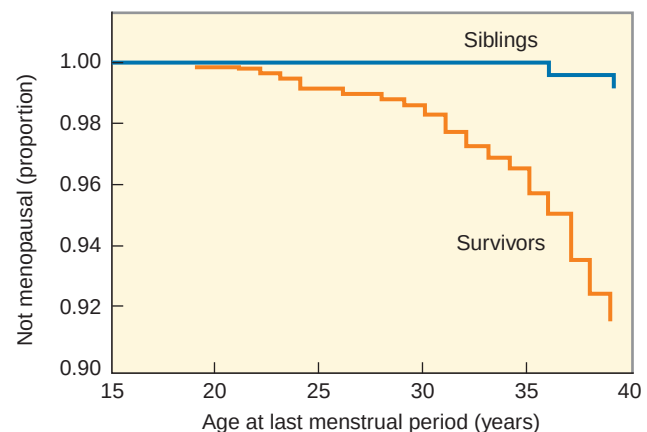


Figure 19.16 Cumulative incidence of nonsurgical premature menopause. (From Green DM, Sklar CA, Boice JD Jr, et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2009;27:2374–2381, with permission.)

Table 19.10
Evaluation of Patients at Risk for Late Effects: Ovarian

Late Effects	Causative Treatment			Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
	Chemotherapy	Radiation	Surgery			
Ovarian failure	Nitrogen mustard, cyclophosphamide, procarbazine, busulfan, melphalan, dacarbazine, carmustine, lomustine, ifosfamide	4–12 Gy Tolerance decreases with increasing age	Oophorectomy or oophorectomy	Delayed, arrested, or absent pubertal development, including breasts, female escutcheon, female habitus, vaginal estrogen effect, development of body odor and acne Changes in duration, frequency, and character of menses (cramping) Estrogen deficiency: hot flashes, vaginal dryness, dyspareunia, low libido, infertility	Tanner stage Leuteinizing hormone, follicle-stimulating hormone, estradiol: 1. Age 12 years 2. Failure of pubertal development 3. Baseline when fully mature 4. As needed Assess basal body temperature (midcycle elevation suggests ovulation) Dehydroepiandrosterone for failure of development	Hormone replacement (estrogen), anticipatory guidance regarding symptoms of estrogen deficiency and early menopause Referral to reproductive endocrinology Alternative strategies for parenting, early intervention (hormone replacement may prevent osteoporosis, atherosclerosis)

From Constine LS, Hobbie W, Schwartz C. Facilitated assessment of chronic treatment by symptom and organ systems. In: Schwartz C, Hobbie W, Constine L, et al., eds. *Survivors of Child and Adolescent Cancer: A Multi-Disciplinary Approach*. Berlin: Springer-Verlag; 2005:17–34, with permission.

ova and primary follicle, these functions differ in the testes because of the differing sensitivity of the spermatogonia and Leydig cells to cytotoxic therapy. Therefore, the effects of surgery, radiation, and chemotherapy must be considered in the context of various specific functions.

Pathophysiology

Spermatogenesis, or the formation of spermatozoa from immature germ cells, takes place in the seminiferous epithelium in the tubules. The least differentiated germ cells, the spermatogonia, divide to form spermatocytes. Immediately after formation, these cells undergo meiosis to form spermatids, which then metamorphose into motile spermatozoa. A constant supply of germ cell precursors is essential to the continuous production of spermatozoa, which are then transported through the lumen of the seminiferous tubules into the epididymis, where they are stored. Leydig cells are the primary androgen-secreting cells and account for at least 75% of the total testosterone produced by the normal man (164). Normal secretion of LH by the pituitary gland is essential for Leydig cell function; LH levels rise if inadequate androgen is produced. The physiologic role of FSH in spermatogenesis is to trigger an event in the immature testis that is essential for the completion of spermiogenesis. FSH levels rise if such spermatid differentiation is compromised. Once the process of spermatogenesis is established, it proceeds continuously as long as the supply of testosterone is available. Testosterone

also stimulates the development of male secondary sex characteristics and, through negative feedback, pituitary LH secretion. Measurement of testosterone production by the testis therefore is of major significance in the evaluation of testicular function.

Clinical Manifestations

There can be no question that RT can cause infertility. The testes can be irradiated directly, by scattered irradiation, or by radiation transmitted through shielding blocks. Because the spermatogonia are exquisitely sensitive to radiation, even small dosages can produce measurable damage. Depression of sperm counts is discernible at dosages as low as 15 cGy. This decrease in sperm counts may evolve 3–6 weeks after irradiation, and, depending on the dosage, recovery may take 1–3 years. The germinal epithelium is damaged by much lower dosages (less than 1 Gy) of RT than are Leydig cells (20–30 Gy) (165). Complete sterilization may occur with fractionated irradiation to a dosage of 1–2 Gy. Spermatocytes generally fail to complete maturation division at dosages of 2–3 Gy and are visibly damaged after 4–6 Gy with resulting azoospermia. Higher dosages are necessary to damage spermatids that will damage the more sensitive spermatocytes. At the highest dosages, permanent sterility is common. At lower dosages, this reduced sperm count is seen 60–80 days after exposure, which is the time at which maturation would otherwise be complete (166).

A variety of studies have shown that multiple small fractions of radiation are more toxic to spermatogenesis than a large, single fraction. This has been called the reverse fractionation effect. It is the result of the extreme radiosensitivity of the testicular germinal epithelium, the small number of stem cells, and rapid cell turnover (166). Table 19.11 summarizes the fractionated dose-related effect on spermatogenesis and Leydig cell function (152).

For abdominal RT, the effect of the testes results from scatter. Sklar et al. (167) evaluated the effect of 12-Gy radiation to the abdomen on testicular function of long-term ALL survivors and found 55% to have evidence of germ cell dysfunction. Scatter from abdominal radiation with dosages greater than 20 Gy for HL can cause transient elevation in

FSH and oligospermia, but there is no effect with lower dosages. Shalet et al. (168) evaluated 10 men treated for the Wilms tumor as a child. After scattered irradiation dosages of 2.7–9.8 Gy in 20 fractions, 8 (80%) had oligospermia or azoospermia and 7 (70%) had an elevated FSH. When patients are treated for HL, the scattered dosage to the testes from a mantle or para-aortic field is negligible. However, when the pelvis is treated, the calculated dosage depends on the relative location of the testes to the inguinal field, with dosages ranging from 3% to 10% without a specially designed testes shield and less than 1% with such a shield. Therefore, less than 2 Gy is delivered or scattered with well-designed shielding, and this dosage can be reduced further with the use of multileaf collimation. That is, the transmitted dosage

Table 19.11
Effect of Fractionated Testicular Irradiation on Spermatogenesis and Leydig Cell Function

Testicular Dosage (Gy)	Effect on Spermatogenesis	Effect on Leydig Cell Function
<0.1	No effect.	No effect
0.1–0.3	Temporary oligospermia Complete recovery by 12 months	No effect
0.3–0.5	Temporary azoospermia at 4–12 months after RT 100% recovery by 48 months	Variable
0.5–1.0	100% temporary azoospermia for 3–17 months after RT Recovery beginning at 8–26 months	Transient rise in FSH with eventual normalization
1–2	100% azoospermia from 2 months to at least 9 months Recovery beginning at 11–20 months, with return of sperm counts at 30 months	Transient rise in FSH and LH
2–3	100% azoospermia beginning at 1–2 months Some suffer permanent azoospermia; others show recovery starting at 12–14 months	Prolonged rise in FSH with some recovery Slight increase in LH
3–4	Reduced testicular volume 100% azoospermia Rare that can take 4–5 years All have reduced testicular volume	No change in testosterone Permanent elevation in FSH Transient rise in LH Reduced testosterone response to HCG stimulation
12	Permanent azoospermia Reduced testicular volume	Elevated FSH and LH Low testosterone Decreased or absent testosterone response to HCG stimulation Testosterone replacement may be needed to ensure pubertal changes
>24	Permanent azoospermia Reduced testicular volume	Effects more severe and profound than at 12 Gy Prepubertal testes appear more sensitive to the effects of radiation Replacement hormone treatment probably needed in all prepubertal cases

RT, radiotherapy; FSH, follicle-stimulating hormone; LH, luteinizing hormone; HCG, human chorionic gonadotropin.

Modified from Green DM. Fertility and pregnancy outcome after treatment for cancer in childhood or adolescence. *Oncologist* 1997;2:171–179, with permission.

through the leaves is less than that through cut blocks. The available data on males treated for HL suggest that fertility is either maintained or only transiently depressed.

The effects of RT are often combined with those of chemotherapy, particularly alkylating agents. The germinal epithelium of prepubertal testes is susceptible to damage produced by several chemotherapeutic agents including cyclophosphamide, nitrogen mustard, and procarbazine. Testicular biopsies after chemotherapy have demonstrated aplasia of the germinal epithelium. Spermatogenesis is highly sensitive to cyclophosphamide, with a dose-response relationship and an effect exacerbated by coadministration of other alkylating agents, such as procarbazine. This was illustrated in a study by Bokemeyer et al. (169) in which long-term gonadal toxicity was compared among survivors of HL and NHL. Both groups had received comparable median cumulative dosages of cyclophosphamide, but only the patients with HL received procarbazine. The incidence of gonadal toxicity was more than three times higher in the men in the HL group. The only men in the NHL group who had FSH elevation had received far higher dosages of cyclophosphamide than the mean (169). There has been a consensus that boys who receive less than 4 g/m² of cyclophosphamide without any other alkylating agents and without testicular or cranial radiation are likely to retain their fertility. However, in a report from Hobbie et al, even four cycles of cyclophosphamide, vincristine, procarbazine, prednisone (COPP)/ABV (doxorubicin, bleomycin, vinblastine), where procarbazine was given in addition to the cyclophosphamide, without RT, can result in sterility in males (170).

More recently, ifosfamide has been used as part of multimodality therapy for a variety of childhood cancers, often in combination with cyclophosphamide or abdominopelvic RT. Little is known about its long-term gonadal toxicity. Several studies have looked at small groups of male survivors and ifosfamide appears to be more sparing on fertility and a dose effect of >60 g may be important (171,172).

In a study of 248 adult male long-term survivors of childhood cancer, patient characteristics, treatment modalities, testicular size, and endocrinological parameters including inhibin B, LH, FSH, and testosterone were evaluated. Inhibin B was lower in survivors than controls and was the most sensitive discriminator between survivors and controls. Significantly decreased inhibin B levels and increased FSH levels were found in men treated for HL and NHL, acute-myeloid leukemia, neuroblastoma, and sarcoma as compared to other malignancies. Cumulative dosages of procarbazine and cyclophosphamide were the only independent chemotherapy-related predictors for the decrease of inhibin B levels and the increase of FSH levels. Age at the time of treatment did not influence post-treatment inhibin B or FSH levels (173). A retrospective study was conducted of gonadal and sexual function of 77 adult male survivors of childhood malignancies treated at a single center from 1970 to 1989 and followed for a median of 13 years. One third of the patients were treated for hematologic malignancies, one third for CNS tumors, and one third for other malignancies. Eleven patients needed androgen substitution after treatment for tumors of the HP region or ALL, including testicular irradiation or orchiectomy. In three patients the testicles were removed. The other eight had small testicles, those providing sperm samples had azoospermia, and sexual function was disturbed in most of them. Most of the remaining 66 patients had small testicles. Normozoospermia was found in 63%,

oligozoospermia in 20%, and azoospermia in 17%. Although there was a highly significant correlation between testicular volume and sperm test, 25% of patients with testicles of less than 10 mL had normozoospermia. Sexual function was normal in 46 patients. Twenty-one patients had no signs of gonadal dysfunction (174). In a retrospective cohort study, proven fertility (ever fathered a pregnancy) was evaluated by self-report among 213 men treated for ALL before the age of 18 on protocols of the Children's Cancer Group (CCG) and compared with male siblings. Proven fertility of male survivors was not different from that of controls (relative fertility (RF) = 0.95, 95% CI 0.63–1.43). However, married men treated before the age of 10 with high-dose (24 Gy) cranial RT, without spinal RT, had only 9% of the fertility of controls. High-dose cranial RT at older ages was not associated with a statistically significant fertility deficit (175). In a study from the Dana Farber Cancer Center, gonadal function was studied in 17 adult male survivors of childhood sarcomas treated with high-dose pulse cyclophosphamide therapy. Of the 17 males who underwent semen analysis, 10 (58.8%) had azoospermia, 5 (29.4%) had oligospermia, and only 2 (11.8%) were found to have a normal sperm count. All patients treated prior to the onset of puberty had an abnormal semen analysis. The two patients with normal sperm counts received the lowest doses of cyclophosphamide (<7.5 g/m²). The baseline FSH level was elevated in only 10 of 14 patients with abnormal sperm counts (71.4%). Testosterone levels were normal in 15 of 16 patients (93.8%); however, the baseline LH level was elevated in 6 of 15 patients with normal testosterone levels (40%). GnRH-stimulated LH levels were more than three times that of baseline in 13 of 14 patients (92.9%), suggesting some degree of Leydig cell insufficiency (176).

The limited data available indicate that chemical changes in Leydig cell function are observable after direct testicular irradiation. Shalet et al. (177) studied 11 boys irradiated with 24 Gy in 12–16 fractions for a testicular relapse of ALL. Abnormalities of gonadotropin secretion consistent with testicular damage were seen in nine (82%) of the boys. The mechanism for the increase in FSH is not entirely clear, but it is inversely proportional to the loss of germ cells in the seminiferous tubules. A study of boys who had received 24 Gy of testicular irradiation and who were followed up, on average, 3.8 years after irradiation found that basal testosterone levels were normal in the 12 prepubertal boys. Basal LH levels were normal in nine boys and elevated in three. Plasma testosterone response to human chorionic gonadotropin (HCG) was diminished in 10 and normal in 2. There were nine pubertal patients. Basal testosterone levels were normal in three and diminished in six. Response of testosterone to HCG was normal in two and diminished in seven. There was a correlation between age and response to HCG stimulation (178). Figure 19.17 depicts the relationship of radiation dosage to testosterone production as gleaned from several reports (164).

With the growing use of BMT to treat malignant and non-malignant diseases, the effects of the transplantation preoperative regimen on reproduction are of interest. High dosages of alkylating agents often are used in the treatment program. After 200 mg/kg of cyclophosphamide and marrow transplantation for aplastic anemia, 18 prepubertal boys who were 2–13 years old at the time of transplantation were evaluated, on average, 9 years after transplant. All boys over 13 years of age have shown normal progression through puberty and have

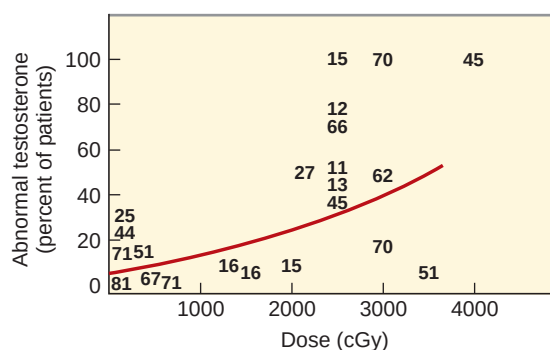


Figure 19.17 Percentage of patients with an abnormal testosterone value plotted against the stated radiation dosage to the testicles. The curve shows the best fit (extrapolated from the values by logistic regression). (From Izard M. Leydig cell function and radiation: a review of the literature. *Radiother Oncol.* 1995;34:1–8, with permission; see Fig. 4 for references from which data were obtained.)

demonstrated normal LH, FSH, and testosterone levels. In eight patients who underwent semen analysis, two are azoospermic and six are normal. Another population of prepubertal boys who received either TBI or TBI plus testicular irradiation have been studied. All boys who received TBI plus additional testicular irradiation of 18–24 Gy had delayed development and elevated FSH and LH levels with diminished testosterone levels. The majority of those who received TBI alone had normal LH levels with elevated FSH (179). Table 19.12 reviews several testicular late effects with respect to causative treatments, signs and symptoms, screening and diagnostic tests, and management and intervention (41).

Reproduction and Offspring

Many survivors of childhood cancer previously treated with cytotoxic therapy remain fertile, so pregnancy outcomes and the risk of cancer or genetic disease in offspring must be addressed. Young women who have been exposed to RT below the diaphragm are also at risk of impaired development of the uterus, which can result in adverse pregnancy outcomes. The magnitude of the risk is related to the radiation field, total dosage, and fractionation schedule. This can lead to premature labor and low-birth weight infants. Female long-term survivors treated with TBI and marrow transplantation are also at risk of ovarian follicular depletion, impaired uterine growth and blood flow, and early pregnancy loss and premature labor if pregnancy is achieved. Despite standard hormone replacement, the uterus of these young girls is often reduced to 40% of normal adult size. Uterine volume correlates with the age at which radiation was received (180).

With more childhood cancer survivors retaining their fertility, pregnancy outcome data are now available. In the CCSS, 5149 female participants were compared with 1441 female siblings and the RR for ever having been pregnant by survivors was 0.81. Risk factors included hypothalamic RT ≥ 30 Gy, ovarian/uterine RT dose of >5 Gy, high alkylating doses, treatment with lomustine or cyclophosphamide (161). In the same cohort, Green et al. (181) evaluated pregnancy outcomes of partners of male survivors. Among 4106 sexually active men, 1227 reported that they sired 2323 pregnancies, which resulted in 69% live births, 13% miscarriages, 13% abortions, and 5% unknown or in gestation at the time of

analysis. Compared with partners of male siblings, there is a lower chance of live births (RR = 0.77) but no significant differences of pregnancy outcome by treatment. The rate of miscarriage was higher for the partners of male survivors treated with more than 5000 mg/m² of procarbazine, which includes HL survivors treated with more than six cycles of MOPP or cyclophosphamide, vincristine, procarbazine, prednisone (COPP) chemotherapy.

In the NWTS, records were obtained for 427 pregnancies of more than 20 weeks' duration. In this group, there were 409 single and 12 twin live births. Early or threatened labor, malposition of the fetus, lower birth weight (less than 2500 g), and premature delivery (less than 36 weeks) were more common among women who had received flank radiation, in a dose-dependent manner (182). In the CCSS, offspring of female survivors who received uterine RT doses of >5 Gy were more likely to be premature or small for gestational age (161). However, there was no evidence for an increased risk of simple malformations, cytogenetic syndromes, or single-gene defects (160,183). In a report of 2198 offspring of adult survivors treated for childhood cancer between 1945 and 1975 compared with 4544 offspring of sibling control subjects, there were no differences in the proportion of offspring with cytogenetic syndromes, single-gene defects, or simple malformations. There was similarly no effect of type of childhood cancer treatment on the occurrence of genetic disease in the offspring. Survivors treated with abdominal RT or alkylating agents did not have a higher risk of offspring with genetic disease than did survivors not exposed to these agents (184). Similar results were reported in a single-institution study of 247 offspring of 148 cancer survivors (185). A large population-based study from Denmark, which included 1688 female survivors, found no differences between the survivors, their sisters or women in the general population for any adverse pregnancy outcomes with the exception of a 23% increased risk for spontaneous abortion related to RT (186).

Preservation of fertility and successful pregnancies may occur after BMT, although the conditioning regimens, which include TBI, cyclophosphamide, and busulfan, are highly gonadally toxic. In a group of 21 female patients who had received a bone marrow transplant in the prepubertal years, 12 (57%) were found to have ovarian failure when examined between the age of 11 and 21 years, and the association with busulfan was significant (187). Sanders et al. (188) evaluated pregnancy outcomes in a group of women treated with bone marrow transplant. Among 708 women who were postpubertal at the time of transplant, 116 regained normal ovarian function and 32 became pregnant. Among 82 women who were prepubertal at the time of transplant, 23 had normal ovarian function and 9 became pregnant. Of the 72 pregnancies in these 41 women, 16 occurred in those treated with TBI, and 50% resulted in early termination. Among the 56 pregnancies in women treated with cyclophosphamide without TBI or busulfan, 21% resulted in early termination. There were no pregnancies among the 73 women treated with busulfan and cyclophosphamide, and only 1 retained ovarian function.

Progress in reproductive endocrinology has resulted in the availability of several options for preserving or permitting fertility in patients about to receive potentially toxic chemotherapy or RT (189). For males, cryopreservation of spermatozoa before treatment is an effective method to circumvent the sterilizing effect of therapy. Although pretreatment semen quality

Table 19.12
Evaluation of Patients at Risk for Late Effects: Testicular

Late Effects	Causative Treatment			Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
	Chemotherapy	Radiation	Surgery			
Germ cell damage: oligospermia and azoospermia	Cyclophosphamide, 1–6 Gy nitrogen mustard, lomustine and carmustine, procarbazine, ifosfamide, busulfan, melphalan, dacarbazine		Orchiectomy or surgical manipulation	Testicular atrophy (softer and smaller), failure to impregnate	Tanner stage, inquire regarding previous sperm banking, determine testicular size and consistency LH, FSH, testosterone for failure of pubertal development, for base-line when sexually mature, and for failure to impregnate (repeat q3 years for possible recovery) Analysis of sperm at maturity or for failure to impregnate (repeat q3–5 years to assess recovery)	Instruct on testicular self-examination Anticipatory guidance regarding germ cell damage Referral to reproductive endocrinology Infertility counseling Alternative strategies for fathering
Leydig cell damage: testosterone deficiency	Cyclophosphamide Etoposide	>24 Gy to the testes (direct or scattered from pelvis)	Orchiectomy	Delayed, arrested, or absent pubertal development, pubic and axillary hair (female hair pattern), lack of penile and testicular enlargement, voice change, body odor and acne, testicular atrophy (softer and smaller)	LH and testosterone at age 13 years, failure of pubertal development, baseline if sexually mature, changes in libido or sexual performance	Testosterone replacement Anticipatory guidance regarding testosterone deficiency

FSH, follicle-stimulating hormone; LH, luteinizing hormone.

From Constine LS, Hobbie W, Schwartz C. Facilitated assessment of chronic treatment by symptom and organ systems. In: Schwartz C, Hobbie W, Constine L, et al., eds. *Survivors of Child and Adolescent Cancer: A Multi-Disciplinary Approach*. Berlin: Springer-Verlag; 2005:17–34, with permission.

in patients with cancer has been shown to be less than that noted in healthy donors, the percentage decline in semen quality and the effect of cryodamage to spermatozoa from patients with cancer are similar to that of normal donors (190–192). For those unable to sperm bank, newer technologies such as testis sperm extraction may be an option, as recently demonstrated for male survivors of germ cell tumors who had postchemotherapy nonobstructive azoospermia (193). Further micromanipulative technologic advances such as intracytoplasmic sperm injection may be able to render sperm extracted surgically, or even poor-quality cryopreserved spermatozoa from cancer patients, capable of successful fertilization (193,194). In prepubertal and postpubertal females, cryopreservation of ovarian cortical tissue or enzymatically extracted follicles and the in vitro maturation of prenatal follicles are of

potential clinical use. Another option available to the postpubertal female is the stimulation of ovaries with exogenous gonadotropins and retrieval of mature oocytes for cryopreservation. However, only a few oocytes can be harvested after stimulation of the ovaries (195). In vitro fertilization and subsequent embryo cryopreservation have also been successful. These options may not be readily available to the pediatric and adolescent patient, and the necessary delay in cancer therapy for ovarian stimulation or in vitro fertilization cycles often renders these interventions impractical (196). Furthermore, all these approaches harbor the risk that malignant cells will be present in the specimen and reintroduced in the patient at a later date. Those with hematologic or gonadal tumors would be at greatest risk for this eventuality (195,196).

With increased use of assisted fertility techniques in survivors of childhood cancer, the risk of congenital anomalies must be followed closely due to reports of increased anomalies in offspring born by in vitro fertilization or intracytoplasmic sperm injection (386–390) (197–201).

Risk of cancer in offspring remains a concern of childhood cancer survivors. In a study of 5847 offspring of survivors of childhood cancers treated in five Scandinavian countries, in the absence of a hereditary cancer syndrome (such as hereditary retinoblastoma), there was no increased risk of cancer (202). Preliminary data from the CCSS indicate that the risk of cancer in offspring was not significantly elevated, but this was based on a small number of offspring ($n = 11$). However, among survivors who themselves had second neoplasms or SMNs, risk of cancer in offspring was significantly elevated ($SIR = 15$) and much higher than for offspring of CCSS non-SMN cases ($SIR = 1.0$) (203). Further follow-up of offspring is needed to see whether patterns of cancer in offspring change with elapsed time.

Kidney

Pathophysiology

The progression of renal dysfunction after irradiation is grouped into three periods. The acute period (up to 6 months) is rarely symptomatic, and the glomerular filtration rate may be low. In the subacute period (6–12 months) the signs and symptoms include dyspnea on exertion, headaches, ankle edema, lassitude, anemia, hypertension, albuminuria, papilledema, elevated blood urea, and urinary abnormalities (granular and hyalin casts, red blood cells). Death might result from chronic uremia or left ventricular failure, pulmonary edema, pleural effusion, and hepatic congestion. In the chronic period (generally after 18 months) either benign or malignant hypertension is seen, depending on the severity of the renal insult. Chronic radiation nephropathy in its mildest forms may not be diagnosed until >10 years after therapy. Abnormalities may include only proteinuria and azotemia with urinary casts and mild or no hypertension.

The pathologic process is a progressive arteriolo-nephrosclerosis. The lesion involves the microvasculature with injury to the intercellular connections between the renal capillary and arterioles. There is degeneration and sclerosis of these arterioles, with narrowing or occlusion of the lumen and secondary degeneration of dependent structures (glomeruli, tubules). Associated changes in connective tissue include a thickened basement membrane, increased interstitial connective tissue, hyalinization, and fibrosis. Decreased perfusion of the kidney can occur with capillary and venous thrombosis and, eventually, necrosis. Withers et al. (204) used animal data to argue for a different pathogenesis, with the essential lesion involving the tubules and with secondary loss of nephrons and parenchymal cell depletion.

Clinical Manifestations

Radiation nephropathy is dose-related. Dosages of >25 Gy to both kidneys can cause renal failure at delayed intervals of more than 6 months (205). The effect of RT on the kidney has best been examined in survivors of pediatric Wilms tumor, where unilateral nephrectomy is also common. Unilateral irradiation at dosages of 14–20 Gy may reduce the ability of the contralateral (untreated) kidney to undergo compensatory

hypertrophy. Ritchey et al. (206) examined the spectrum of renal failure in 55 patients among 5823 patients treated for the Wilms tumor from the NWTSG. The incidence of renal failure at 16 years was 0.6% for patients with unilateral disease and 13% for patients with bilateral disease. The most common causes of renal failure were bilateral nephrectomy for persistent or recurrent tumor, progressive tumor in the remaining kidney without nephrectomy, Denys–Drash syndrome, and radiation nephritis. Long-term renal function was subsequently evaluated in 81 children with synchronous bilateral Wilms tumor who received treatment. With a median follow-up of 27 months, 28 patients had elevated blood urea nitrogen or serum creatinine levels. Of those, 18 had moderate and 10 had marked renal insufficiency. There was no dose–response relationship for chemotherapy, and tumor recurrence necessitating additional surgery increased the risk of renal dysfunction. Those with less than one kidney remaining had more marked dysfunction (207). In a study of 40 Wilms tumor survivors treated in England with combined surgery and chemotherapy, with and without radiation therapy, no significant nephrotoxicity was seen (208). A comprehensive evaluation of end-stage renal disease (ESRD) was ascertained in 5910 patients enrolled in NWTSG during 1969 to 1994. Cumulative incidence of ESRD at 20 years from diagnosis of unilateral Wilms tumor was 74% for patients with the Denys–Drash syndrome, 36% for patients with WAGR, 7% for male patients with hypospadias or cryptorchidism, and 0.6% for patients with none of these conditions. The incidence of ESRD after diagnosis of bilateral Wilms tumor was 50% for the Denys–Drash syndrome, 90% for WAGR, 25% for male genitourinary anomaly, and 12% for those without these conditions. ESRD in patients with WAGR or GU anomalies tended to occur relatively late, often during or after adolescence. Figures 19.18 and 19.19 show the cumulative incidence curves for unilateral and bilateral Wilms tumor, respectively, from this analysis (209). This confirms an earlier study from this group showing higher risk for patients with these predisposition syndromes. In that earlier study,

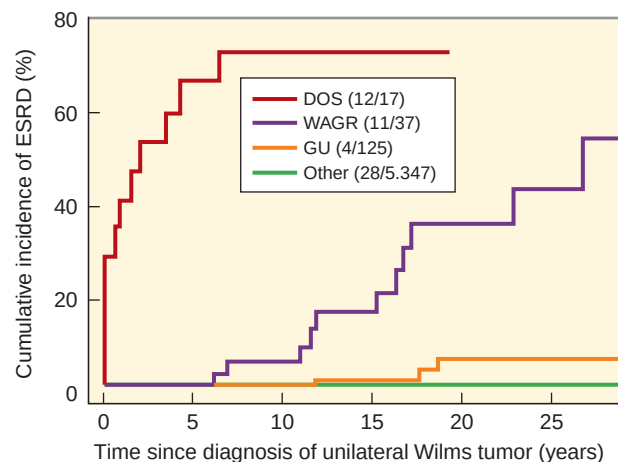


Figure 19.18 Cumulative incidence of end-stage renal disease in survivors of unilateral Wilms tumor. (From Breslow NE, Collins AJ, Ritchey ML, et al. End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. *J Urol.* 2005;174:1972–1975, with permission.)

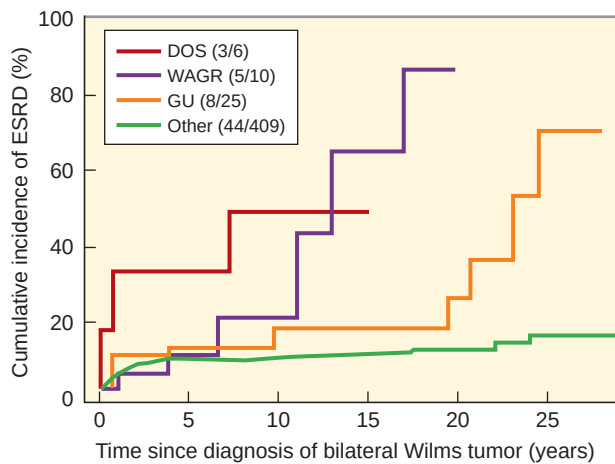


Figure 19.19 Cumulative incidence of end-stage renal disease in survivors of bilateral Wilms tumor. (From Breslow NE, Collins AJ, Ritchey ML, et al. End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. *J Urol*. 2005;174:1972–1975, with permission.)

presence of intralobar nephrogenic rests in the unilateral disease group without a defined syndrome resulted in an elevated cumulative risk of renal failure at 20 years of 3.3%, compared with 0.7% without this pathologic finding (210).

Dose–volume histograms of renal radiation correlated with various renal function endpoints will be necessary for accurate determination of functional tolerance levels. In a review of several reports, Cassady (205) determined a threshold dosage of approximately 15 Gy delivered with conventional fractionation (in the absence of interactive drugs and underlying renal disease) as a reasonable estimate, and dosages of >25 Gy to the total renal mass are likely to eliminate useful renal function in patients followed for sufficiently long periods of time (Fig. 19.20).

Late renal dysfunction has been documented after TBI before BMT for childhood malignancies. Tarbell et al. (211) reported a 35% incidence in children with ALL and a 71% incidence in children with neuroblastoma who received fractionated TBI (12–14 Gy over 3–4 days). All patients had anemia, hematuria, and elevated blood urea nitrogen and creatinine levels. Renal biopsies in two patients showed changes

consistent with radiation nephropathy or hemolytic uremic syndrome. The onset of renal dysfunction after TBI is 3–6 months. Therefore, the time course is similar to that of classically described radiation nephritis. Whereas Tarbell et al. (211) found that renal injury occurs at a young age, Lonnerholm et al. (212) found an 18% incidence of renal dysfunction in autografted children without an apparent age effect. With more modern techniques and longer interfraction intervals for TBI, less than 15% of children will develop chronic renal insufficiency or hypertension, and the risk is related to both the nephrotoxic agents used and the TBI fractionation scheme and interfraction interval (148,213). Of interest is that proximal tubular dysfunction is more commonly abnormal than distal tubular function.

Chemotherapy can also adversely affect renal function. Cisplatin at dosages greater than 200 mg/m² can result in glomerular or tubular injury and renal insufficiency. Other nephrotoxic agents such as aminoglycosides, amphotericin, and ifosfamide may further increase risk. Effects can be seen acutely and may progress after completion of therapy (214). A few small studies examining children treated with carboplatin have evaluated short- and long-term nephrotoxicity related to carboplatin, finding none significant to date (215,216).

Ifosfamide can also cause glomerular and tubular toxicity, with renal tubular acidosis, or the Fanconi syndrome. Dosages greater than 60 g/m², age less than 5 years at the time of treatment, and combination with cisplatin and carboplatin increase risk. Abnormalities in glomerular filtration are less common and when found are not clinically significant. More common are abnormalities with proximal greater than distal tubular function, although the prevalence of these findings is uncertain, and further study of larger cohorts with longer follow-up is needed (217–219). A study examining grades 3–4 ifosfamide-induced nephrotoxicity among adult and pediatric patients found a prevalence of 17% in both, and neither age nor cumulative ifosfamide dose was a risk factor (220). Table 19.13 reviews several renal late effects with respect to causative treatments, signs and symptoms, screening and diagnostic tests, and management and intervention (41).

Digestive Tract

The esophagus, stomach, pancreas, and small and large intestines are irradiated in a variety of pediatric malignancies. Although primary tumors of these organs are rare in childhood,

Figure 19.20 Radiation dose–response curve for the occurrence of symptomatic radiation nephropathy generated from data presented in several reports. An approximate threshold dosage of 15 Gy (conventional fractionation) is seen, and a plateau is noted beyond dosages of 30 Gy. (Modified from Cassady JR. Clinical radiation nephropathy. *Int J Radiat Oncol Biol Phys*. 1995;31:1249–1256, with permission.)

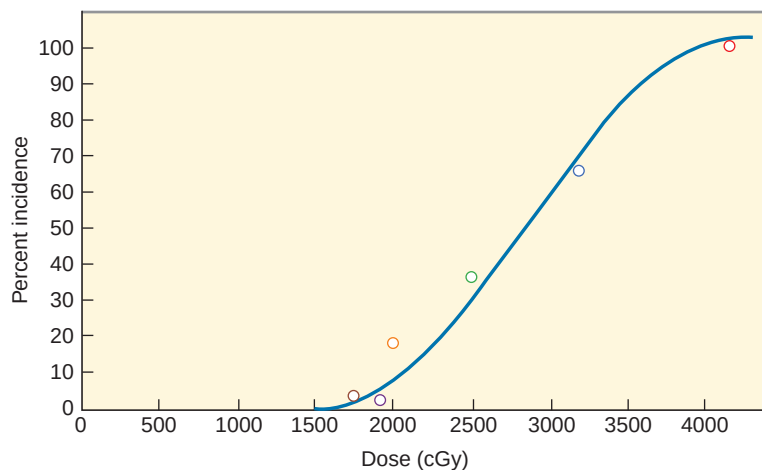


Table 19.13

Evaluation of Patients at Risk for Late Effects: Genitourinary

Late Effects	Causative Treatment		Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
	Chemotherapy	Radiation			
Glomerular dysfunction	Cisplatin, carboplatin		Asymptomatic or with fatigue, poor linear growth, anemia, oliguria	Annual: blood pressure, height, weight, hemoglobin and hematocrit, urinalysis, creatinine, BUN; creatinine clearance baseline and q3 years Same as for glomerular dysfunction	Low-protein diet, dialysis, renal transplant
Hypoplastic kidney and renal arteriosclerosis		20–30 Gy 10–15 Gy with chemotherapy	Fatigue, poor linear growth, hypertension, headache, edema (ankle, pulmonary), albuminuria, urinary casts, hepatomegaly		Same as for glomerular dysfunction
Tubular dysfunction Nephrotic syndrome	Cisplatin, carboplatin, ifosfamide	20–30 Gy	Seizures ($\downarrow$ Mg), weakness ($\downarrow$ PO ₄), glycosuria, poor linear growth Proteinuria Edema	Same as for glomerular, and Mg, PO ₄ (24-hour urine for Ca, PO ₄) Urinalysis q year, blood pressure q yr Serum protein, albumin, Cr, BUN	Mg supplement PO ₄ supplement Low-salt diet Diuretics
Bladder: fibrosis or hypoplasia (reduced bladder capacity)	Cyclophosphamide Ifosfamide	> 30 Gy prepubertal > 50 Gy postpubertal	Urgency, frequency, dysuria, incontinence, (nocturia), pelvic hypoplasia	24-hour urine for protein, Cr Urinalysis q year (cystoscopy, intravenous pyelogram, ultrasound: volumetrics)	Exercises to increase bladder capacity Surgical referral
Hemorrhagic cystitis	Cyclophosphamide Ifosfamide	RT enhances chemotherapy effect	Hematuria, frequency, urgency, dysuria, bladder tenderness	Urinalysis q year to rule out UTI, renal calculi Cystoscopy if hematuria on two exams	Transfusion, antispasmodics, formalin, counsel regarding risk of bladder cancer
Prostate		40–60 Gy (lower dosages inhibit development; higher dosages cause atrophy)	Decreased volume of seminal fluid Hypoplastic or atrophied prostate	Examination of prostate gland Semen analysis $\times$ 1 (ultrasound)	Counsel regarding possible infertility caused by inadequate seminal fluid Monitor prostate (exam, possibly prostate-specific antigen)
Vagina: fibrosis, diminished growth	Actinomycin D, doxorubicin enhance RT effect	> 40 Gy	Painful intercourse, vaginal bleeding, small vaginal vault	Pelvic exam (possibly under anesthesia) for baseline, during puberty, and as needed	Dilations Reconstructive surgery Potential need for cesarean section
Uterus: fibrosis, decreased growth		> 20 Gy (prepubertal) 40–50 Gy (postpubertal)	Multiple sponta neous abortions Low-birth weight infants Small uterus	Pelvic exam for baseline, at puberty, then annually	Possibly endometrial biopsy Counsel regarding pregnancy
Ureter: fibrosis		50–60 Gy	Frequent UTIs, pelvic hypoplasia, hydronephrosis	Urinalysis q year Urethrogram	UTI prophylaxis
Urethra: strictures		> 50 Gy GU	Frequent UTIs, dysuria, stream abnormalities	Urinalysis q year Voiding cystogram	UTI prophylaxis Surgical intervention

BUN, blood urea nitrogen; RT, radiotherapy; UTI, urinary tract infection; GU, genitourinary.

From Constine LS, Hobbie W, Schwartz C. Facilitated assessment of chronic treatment by symptom and organ systems. In: Schwartz C, Hobbie W, Constine L, et al., eds. *Survivors of Child and Adolescent Cancer: A Multi-Disciplinary Approach*. Berlin: Springer-Verlag; 2005:17–34, with permission.

they may be incidentally irradiated in the treatment of HL and NHL, the Wilms tumor, neuroblastoma, soft tissue sarcomas, and bone tumors.

The direct effect of digestive tract irradiation is loss of regenerating cells lining the gut. Radiation damage of the fine vasculature of the digestive tract may progress to obliterative vasculitis, with the ultimate development of ischemia (221). Acute radiation injury results from the depletion of normally proliferating cell, mucosal sloughing, villus shortening, and subsequent inflammatory infiltration and edema. The patient may suffer from odynophagia, dysphagia, abdominal pain, or diarrhea, depending on the site irradiated. Late radiation injury to the digestive tract is attributable to vascular injury. As the radiation vasculopathy progresses to obliteration, necrosis, ulceration, stenosis, or perforation may result (221). Late radiation enteropathy is characterized by malabsorption, pain, and recurrent episodes of bowel obstruction, as well as perforation, infection, and death. The onset is generally 6–24 months after the conclusion of RT. Donaldson et al. (222) evaluated 44 children who received abdominal irradiation for lymphoma, the Wilms tumor, or other malignancies. Eleven percent of the entire population and 36% of the long-term survivors developed bowel obstruction. Contributing factors included prior abdominal surgery, the use of concurrent actinomycin D, and very young age. Late radiation injury to the digestive tract is attributable to vascular injury. Necrosis, ulceration, stenosis, and perforation can occur and are characterized by malabsorption, pain, recurrent episodes of bowel obstruction, perforation, and infection (221). In general, fractionated dosages of 20–30 Gy can be delivered to the small bowel without significant long-term morbidity. Dosages greater than 40 Gy are needed to cause bowel obstruction or chronic enterocolitis (223). Sensitizing chemotherapeutic agents such as actinomycin D and anthracyclines can increase this risk. In a report of 42 survivors of the Wilms tumor treated from 1968 to 1994 with megavoltage RT, actinomycin D, and vincristine with or without doxorubicin, the actuarial incidence of bowel obstruction at 5, 10, and 15 years was 9.5%, 13.0%, and 17.0%. Of 23 patients, 5 irradiated within 10 days of surgery and 1 of 19 irradiated after 10 days developed bowel obstruction (83). In a report from the Intergroup Rhabdomyosarcoma Study Committee, extended follow-up of 86 children and adolescents who were treated for paratesticular rhabdomyosarcoma on the Intergroup Rhabdomyosarcoma Studies I and II (IRS I–II) revealed that 4 patients who underwent abdominal RT had chronic diarrhea (224).

The prevention and management of radiation digestive tract injury relies primarily on the exclusion of normal tissues from the treatment beam whenever possible. For the esophagus, stomach, and large bowel, this usually relies on beam direction planning and patient positioning. For the mobile portions of the small bowel, the clinician also evaluates the prone versus supine position; the use of compression, tilt tables, and false table tops; surgical placement of omental slings and absorbable mesh; and other techniques. The patient with acute radiation enteropathy may be helped by symptomatic interventions. Medical therapy for late-onset radiation enteritis is unsatisfactory and has relied on intermittent steroids, sulfasalazine, parenteral nutrition, and other supportive care. Surgical resection of damaged or obstructed bowel may be used, but there is a high incidence of anastomotic dehiscence, operative mortality, and reobstruction (221).

Pancreas

In the course of abdominal RT or TBI, damage to the islet cells of the pancreas can occur and there is now emerging evidence on the increased risk of diabetes mellitus (DM) in long-term survivors of childhood cancer. This may be the result of direct cytotoxicity to pancreatic cells from abdominal RT, but may also be a long-term implication from the metabolic syndrome, which was discussed earlier in this chapter. In a study of 8599 survivors from the CCSS, DM was reported in 2.5% of the survivors compared with 1.7% of the siblings. After adjustment for body mass index, age, sex, race/ethnicity, household income, and insurance, the survivors were 1.8 times more likely than the siblings to report DM. In adjusted models, TBI was associated with a sevenfold increased risk, abdominal irradiation with a 2.7-fold increased risk, alkylating agents with a 1.7-fold increased risk, and age 0–4 years at diagnosis with a 2.4-fold increased risk (225).

Liver

The clinical signs and symptoms of radiation hepatitis include abdominal pain, increased girth, ascites, weight gain, jaundice, and elevation of liver enzymes. Severe thrombocytopenia can be seen, most commonly in children who have also been treated with actinomycin D.

In the acute phase of radiation injury (less than 3 months after irradiation), the liver is hyperemic and enlarged in the treated area (226). Dilatation and sinusoidal congestion accompanied by atrophy around the central vein of the lobule may be seen. As the chronic phase evolves (more than 3 months after treatment), characteristic central vein lesions develop. The lumen narrows progressively with fibrotic changes involving the intima, leading to increasing sinusoidal congestion and liver cell atrophy. Inflammatory exudate is uniformly absent. After 6 months and up to 6 years after irradiation, the distance between the central vein and portal space decreases, indicating the atrophy of hepatocytes. Nodules of regeneration are rare. Central veins become small and inconspicuous, and lobules are distorted or collapsed. Concentric fibrosis in the portal spaces around the portal veins occurs. This pathologic picture has been classified as veno-occlusive disease, a process that is accelerated after BMT and can be seen with weeks of conditioning with TBI; with modern chemotherapy and RT, it is the most critical hepatic toxicity. It is characterized by occlusion and obliteration of the central veins of the hepatic lobules, with retrograde congestion and secondary necrosis of hepatocytes. Although there may be a dose effect of RT, this complication is also reported after conditioning regimens with cyclophosphamide and busulfan alone. Preexisting hepatic disease, including infection, and GVHD may increase the risk (227). Of particular interest is a report from the IRS on the occurrence of veno-occlusive disease in children treated with vincristine, actinomycin D, and cyclophosphamide. Of 821 patients, 10 patients (1.2%) treated according to IRS-IV had evidence of veno-occlusive disease. This incidence was greater than in previous studies and considered to be associated with an escalation of the cyclophosphamide dosage in IRS-IV (228).

The cumulative dosage, volume of liver irradiated, and additional treatment with chemotherapy are important risk factors for hepatic fibrosis. Radiation hepatopathy can occur

with dosages of 30–40 Gy to the entire liver, but significantly higher dosages to focal volumes can be given with few clinical complications (229). Lower dosages can be associated with hepatopathy if the child is also receiving sensitizing chemotherapy. This is evident in a series of children treated for the Wilms tumor, neuroblastoma, or hepatoma with RT to the liver and chemotherapy. Fractionated dosages to 12–25 Gy caused abnormal liver function tests and radionuclide scans in 50% of patients, 25–35 Gy caused abnormalities in 63%, and more than 35 Gy was toxic in 86%. In the NWTSG, 16 out of 303 patients (5.3%) had liver toxicity. The dosages of radiation to portions of the liver ranged from less than 15 Gy to more than 30 Gy, with right flank or whole abdomen radiation increasing risk significantly more than isolated left flank radiation. The injury was manifest as thrombocytopenia, hepatomegaly, ascites, and, in four cases, hepatic failure. It was interesting to note that 8.6% of patients receiving right flank or whole abdomen irradiation exhibited toxicity, as opposed to 2% of patients receiving left flank irradiation. All patients received chemotherapy, including vincristine, actinomycin D, and, in some patients, doxorubicin (230).

The volume of liver irradiated influences tolerance to dosage. The regenerating liver (e.g., after partial hepatectomy) appears to be even less tolerant to irradiation. New developments in three-dimensional organ imaging, in combination with the available clinical data, allow reasonable predictions of the probability of liver injury as a function of radiation dosage (231).

Table 19.14 reviews several gastrointestinal and hepatic effects with respect to causative treatments, signs and symptoms, screening and diagnostic tests, and management and intervention (41).

Eye

The eye is composed of several tissues that vary greatly in their radiosensitivity. Acute reactions include iridocyclitis, keratitis, conjunctivitis, and blepharitis. Delayed reactions, which generally occur after 6 months, include retinopathy, optic neuropathy, lacrimal gland atrophy or duct stenosis, glaucoma resulting from iridocyclitis, cataract, corneal vascularization and scarring, conjunctival telangiectasia, and eyelid atrophy with entropion or ectropion.

Retina

Radiation retinopathy is characterized by a slowly progressive microangiopathy, which may result in macular edema, capillary nonperfusion, retinal and disc neovascularization, vitreous hemorrhage, and traction retinal detachment. The microangiopathic changes may appear 6 months to 3 years after therapy (232). Visual loss is painless unless neovascular glaucoma develops. Using 1.8–2 Gy per fraction, the threshold for injury is 46 Gy, although the frequency is rare below dosages of 60 Gy. As fraction size increases beyond 2.5 Gy, the frequency of injury increases (233). It is important to note that certain chemotherapeutic agents can cause retinal toxicity, and the risk is higher in children with impaired renal function who thereby accumulate drugs (234).

Lacrimal Apparatus

Radiation may cause scarring of the canaliculi and puncta, ectropion of one punctum, failure of the lacrimal pump sec-

ondary to decreased eyelid mobility, and reflex lacrimation associated with ectropion, entropion, or conjunctival keratinization (232). Secondary symptoms can develop within months and be fully developed by 1 year. The patient may suffer from excess tearing, a foreign body sensation, and photophobia secondary to corneal epithelial damage. When injury is severe, corneal ulceration, opacification, and vascularization sufficient to cause visual loss occur. Injury is rare at dosages less than 45 Gy and common above 60 Gy (235).

Lens

Whereas retinitis and lacrimal duct abnormalities are caused only by high RT dosages, low-dose irradiation damages the germinal zone of the epithelium on the equator of the lens (236). The radiation-induced cataract is a central, posterior subcapsular opacity that appears as a dot at the posterior pole of the lens. As the cataract enlarges, small vacuoles and granules appear around it. With continued enlargement, the opacity develops a clear center, giving it a doughnut-shaped appearance (232). This progresses to the anterior pole, and the cortex then becomes opaque. Merriam and Focht (237) reported an evaluation of the dose–response relationship in 1958. After single doses of 200 R, abnormalities were detected but were not clinically significant until dosages exceeded 400 R. With fractionated irradiation, a 60% frequency (progressive in one half) was seen after 750–950 R, whereas 100% was seen after 1150 R. Other investigators have suggested a threshold for damage of about 2000 R (238). Reevaluation of atomic bomb survivor data suggests a 20–40% incidence of radiation cataract after a single eye dosage of 5 Gy mixed photons and neutrons (239). The interval to abnormality in various studies is 2–3 years but ranges from 6 months to 35 years depending on dosage.

Patients treated with TBI are also at greater risk of cataracts. Risk ranges from approximately 10% to 60% at 10 years depending on the total dosage and fractionation, with a shorter latency period and more severe cataracts noted after single fraction and higher-dose or higher-dose rate TBI. Deeg et al. (240) reported that 80% of patients were affected after a single dose of 10 Gy but only 19% after fractionated regimens to 12–15 Gy. In a report from France on 494 patients undergoing TBI, high instantaneous dose rate (more than 9 cGy/min) was identified as the main risk factor for cataractogenesis (241).

Corticosteroids and GVHD may further increase risk. Young children may actually be at a lower risk than adolescents and adults (453, 454, 457) (242–244). Belkacemi et al. (245) reported on cataracts after TBI in a group of 1063 survivors of leukemia treated with HSCT from the European Group for Blood and Marrow Transplantation. The overall 10-year cataract incidence was 50%: 60% in those who were treated with single-fraction TBI, 43% in those treated with six fractions or less, and only 7% in those treated with more than six fractions of TBI. In those who received lower-dose rate RT (0.04 Gy/min or less), the 10-year incidence was 30%, compared with 59% in those treated with more than 0.04 Gy/min. These data are shown in Figure 19.21. Independent risk factors for cataracts in multivariate analysis were age greater than 23 years, higher-dose rate RT (more than 0.04 Gy/min), allogeneic transplantation, and corticosteroid exposure of more than 100 days.

Radiation-induced cataracts are one of the reported complications of retinoblastoma treatment. Based on first principles,

Table 19.14
Evaluation of Patients at Risk for Late Effects: Gastrointestinal

Late Effects	Causative Treatment			Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
	Chemotherapy	Radiation	Surgery			
Enteritis	Actinomycin D, doxorubicin enhance RT effect	>30 Gy	Abdominal surgery enhances RT effect	Abdominal pain, diarrhea, decreased stool bulk, emesis, weight loss, poor linear growth	Height and weight q year, Stool guaiac q year, CBC with MCV q year, total protein and albumin q3–5 years, absorption tests, vitamin B ₁₂ level, and contrast studies	Dietary management, refer to gastroenterologist
Adhesions		RT enhances effect	Laparotomy	Abdominal pain, bilious vomiting, hyperactive bowel sounds	Abdominal radiograph	NPO, gastric suction, adhesion lysis
Fibrosis: esophagus (stricture)	Actinomycin D, doxorubicin (RT enhancers)	40–50 Gy	Abdomen	Dysphagia, weight loss, poor linear growth	Height and weight q year, CBC q year, barium swallow and endoscopy as needed	Esophageal dilation Antireflux surgery
Fibrosis: small intestines		>40 Gy	Abdomen	Abdominal pain, constipation, diarrhea, weight loss, obstruction	Height and weight q year, CBC with MCV q year, serum protein and albumin q3–5 years, upper GI, small bowel biopsy	High-fiber diet, decompression, resection, balloon dilation
Fibrosis: large intestine, colon		>40 Gy	Abdomen	Abdominal colic, rectal pain, constipation, melena, weight loss, obstruction	Height and weight q year, rectal exam, stool guaiac q year, lower GI, colonoscopy	Stool softeners, high-fiber diet
Hepatic fibrosis and cirrhosis	MTX, actinomycin D, 6MP 6TG	>30 Gy	Massive resection	Itching, jaundice, spider nevi, bruising Portal hypertension: esophageal varices, hemorrhoids, hematemesis Encephalopathy	Height and weight q year, CBC, reticulocyte count, platelets q year, liver function tests q2–5 years Hepatic screen Liver biopsy Endoscopy	Hepatitis screen (hepatitis A, B, C/CMV), diuretics, liver transplant Varices: sclerosis, vascular shunting

RT, radiotherapy; CBC, complete blood cell count; MCV, mean cell volume; GI, gastrointestinal; 6MP, 6-mercaptopurine; 6TG, 6-thioguanine; NPO, nothing per mouth.

From Constine LS, Hobbie W, Schwartz C. Facilitated assessment of chronic treatment by symptom and organ systems. In: Schwartz C, Hobbie W, Constine L, et al., eds. *Survivors of Child and Adolescent Cancer: A Multi-Disciplinary Approach*. Berlin: Springer-Verlag; 2005:17–34, with permission.

one might think that an unblocked anterior beam for all or part of the treatment, as opposed to an angled lateral lens-sparing setup, would have a higher incidence of cataract formation. However, these data are equivocal, and cataracts may occur after either technique (246). This is almost certainly because variations in daily setup make complete lens sparing unlikely with

most lateral approaches. If a radiation-induced cataract causes visual impairment in the patient with retinoblastoma, it may be removed. Persistent tumor is a contraindication to cataract removal. Final visual acuity after cataract removal depends on the presence or absence of macular tumor, the existence of radiation-induced keratopathy or retinopathy, severe amblyopia, a

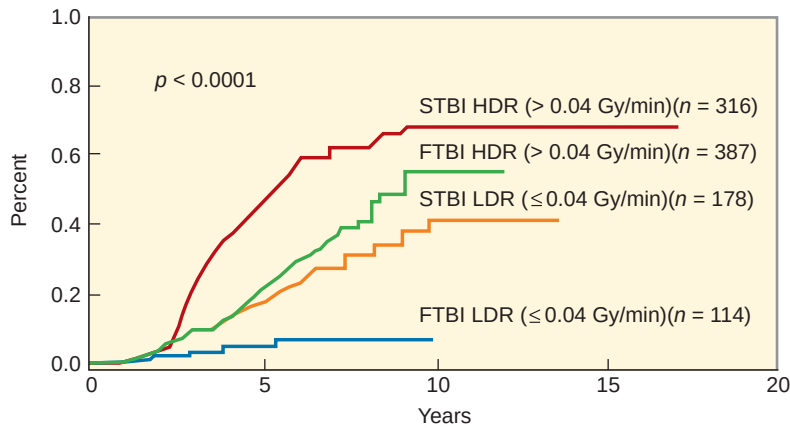


Figure 19.21 Product-limit estimates for cataract incidence according to fractionation and dose rate. FTBI, fractionated total body irradiation; HDR, high dose rate (>0.04 Gy/min); LDR, low dose rate (≤ 0.04 Gy/min); STBI, single-dose total body irradiation. (From Belkacemi Y, Labopin M, Vernant JP, et al. Cataracts after total body irradiation and bone marrow transplantation in patients with acute leukemia in complete remission: a study of the European Group for Blood and Marrow Transplantation. *Int J Radiat Biol Oncol Phys.* 1998;41(3):659–668, with permission.)

history of rhegmatogenous retinal detachment, and tumor control. In the absence of negative factors, visual acuity after cataract removal would be expected to be in the 20/20 to 20/50 range (247).

Optic Nerve

Injury to the distal nerve end produces ischemic optic neuropathy, whereas more proximal injury produces retrobulbar optic neuropathy. These are potentially blinding complications. The peak onset is 1–2 years, manifested by visual field deficits or central scotoma (248).

Lid

Rounding of the lid margins is not seen below 40 Gy, and ectropion is uncommon below 60 Gy. The eyelash usually is spared by anterior megavoltage beams so that it may remain partially intact (232).

Orbit

For survivors of retinoblastoma, a small orbital volume may result after either enucleation or RT. Age less than 1 year may increase risk, but this is not consistent across studies (249). Better management of prosthetic implants and newer methods of delivering RT are likely to reduce risk (249). Newer strategies for treating retinoblastoma use chemotherapy to reduce tumor size, combined with local ophthalmic therapies that include thermotherapy, cryotherapy, and plaque radiation. These strategies may be associated with local complications that can affect vision, particularly tumors located near the macula and fovea increase the risk of complications leading to visual loss (250–253).

One group of patients at risk for all of the aforementioned complications are survivors of orbital rhabdomyosarcoma, who are at risk of dry eye, cataract, orbital hypoplasia, ptosis, retinopathy, keratoconjunctivitis, optic neuropathy, lid epithelioma, and impairment of vision after RT dosages of 30–65 Gy. The higher dosages (more than 50 Gy) are associated with lid epitheliomas, keratoconjunctivitis, lacrimal duct atrophy, and severe dry eye. Retinitis and optic neuropathy may also occur after dosages of 50–65 Gy, and even at lower total dosages if the individual fraction size is greater than 2 Gy (248). Cataracts are reported after lower dosages of 10–18 Gy (236,254).

Table 19.15 reviews several late effects involving the eye with respect to causative treatments, signs and symptoms,

screening and diagnostic tests, and management and intervention (41).

Hearing

The auditory apparatus may be irradiated during the treatment of brain tumors, aerodigestive tract malignancies, soft tissue sarcomas, and lymphoma. Fractionated dosages of more than 50 Gy can produce permanent changes in the temporal bone and adjacent soft tissues, including empty lacunae in the bone, resorption, absent marrow, and replacement by fibrous tissue. Temporal bone osteoradionecrosis is extremely rare with modern pediatric RT technique. Radiation changes in the external auditory canal may include thickening of the epithelium overlying the tympanic membrane, atrophic ceruminous glands, and absent hair follicles. On occasion, the combination of abnormal epithelium of the external auditory canal and bacterial overgrowth can produce a persistent otitis externa necessitating the use of wicks, otic antibiotics, and otic steroid preparations (255).

Cranial irradiation alone rarely has a significant effect on hearing. RT can result in cochlear damage, with sensorineural hearing loss (SNHL) occurring in about 25% of patients treated with dosages approaching 60 Gy, but SNHL has been considered rare at lower RT dosages in the absence of cisplatin. Recent data suggest that cochlear dosages of 30–50 Gy can cause intermediate-frequency SNHL and that CSF shunting procedures increase the risk (256). At dosages as low as 270 mg/m², cisplatin can result in hearing loss when combined with cranial RT dosages of 40–50 Gy (257). The sequence of chemoradiotherapy appears to influence risk. Risk and severity of ototoxicity are greater when cisplatin is administered after cranial radiation (Fig. 19.22) (258).

Hearing loss in the speech range (0.5–3 kHz), which may compromise language reception and expression, is reported with cumulative cisplatin dosages of at least 360 mg/m², and a 25% incidence of hearing loss is reported with dosages greater than 720 mg/m² in the absence of any RT. Fifty percent of children treated with cisplatin dosages greater than 450 mg/m² have SNHL in the high-frequency range (6–8 kHz). Younger age at the time of administration increases risk (258,259). Carboplatin may be less ototoxic, but further follow-up in patients treated with high cumulative dosages is necessary before a clear dose threshold can be established (259–261). A German study of children treated for neuroblastoma demonstrated the influence of both cisplatin and carboplatin on hearing, again in

Table 19.15

Evaluation of Patients at Risk for Late Effects: Eye

Late Effects	Causative Treatment		Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
	Chemotherapy	Radiation			
Lacrimal glands: decreased tear production	5FU	>40 Gy	Dry, irritated red eye, foreign body sensation, positive fluorescein staining	Penlight or slit lamp exam, fluorescein staining	Tear replacement, occlude lacrimal puncta, education regarding avoiding rubbing lids when puncta plug is intact
Lacrimal duct: fibrosis	5FU	>50 Gy	Tearing	Ophthalmic exam	Dilation of duct
Eyelids:		>50 Gy	Blepharitis, bleeding and crusted lesion, previous infections	Physical exam Slit lamp or penlight exam	Topical and oral steroids, skin balm
Ulceration		>50 Gy	Enlarged, tortuous blood vessels	Open and closed eyelid exam	Teach: lid hygiene, radiosensitizing drugs, UV protection
Telangiectasia			Pigmentary changes		Avoid trauma, harsh soaps and lotions
Conjunctiva: Necrosis Scarring		Radioactive plaque therapy	Dry, irritated eye, foreign body sensation, irregular rough conjunctival surface, telangiectasia	Slit lamp or penlight exam Fluorescein stain	Steroids and antibiotic drops Tear replacement (resolves spontaneously)
Subconjunctival hemorrhage		>45 Gy	Irritated eye, foreign body sensation, dry, irregular conjunctival surface		Patching Tear replacement
Sclera: thinning		>50 Gy	May be asymptomatic, dry eyes, foreign body sensation, gray, charred, blue sclera	Slit lamp or penlight exam	Antibiotic drops Avoid trauma Protective glasses
Cornea: ulceration		>45 Gy	Pain, foreign body sensation, decreased VA, photosensitivity	Slit lamp or penlight exam Fluorescein staining	Tear replacement, antibiotics, soft bandages, soft contact lens, surgery, ophthalmology
Neovascularization		>50 Gy	Increased tearing, increased vessels surrounding edge of cornea	Slit lamp exam	Same as ulceration
Keratinization		>50 Gy	Decreased corneal sensation, photosensitivity, fluorescein staining	Slit lamp exam Fluorescein staining	
Edema		>40 Gy	Decreased visual acuity, hazy cornea	Penlight or slit lamp exam: white, opaque cornea	

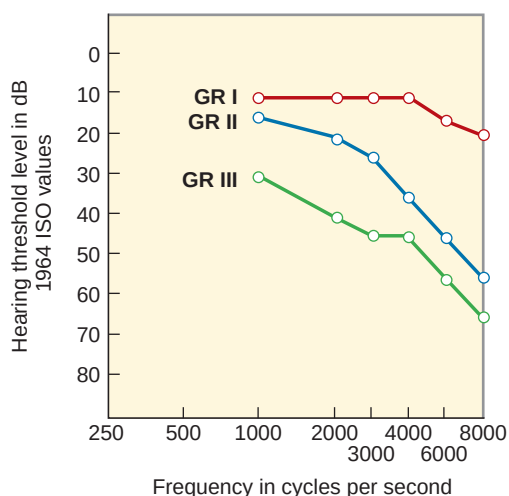


Figure 19.22 Mean hearing thresholds for three groups of patients with brain tumors. Group I (GRI; red) received cranial irradiation only, group II (GRII; blue) received cisplatin, and group III (GRIII, green) received cranial irradiation, then cisplatin. (From McHaney V, Kavnar E, Meyer W, et al. Effects of radiation therapy and chemotherapy on hearing. In: Green DM, D'Angio GJ, eds. *Late Effects of Treatment for Childhood Cancer*. New York: Wiley-Liss; 1992:7–10, with permission.)

the absence of RT. For cisplatin, there was 12% hearing impairment at dosages of 1–200 mg/m², 13% at dosages of 201–400 mg/m², 26% at dosages of 401–600 mg/m², and 22% at 601–800 mg/m². There was an additional effect of carboplatin when given as high-dose therapy with autologous stem cell infusion, where 40% of patients developed hearing loss after a dosage of 1500 mg/m². (262) In a series of patients with neuroblastoma treated at Memorial Sloan-Kettering Cancer Center and in the Children's Oncology Group, hearing was evaluated after cumulative doses of cisplatin of 400 mg/m², 600 mg/m², and a combination of myeloablative doses of carboplatin and 600 mg/m² of cisplatin. Severe (grade 3/4) deficits affected 25% of patients receiving cumulative doses of cisplatin of 400 mg/m², 54% patients receiving cumulative doses of cisplatin of 600 mg/m², and 50% of patients receiving that dose of cisplatin, followed by myeloablative doses of carboplatin. Patients <5 years at diagnosis had greater ototoxicity than adolescents or young adults (263).

Hearing loss in the child with cancer merits detailed attention because it may lead to additional difficulties with communication, speech and language acquisition, and development of learning skills.

Table 19.16 reviews several late effects involving the ear with respect to causative treatments, signs and symptoms, screening and diagnostic tests, and management and intervention (41).

Teeth and Salivary Glands

Radiation-induced damage to developing teeth causes cosmetic and functional difficulties throughout life. The age of the child at the time of therapy and the radiation dosage determine the consequences. Teeth begin to develop from the dental lamina 6 weeks after conception. The crowns of deciduous incisors are fully formed at birth. Calcification begins 3–5 months after birth in the central incisors, canines, and first molars; by 1 year in the maxillary lateral incisors; and by

2.5 years in premolars. By the end of the third year, the whole deciduous dentition is developed (264).

Developing teeth are irradiated in the course of treating malignancies of the head and neck. The defects that occur include destruction of the tooth germ causing tooth agenesis, stunted growth of the whole tooth or its root, impaction, incomplete calcification, premature closures of apices, premature eruption, tapering roots with apical constriction, delayed development, and caries (264). Maxillofacial abnormalities include trismus, abnormal occlusal relationships, and facial deformities. Tooth defects are most severe before histodifferentiation and incremental calcification of the tooth buds, and the extent of damage is not apparent until the teeth erupt.

Dosages of 20–40 Gy can cause root shortening or abnormal curvature, dwarfism, and hypocalcification. More than 85% of survivors of head and neck rhabdomyosarcoma who receive radiation dosages of more than 40 Gy may have significant dental abnormalities, including mandibular or maxillary hypoplasia, increased caries, hypodontia, microdontia, root stunting, and xerostomia (236). In a study of 68 long-term survivors of childhood cancer, Jaffe et al. (95) found that 82% of patients receiving maxillofacial radiation exhibited dental abnormalities. Children treated with 18–30 Gy for leukemia are less frequently affected, with about 40% showing root or crown abnormalities of the maxillary first molars. Children who undergo BMT for high-risk neuroblastoma are clearly at high risk for microdontia, impaired tooth development, and compromised occlusion. These abnormalities are greater if TBI is a component of the conditioning regimen, but they occur even without TBI (265).

Chemotherapy for the treatment of leukemia can cause shortening and thinning of the premolar roots and enamel abnormalities (266). This could result from direct inhibiting effects of chemotherapy, altered marrow milieu caused by leukemic involvement, or systemic factors altering growth. Radiographic abnormalities are common after RT for leukemia and sarcoma (266,267).

When 10 Gy of TBI is administered for BMT, impaired root development resulting in short, V-shaped roots is found in all patients, whereas microdontia, enamel hypoplasia, and premature apical closure are found in 30–50% (268). These effects seem to result from irradiation, not chemotherapy.

Salivary gland irradiation causes a qualitative and quantitative change in salivary flow. When salivary glands are irradiated, acinar cells are destroyed and replaced by ductal remnants and loose connective tissue. Such damage is evident after 20 Gy of fractionated irradiation. Salivary flow rate drops rapidly during a course of fractionated irradiation. Post-RT xerostomia is irreversible if all major salivary glands are treated with dosages of 50–60 Gy. Stimulated and non-stimulated salivary flow are primarily from the parotid and submandibular glands. In Fromm's study of children treated for head and neck sarcomas, about 40% of parotid glands had absent secretions, and these patients received the highest radiation dosage (mean 51 Gy) (267). Patients treated with less than 40 Gy were not affected. Among patients treated for HL with 40 Gy to regions including the submandibular glands, flow rate reductions of about 55% have been documented (269). The radiation dose–response relationship in the effect of radiation on parotid salivary flow is seen in Figure 19.23 (270). In normal saliva, cariogenesis is diminished by salivary antimicrobial substances. Radiation-induced

Table 19.16
Evaluation of Patients at Risk for Late Effects: Ear

Late Effects	Causative Treatment		Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
	Chemotherapy	Radiation			
Chronic otitis		>35 Gy	Dryness and thickening of canal and tympanic membrane Conductive hearing loss Perforation of tympanic membrane	Otoscopic exam Audiometry	Antibiotic therapy, decongestants, myringotomy, PE tubes, preferential seating in school, amplification
Sensorineural hearing loss	Cisplatin, carboplatin	30–50 Gy Cranial radiotherapy enhances the platinum effect	High frequency hearing loss (bilateral) Tinnitus Vertigo	Conventional pure tone audiogram baseline and then q2–3 year Bilateral symmetric, reversible	Preferential seating in school Amplification
Decreased cerumen production		30–40 Gy	Hard and encrusted cerumen in canal Hearing impairment Otitis externa	Examination of canal	Periodic cleaning ear canal, cerumen-softening agents, otitic drops for otitis externa Keep ear dry: ear plugs, drying solution
Chondritis Chondronecrosis		50 Gy 60 Gy	Cauliflower ear	Inspection of auricle	Antibiotics, surgical repair (reconstruction may be hampered by poor blood supply)

PE, pressure equalization.

changes in salivary pH and quantity produce a highly cariogenic microflora along with a decrease in protective salivary electrolytes and immunoproteins. These circumstances render the patient highly susceptible to radiation-induced caries.

Before radiation and chemotherapy a dental evaluation is indicated. As possible foci of infection, loose exfoliating primary teeth and orthodontic appliances should be removed. The daily use of topical fluoride can dramatically reduce the frequency of radiation caries in the treated patient. Xerostomia is palliatively treated with saliva substitutes and sialagogues. Data support the efficacy of pilocarpine in improving saliva production and relieving symptoms of xerostomia, with minor risks that are limited predominantly to sweating (271).

Table 19.17 reviews several dental and salivary late effects with respect to causative treatments, signs and symptoms, screening and diagnostic tests, and management and intervention (41).

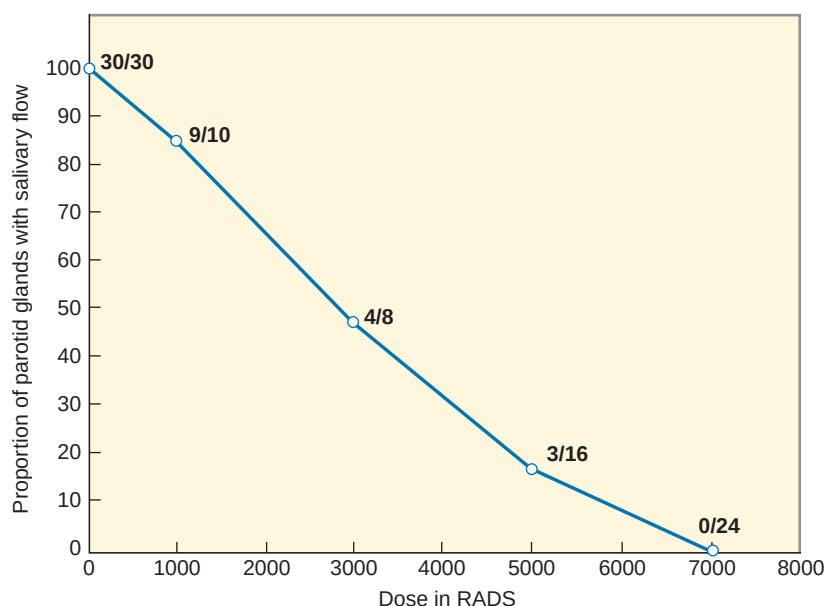
Bone Marrow

The hematopoietic progenitor cells and their offspring are cradled on a stroma of endothelial cells, adventitial cells, fibroblasts, macrophages, and fat cells. Mechanisms of marrow-induced failure include direct killing of hematopoietic

progenitor cells, accessory cells (e.g., lymphocytes and monocytes), damage to the stroma and microcirculation, and disturbance of hematopoietic growth and regulatory factors (272).

The bone marrow is extremely sensitive to irradiation, to the degree that some injury is produced by any fractional dosage. Irradiated bone marrow becomes hypocellular. There is destruction of fine vasculature followed by fatty marrow replacement of the normal hematopoietic marrow (273). If the radiation dosage is sufficiently high, destruction of the sinusoidal circulation precludes migration of hematopoietic cells from distant nonirradiated sites. After 40-Gy fractionated irradiation, 85% of irradiated sites show a return of activity in 2 years; in 55% of those areas, recovery becomes complete. Conversely, single doses of 20 Gy to localized regions can produce permanent aplasia. Radiation-induced changes in bone marrow may be detected by increased signal intensity on MRI because of the decreased T1 relaxation time of the increased fatty marrow content. MRI findings support those of nuclear medicine scanning and bone marrow aspiration studies, namely that dosages of up to 40 Gy, to limited areas, do not preclude repopulation of the irradiated marrow in the years after treatment (274).

Figure 19.23 Proportion of unirradiated and irradiated parotid gland with measurable salivary flow as a function of radiation dosage. (From Marks J, Davis C, Gottsman V, et al. The effects of radiation on parotid salivary function. *Int J Radiat Oncol Biol Phys.* 1981;7:1013–1019, with permission.)



Dosages greater than 50 Gy seem to produce irreversible depletion of myeloid tissue (275).

The regenerative capacity of the bone marrow depends on the volume irradiated (276). After irradiation to less than 25% of the bone marrow, the unexposed portion is stimulated and successful in compensating for hematopoietic demands, and the treated portion may never regenerate. When volumes in excess of 50% are irradiated, the unexposed bone marrow is not adequate to meet the body's demands. Consequently,

the paradoxical phenomenon of in-field regeneration is seen 2–5 years later, and extension of bone marrow activity into previously quiescent long bones is seen within 1–2 years.

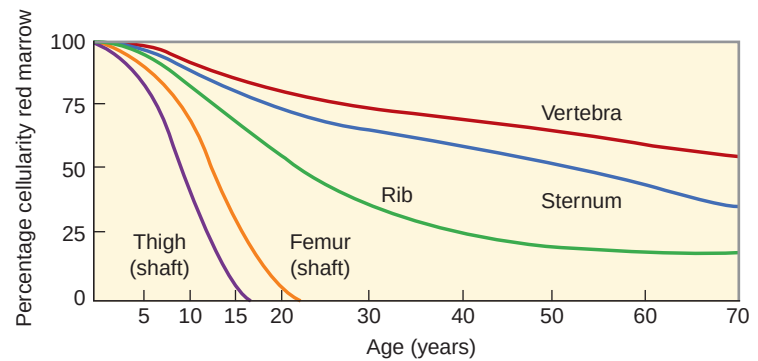
Differences between children and adults in the response of the bone marrow to irradiation relate primarily to the differing extent of active bone marrow at different ages (277). In the immediate postnatal period, conversion from active red to fatty yellow marrow begins and is first evident in the extremities. This conversion progresses from peripheral

Table 19.17
Evaluation of Patients at Risk for Late Effects: Teeth

Late Effects	Causative Treatment		Signs and Symptoms	Screening and Diagnostic Tests	Management and Intervention
	Chemotherapy	Radiation			
Xerostomia (decreased salivary gland function)		>40 Gy, and >50% of gland must be radiated	Decreased salivary flow, dry mouth, altered taste perception, dental decay, Candida (thrush)	Dental examination, salivary flow studies, attention to early caries, periodontal disease	Encourage meticulous oral hygiene, saliva substitution, prophylactic fluoride, dietary counseling regarding avoiding fermentable carbohydrates, nystatin for oral candidiasis, pilocarpine
Abnormal tooth and root development	Vincristine, cyclophosphamide, actinomycin D, 6MP, procarbazine, nitrogen mustard	Generally 10 Gy can destroy developing roots	Enamel appears pale, teeth appear small, uneven, malocclusion	Dental exam q6 months with attention to early caries, periodontal disease, and gingivitis Panorex and bite-wing radiographs for baseline (age 5–6)	Careful evaluation before tooth extraction, endodontics, and orthodontics Fluoride Antibiotics as needed to reduce risk of infection (e.g., with trauma)

6MP, 6-mercaptopurine.

Figure 19.24 The relative amount of red and yellow bone marrow in different anatomic sites as a function of age. (From Kricun ME. Red–yellow marrow conversion: its effect on the location of some solitary bone lesions. *Skeletal Radiol* 1985;14:10–19, with permission.)



(appendicular) toward the central (axial) skeleton and from diaphyseal to metaphyseal in individual long bones (Fig. 19.24).

The acute and chronic effects of chemotherapeutic agents on the hematopoietic compartment will not be detailed in this section. However, radiation oncologists must be familiar with the acute myelosuppressive effects of various drugs, and they are summarized in Table 19.18.

CONCLUSIONS AND FUTURE DIRECTIONS

RT and chemotherapy can result in adverse long-term physiologic sequelae for survivors of childhood cancer. However, these treatment modalities have resulted in a markedly increased

survival rate for almost all pediatric malignancies. Therefore, it is essential to balance the benefits against risks. Both length of survival and the impact of physiologic late effects on the quality of that survival must be considered in therapy selection.

The pathophysiologic mechanisms of damage from RT and chemotherapy to normal tissues are well described. However, what is unclear is the interindividual variation in responses to the same therapeutic exposures. Although many children and adolescents are treated with the same RT dosages, fields, and volumes, there is a significant degree of variability in the proportion that develops radiation-related toxicities. For some, the cytotoxicity of chemotherapy may enhance the RT effects. However, little is known about host-related factors, such as genetic susceptibility. This may include inherited differences in radiation sensitivity to normal tissue or genes of xenobiotic metabolism, nucleotide provision, or DNA repair.

Table 19.18

Antineoplastic Drug Category and Agent with Their Relative Degree and Duration of Myelosuppression

Drug or Drug Class	Degree of Suppression ^a	Myelosuppression Nadir (Days)	Time to Marrow Recovery (Days)
Anthracycline	III	6–13	21–24
Vinca alkaloids	I–II	4–9	7–21
Mustard alkylator	III	7–14	28
Antifolates	III	7–14	14–21
Antipyrimidines	III	7–14	22–24
Antipurines	II	7–14	14–21
Podophyllotoxins	II	5–14	22–28
Alkylators	II	10–21	18–40
Nitrosoureas	III	26–60	35–85
Miscellaneous ^b			
Busulphan	III	11–30	24–54
Cisplatin	I	14	21
Dacarbazine	III	21–28	28–35
Hydroxyurea	II	7	14–21
Mithramycin	I	5–10	10–18
Mitomycin	II	28–42	42–56
Procarbazine	II	25–36	35–50
Bis-piperazinedione	II	11–16	12–25

^aI, mild; II, moderate; III, severe (based on common dosing schedules).

^bAgents differing from their class of compounds.

From Mauch P, Constine L, Greenberger J, et al. Hematopoietic stem cell compartment: acute and late effects of radiation therapy and chemotherapy. *Int J Radiat Oncol Biol Phys*. 1995;31:1319–1339, with permission.

In addition, morbidity and premature mortality have been examined with respect to treatment exposures but not yet in association with other factors such as diet, sun, tobacco, and alcohol exposure that are etiologically related to the major problems in an aging population. New patterns of late morbidity and mortality may emerge as survivors continue to age, and it is only through continued study that such patterns will be identified and interventions for treatment and prevention designed.

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Second Primary Cancers

Smita Bhatia, and Louis S. Constine

Significant improvements in therapeutic options and supportive care strategies have resulted in 5-year survival rates now approaching 65% for adult-onset cancers, and exceeding 80% in children (1). This improvement in survival has resulted in a growing population of cancer survivors. Currently in the United States, there are over 12 million cancer survivors. However, this survival is associated with significant morbidity. In fact, 60–70% of young adult survivors of childhood cancer are reported to develop at least one health-related complication (2); and second primary cancers (SPCs) are the most emotionally and physically devastating of these complications (Fig. 20.1).

SECOND PRIMARY CANCERS: THE SCOPE OF THE PROBLEM

SPCs are defined as histologically distinct malignancies developing at least 2 months after completion of the treatment for the primary malignancy. Several large epidemiologic studies have demonstrated that the SPC risk after adult-onset primary cancer is modest at best, ranging from no difference from the general population to a twofold greater incidence (3–5). A follow-up of a large cohort of childhood cancer survivors

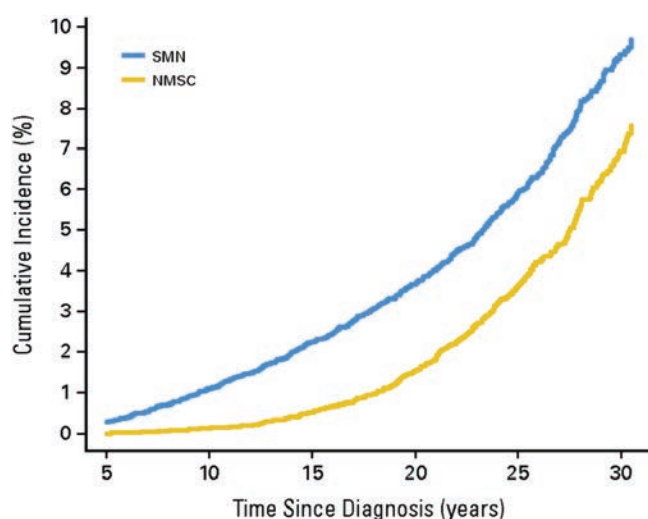


Figure 20.1 Cumulative incidence of second malignant neoplasms and nonmelanoma skin cancers in childhood cancer survivors. (From Meadows AT, Friedman DL, Neglia JP, et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. *J Clin Oncol*. 2009;27:2356–2362, with permission).

demonstrates that the cumulative incidence of second malignant neoplasms (SMNs) exceeds 3% at 20 years after diagnosis of a primary cancer in childhood, representing a sixfold increased risk for cancer survivors, compared to the general population (6). Furthermore, the absolute excess risk of SPCs after a first primary cancer diagnosed and treated during childhood is 1.9 per 1000 patient-years of follow-up of this cohort (6). Data from the Surveillance, Epidemiology, and End Results (SEER) program used to calculate the influence of SPCs on overall incidence trends in childhood cancer revealed higher annual incidence rates for all childhood cancers combined, specifically for acute lymphoblastic leukemia (ALL) and brain tumors, but not for other cancer types because of their rarity. However, excluding SPCs from the analysis had a negligible effect on the observed trends. These studies demonstrate that the relative risk of SPC in survivors of adult-onset cancer is modest at best, and that the high relative risk of SPC after a primary cancer in childhood does not translate into a high absolute risk. However, a recent report indicates that survivors of childhood cancer have a persistent excess risk of an SPC throughout their lives, accompanied by continuous changes in the risk of cancers at specific sites (7). This, combined with the fact that the morbidity and mortality associated with SPCs are substantial, necessitates a need to characterize this complication and identify associated risk factors.

The incidence and type of SPCs differ with the primary cancer diagnosis, type of therapy received, and presence of genetic conditions. Unique associations with specific therapeutic exposures have resulted in the classification of SPCs into two distinct groups: chemotherapy-related myelodysplasia and acute myeloid leukemia and radiation-related solid tumors. Characteristics of therapy-related myelodysplasia and acute myeloid leukemia include a short latency (<3 years from primary cancer diagnosis) and association with alkylating agents and/or topoisomerase II inhibitors (8). Solid SPCs have a strong and well-defined association with radiation, and are characterized by a latency that exceeds 8–10 years (8).

SPCs are a leading cause of nonrelapse late mortality, both in childhood cancer survivors (9), as well as in survivors of adult-onset cancer (10).

RISK FACTORS FOR SECOND CANCERS

Exposures to radiation therapy or to specific chemotherapeutic agents have been shown to increase the risk of SPCs in certain subsets of patients (6,11–14). The types of SPC vary with the primary diagnosis, the type of therapy received, presence of genetic predisposition, and the time from initial

treatment. Follow-up of the Childhood Cancer Survivor Study demonstrates that, after adjusting for exposure to radiation, the risk of SPC was significantly associated with female sex ($p < 0.001$), childhood cancer diagnosed at a younger age ($p < 0.001$), initial cancer diagnosis of Hodgkin lymphoma ($p < 0.001$), and exposure to alkylating agents ($p = 0.02$) (6).

Primary Diagnosis

Hereditary retinoblastoma, Hodgkin lymphoma, and soft tissue sarcomas are over-represented among patients who develop SPCs relative to their incidence in the general population (6,14). This could result from an interaction between the genetic predisposition to develop cancer and the specific cancer therapies, as is clear in patients with hereditary retinoblastoma and familial soft tissue sarcoma (14,15). In individuals with other primary malignancies, such as Hodgkin lymphoma, it is not clear whether the primary diagnosis is an independent risk factor for the development of SPC or whether the specific therapy needed to treat the primary cancer is the major contributor to the development of the SPC. Some associations between first and second cancers are summarized in Table 20.1.

Host-Related Risk Factors

Age at Diagnosis and Treatment of Primary Cancer

Younger age at diagnosis of the primary cancer has been reported to be associated with a higher risk of radiation-associated SPCs (6,11,16). Conversely for secondary myelodysplasia and acute myeloid leukemia, which are strongly linked with specific chemotherapeutic agents, the risk increases with age at diagnosis and treatment of primary cancer (17,18).

Sex

Female sex is associated with a higher risk of SPCs, contributed to primarily by the excess occurrence of secondary breast and thyroid cancers among female cancer survivors (19). Moreover, some studies indicate a greater susceptibility of women to known carcinogens such as cigarette smoke (20). Possible mechanisms that underlie this greater susceptibility include greater activity of cytochrome P450 (CYP) enzymes, enhanced formation of DNA adducts, and the effects of hormones such as estrogen on tumor promotion (20).

Table 20.1
Second Cancers and their Relationship with Primary Cancers

Second Cancers	Primary Cancers	Median Latency (Years)	Risk Factors
Breast cancer	Hodgkin lymphoma	15–20	Radiation Female sex
	Bone tumors		
	Soft tissue sarcomas		
	Acute lymphoblastic leukemia		
	Brain tumors		
	Wilms tumors		
Brain tumors	Non-Hodgkin lymphoma	9–10	Radiation Younger age
	Acute lymphoblastic leukemia		
	Brain tumors		
	Hodgkin lymphoma		
Myelodysplastic syndrome and acute myeloid leukemia	Acute lymphoblastic leukemia	3–5	Topoisomerase II inhibitors Alkylating agents
	Hodgkin lymphoma		
	Bone tumors		
Thyroid cancer	Acute lymphoblastic leukemia	13–15	Radiation Younger age Female sex
	Hodgkin lymphoma		
	Neuroblastoma		
	Soft tissue sarcoma		
	Bone tumors		
	Non-Hodgkin leukemia		
	Retinoblastoma (heritable)		
Bone tumors	Other bone tumors	9–10	Radiation Alkylating agents Splenectomy
	Ewing sarcoma		
	Soft tissue sarcomas		
	Acute lymphoblastic leukemia		
Soft tissue sarcomas	Retinoblastoma (heritable)	10–11	Radiation Younger age Anthracyclines
	Soft tissue sarcoma		
	Hodgkin lymphoma		
	Wilms tumor		
	Bone tumors		
	Acute lymphoblastic leukemia		

Therapy-Related Risk Factors

Radiation

Although ionizing radiation is capable of causing most types of cancer, organs vary in their susceptibility. The risk is highest when exposure occurs at a younger age and increases with increasing dosages of radiation and with increasing follow-up from radiation (21). Radiation-associated SPCs have a long latency period and typically develop in or at the edge of the radiation field. Some well-established radiation-associated SPCs include breast cancer (after Hodgkin lymphoma), thyroid cancer (after Hodgkin lymphoma and ALL), lung cancer (after Hodgkin lymphoma), brain tumors (after other brain tumors and ALL), osteosarcoma (after retinoblastoma, Ewing sarcoma, and other soft tissue sarcomas), and nonmelanoma skin cancers (Table 20.1).

Several principles characterize radiation-induced SPCs (22–24):

- A variety of histologic types of neoplasms can be induced by irradiation. These cancers are indistinguishable morphologically from naturally occurring cancers. The identification of a “radiation signature” in tumors would be important in evaluating SPC. There is evidence that radiation produces a different spectrum of mutations than other genotoxic agents. If these mutations could be discerned and characterized, then one could clearly identify radiation-induced tumors and understand, more completely, the radiation dose–response relationship for induced tumors. In this manner, molecular forensics may affect our understanding of attributable risk (25). Of interest is recent data showing that the risk of an SPC is proportional to the number of premalignant stem cells created, and surviving RT. This is related to cell killing by RT, cellular repopulation between RT fractions and after the last fraction, and the ratio of the proliferation rate of premalignant cells to the proliferation rate of normal cells (Fig. 20.2).
- Low-linear energy transfer (low-LET) radiation (gamma ray, x-ray) is generally less efficient in inducing tumors than high-LET radiation. In a murine hepatocarcinogenesis model, for example, neutron irradiation produced a greater incidence of hepatomas than did gamma irradiation (26). Low-LET radiation appears to become less effective at carcinogenesis per centigray as the dosage falls, whereas high-LET radiation (neutrons, alpha particles) does not (27). With low-LET irradiation there is less tumor induction when the dosage is fractionated or administered at low dose rates; implying that repair of carcinogenic damage is occurring. With high-LET irradiation, the radiobiological effect is higher at low dosages. The carcinogenic effectiveness of high-LET radiation is not diminished and may be increased by dosage fractionation or protraction (28).
- Comparison of the frequency of SPCs in different centers suggests that orthovoltage therapy is more likely to be carcinogenic than megavoltage therapy (24,29). This may be dose-related: By delivering a higher dosage to bone, orthovoltage irradiation may increase the risk of an SPC of bone. The higher risk may also be related to the long follow-up available for orthovoltage patients.
- Although every tissue in the body is at risk for radiation-induced cancer, sensitivity varies according to the tissue. For example, thyroid gland and breast are sensitive to

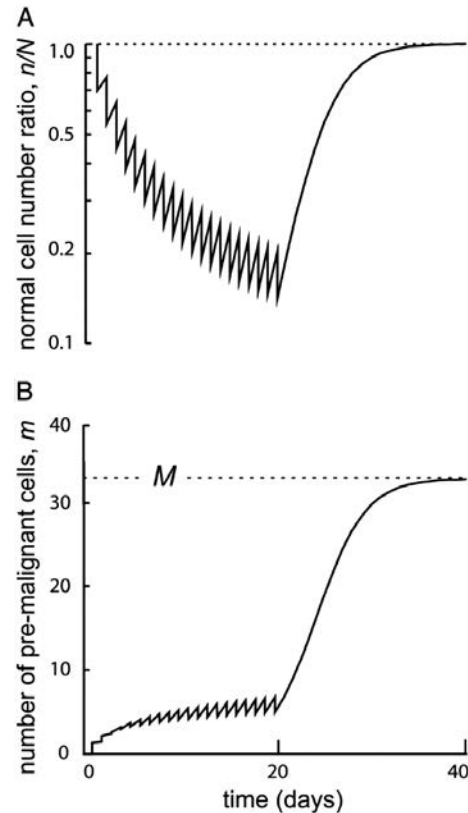


Figure 20.2 Initiation/inactivation/proliferation model of carcinogenesis. Risk of SMN proportional to the number of premalignant stem cells created and surviving RT. Related to: (1) cellular killing, (2) cellular repopulation occurring between fractions and after the last fraction, and (3) the ratio of proliferation rate for premalignant cells to the proliferation rate of normal cells. (From Sachs RK, Brenner DJ. Solid tumor risks after high doses of ionizing radiation. *Proc Natl Acad Sci U S A*. 2005;102:13040–13045, with permission).

cancer induction after low radiation dosages; lymphoid tissue, lung, and liver are susceptible at moderate dosages, and bone at higher dosages. The relationship between dosage and response may vary according to the induced tumor. For example, the development of CNS tumors increases with increasing dose, whereas secondary thyroid carcinomas have a peak incidence after doses of 20–29 Gy but then decrease (Fig. 20.3A,B). Cancer risk from radiation may be given per unit dosage (gray, Gy) or per unit dosage equivalent (Sievert, Sv) where a “quality factor” (Q) is used to take account of the varying biological effectiveness of different radiations (e.g., for a gamma ray $Q = 1$, and for a neutron $Q = 20$). Therefore, dosage in $Sv = \text{dosage in Gy} \times Q$. Detailed literature reviews indicate that the cancer mortality risk for the general population after whole body exposure is 1×10^{-4} to 4×10^{-4} per person-cGy. Pooled results of various partial body exposures give an estimated risk of 1×10^{-4} to 4×10^{-4} per person-cGy ($4 \times 10^2 Sv^{-1}$). The risk based on incidence is about twice that for mortality (27,30). Leukemia data can be fit by a curvilinear dose–response model, whereas skin cancer appears to have a threshold dose–response function, and breast data fit a linear no-threshold model.

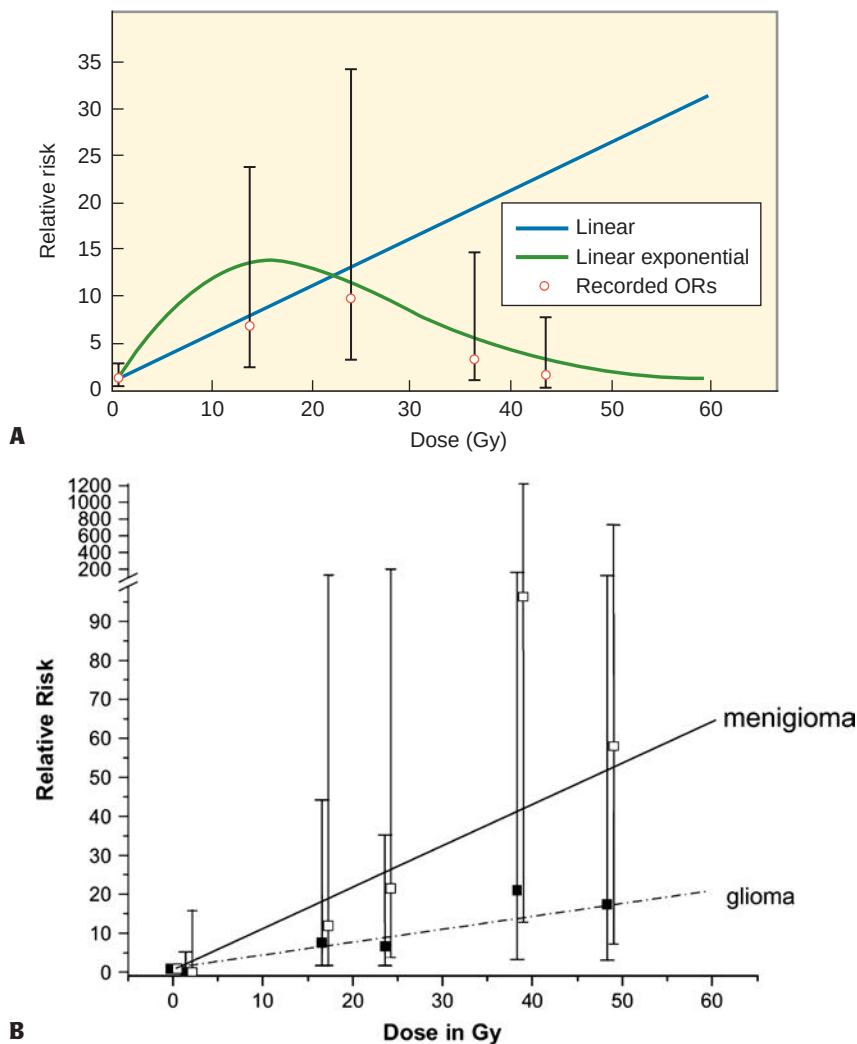


Figure 20.3 A: Dose–response relations between radiotherapy dose and relative risk of second neoplasms. (From Meadows AT, Friedman DL, Neglia JP, et al. Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. *J Clin Oncol.* 2009;27:2356–2362) B: Dose–risk for RT-induced CNS tumors from Childhood Cancer Survivor Study of 14,361 5-year survivors. (From Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2006;98:1528–1537, with permission).

- Radiation induces solid SMNs, within the radiation field and in a dose-dependent fashion (6,11,16,31–34). A recent report assessed the relationship between the radiation dose received inside of the edges of radiation beams throughout the volume of tissue irradiated (thus the integral dose) and the likelihood of developing a secondary malignancy. In a cohort of 4401 patients who were 3-year survivors of all types of childhood cancer, a dose–response relationship was found between the overall risk of an SMN and the estimated integral dose (Table 20.2, Fig. 20.4) (35). As a corollary, data from Diallo et al. showed that a greater volume of tissues receives low or intermediate radiation doses in regions bordering the irradiated volume with modern multiple-beam radiation therapy administrations, including intensity modulated radiation therapy (IMRT) (36). However, in a report that modeled risk for children treated with IMRT versus conventional therapy, an increase was not seen (37). Additional data will be necessary to settle this issue.
- SPCs may also be induced by agents other than radiation (chemotherapy, environmental exposures, hereditary disposition). The low-dose radiation dose–response curve could be influenced by these confounding factors to produce a result that is the sum of two independent rates or may be greater than simple addition would indicate. A variety of chemotherapeutic agents (to be discussed), especially

alkylators, are known to be carcinogenic, and they may be additive or synergistic with radiation. Immunosuppressive agents clearly influence the propensity for tumor induction, as is seen in the setting of organ transplantation (38).

- A large number of irradiated patients are necessary to calculate a radiation carcinogenesis risk with reasonable accuracy.
- Latent periods vary according to the induced tumor. At least two patterns of latent periods for radiation-induced cancer have been described. The first, exemplified by the risk of leukemia in atomic bomb survivors, consists of an early wavelike pulse of increased risk followed by a gradual decline to baseline levels. The second, more typical of solid tumors, is an increase in relative risk of SPCs over many years, which remains constant over time thereafter. The latter pattern suggests that a multi-event pattern of carcinogenesis is involved: the initial event (radiation) is followed by promoting events (i.e., smoking, alcohol, or environmental exposures) over many years (39). Long latent periods complicate the study of radiation-induced cancer because the presence of other carcinogens or disease processes may not be well documented.
- The duration of follow-up for any study population influences the frequency of tumors seen.
- It is unclear whether the risk of tumor development after exposure is simply an absolute increase that is proportional

Table 20.2
Integral Dose as a Risk for Second Cancers

Integral Dose ^b		Integral Dose (kg)	
Exposure	RR ^a	Exposure	RR ^a
0	—	0	
1–46	2.42	0–4.3	2.42
47–179	2.64	4.3–7.5	2.78
179–1560	5.43	7.5–34.5	4.85
<i>Chemotherapy</i>			
Alkylators	1.79		
Intercalculating agents	1.81		

^aAdjusted for age at Dx, sex, and dose.

^bTotal absorbed energy (joules), which depends on dose delivered, irradiated volume and its density, and estimated only for the volume inside the geometrical limits of the beam.

(Modified from Nguyen F, Rubino C, Guerin S, et al. Risk of a second malignant neoplasm after cancer in childhood treated with radiotherapy: correlation with the integral dose restricted to the irradiated fields. *Int J Radiat Oncol Biol Phys*. 2008;70:908–915, with permission).

to the radiation dosage or a relative increase that builds on an underlying spontaneous risk (greater for some patients) of developing a malignancy.

- Age is a critical factor in determining radiation risk. In children, the most common SPCs occur in tissues undergoing rapid proliferation such as bone, thyroid, and breast. An actively proliferating tissue may be more susceptible to malignant transformation in any single cell because of the greater number of cell divisions. This might explain the higher frequency of secondary bone tumors in children than in adults (40). Childhood cancer survivors are likely to develop leukemias or sarcomas, whereas secondarily induced embryonal tumors are rare.

Chemotherapeutic Agents

Alkylating agents and topoisomerase II inhibitors have been shown to increase the risk of secondary myelodysplasia and acute myeloid leukemia (11,41,42). Alkylating agents have also been linked with bone tumors (43,44) and bladder cancer (45). Therapy-related myelodysplasia has been reported after treatment of Hodgkin lymphoma, non-Hodgkin lymphoma, ALL, and sarcomas (8,11,31,34,46,47), with the cumulative incidence approaching 2% at 15 years after therapy (11). The incidence of therapy-related myelodysplasia and acute myeloid leukemia typically peaks 4–6 years from diagnosis of the primary cancer and reaches a plateau after 15 years. The clinical observation that the risk of therapy-related leukemia does not extend beyond 15 years, despite an increasing risk of second neoplasms at other sites, indicates that the at-risk population of cells is no longer present (23). It may be that this period of time allows early pluripotent hematopoietic progenitors to undergo clonal extinction and be replaced from the compartment of resting stem cells by clonal succession. It is possible that stem cells in the resting phase of the cell cycle are relatively protected from the genotoxic effects of chemotherapy and radiation and that the excess risk of therapy-related leukemia would diminish as undamaged cells were recruited into active hematopoiesis. Therapy-related leukemia is associated with a very poor outcome, with an estimated 12-month survival of 10% (48).

Therapy-related myelodysplasia and acute myeloid leukemia is a clonal disorder characterized by distinct chromosomal changes (48–50). Two types are recognized by the WHO classification: alkylating agent–related type and topoisomerase II inhibitor–related type (51).

Alkylating Agent–Associated Acute Myeloid Leukemia and Myelodysplasia

Table 20.3 summarizes the incidence, risk factors, and outcomes among patients with therapy-related leukemia after alkylating agent exposure (11,41,52–59). Alkylating agents associated with t-MDS/AML include cyclophosphamide,

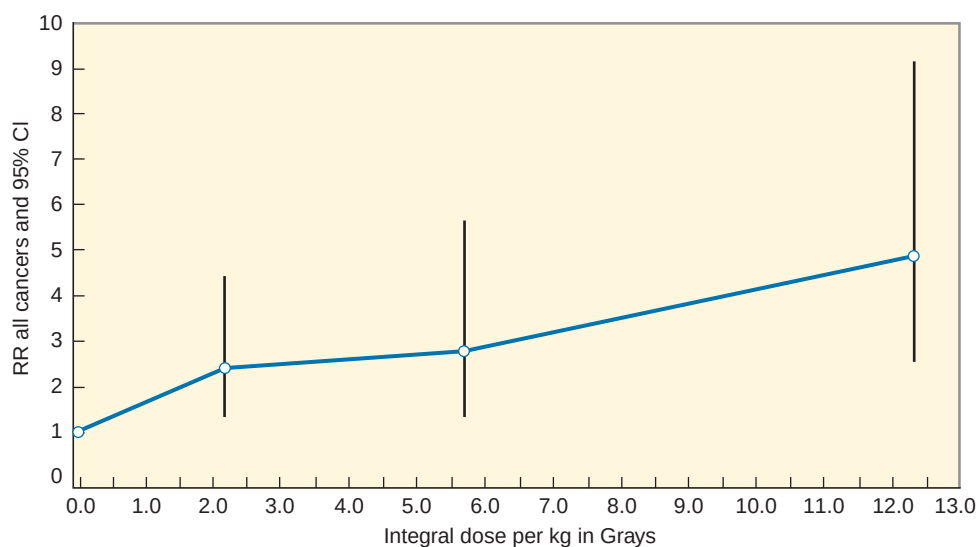


Figure 20.4 Integral dose and SMN risk in pediatric cancer survivors. (Modified from Nguyen F, Rubino C, Guerin S, et al. Risk of a second malignant neoplasm after cancer in childhood treated with radiotherapy: correlation with the integral dose restricted to the irradiated fields. *Int J Radiat Oncol Biol Phys*. 2008;70:908–915, with permission).

Table 20.3**Characteristics of Therapy-Related Myelodysplasia or Acute Myeloid Leukemia After Treatment with Alkylating Agents and Topoisomerase II Inhibitors**

Reference	Primary Cancer	Cohort Size	Cases of MDS and AML	Latency (Years)	Cumulative Probability (%) (Years)	Risk Factors	Percentage Alive
Associated with alkylating agents							
53	HL	694	8	51.6 (16–148)	1.5 (20)	Chemotherapy Relapse	0
54	HL	1641	7	NA	0.8 (30)	NA	NA
55	HL	667	5	49 (31–125)	1.1 (15)	Alkylating agents	0
56	Childhood cancer	9170	19	NA	0.8 (20)	Increasing age	NA
Associated with topoisomerase II inhibitors							
11	HL	1380	24	48 (10–168)	2.8 (14)	HL, Ewing's Alkylating agents Doxorubicin Alkylating agents Older age	0
57	ALL	734	21	39.5 (15–100)	3.8 (6)	Etoposide: weekly or twice weekly	14
58	ALL	205	10	32	5.9 (4)	Etoposide	50
59	NHL	38	5	21	18.4 (4)	Etoposide, twice weekly	60

MDS, myelodysplasia; AML, acute myeloid leukemia; HL, Hodgkin lymphoma; NA, not applicable; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma.

ifosfamide, mechlorethamine, melphalan, busulfan, nitrosoureas, chlorambucil, dacarbazine (60), and platinum compounds (61). Mutagenicity is related to the ability of alkylating agents to form crosslinks and/or transfer alkyl groups to form DNA monoadducts. Alkylation results in inaccurate base pairing during replication and single- and double-strand breaks in the double helix as the alkylated bases are repaired. The risk of alkylating agent-related t-MDS/AML is dose-dependent, with a latency of 3–5 years after exposure (62); it is associated with abnormalities involving chromosomes 5 (–5/del[5q]) and 7 (–7/del[7q]), and a high frequency of multidrug-resistance phenotype (63). The 5q31–33 region of the long arm of chromosome 5 contains at least nine genes involved in hematopoiesis. Defects in any of these genes could disrupt the balance between cell growth and differentiation and play a role in initiation and progression of leukemia. Complete or partial deletions of the long arm of chromosome 7 (7q– and –7) are nonrandom abnormalities observed in therapy-related leukemia.

Topoisomerase II Inhibitor–Associated Acute Myeloid Leukemia

Topoisomerase II catalyzes the relaxation of supercoiled DNA by covalently binding and transiently cleaving and religating both strands of the DNA helix. DNA topoisomerase II inhibitors (epipodophyllotoxins and anthracyclines) stabilize the enzyme-DNA covalent intermediate, decrease the religation rate and cause chromosomal breakage. These events initiate apoptosis, required for antineoplastic activity (64).

Occasionally, repair of chromosomal damage results in chromosomal translocations, leading to leukemogenesis (65,66). Most of the translocations disrupt a breakpoint cluster region between exons 5 and 11 of the band 11q23 and fuse mixed lineage leukemia (MLL) with a partner gene (67,68). In vitro studies provide evidence that epipodophyllotoxins can directly induce MLL rearrangements in hematopoietic cells (69). Topoisomerase II inhibitor–related t-AML presents as overt leukemia often with a high blast count, rather than an initial myelodysplastic presentation (Table 20.4) (70) with a predominance of monocytic phenotypes (M4 and M5), after a latency of 6 months to 3 years; and is associated with balanced translocations involving chromosome bands 11q23 or 21q22. Other translocations include inv(18)(p13q22) or t(17,19)(q22;q12) (70,71).

Dosing schedule has been associated with epipodophyllotoxin-related secondary leukemia (57). Within the subgroups of patients who received epipodophyllotoxins (etoposide or teniposide) twice weekly or weekly, the cumulative risks were 12.3% and 12.4%, respectively. Of the remaining subgroups that included patients who received epipodophyllotoxins every 2 weeks, did not receive epipodophyllotoxins, or received them only during remission induction, the cumulative risk was 1.6%. After adjustment for the frequency of treatment, there was no apparent independent effect of the total dosage of epipodophyllotoxins in this study (57). Another large study from the Cancer Therapy Evaluation Program of the National Cancer Institute described the cumulative risks at 6 years for the development of secondary leukemia to be 3.3%, 0.7%, and

Table 20.4
Features of Chemotherapy-Induced Hematopoietic Malignancies

Property	Alkylating Agents	Epipodophyllotoxins
Median latency	4–6 years (range, 1–20 years)	1–3 years (range 0.5–4.5 years)
Presentation	Myelodysplasia	Abrupt, no preleukemia
Cytogenetic abnormalities	Loss of genetic material, often from chromosomes 5 and 7	Balanced translocations (often include 11q23)
Age	Typically older patients	Younger patients

2.2% at the low (less than 1.5 g/m²), moderate (1.5–3.0 g/m²), and high (more than 3.0 g/m²) dosages of etoposide, respectively, again suggesting a lack of dose–response relationship. A recent study using a case-controlled design explored the dose–response relationship between epipodophyllotoxins and anthracyclines, and the risk of developing secondary leukemia. This study concluded that patients who received 1.2–6.0 g/m² of epipodophyllotoxins or more than 170 mg/m² of anthracyclines have a risk seven times higher than that of patients who received lower dosages or none of these drugs (72).

CONTEMPORARY UNDERSTANDING OF CARCINOGENESIS

Genetic Predisposition

Some cancers tend to aggregate in families, with specific constellations of tumor types observed (e.g., adenocarcinomas or sarcomas) (15,73). Some inherited syndromes clearly predispose patients to the development of SPCs. Patients with the nevroid basal cell carcinoma syndrome who are irradiated for medulloblastoma develop skin cancers in the irradiated fields 6 months to 3 years later. Children with ataxia–telangiectasia may be more prone to irradiation-induced malignancies. Members of families with Li–Fraumeni syndrome have been reported to be at higher risk of multiple subsequent cancers than the general population (12). The risk was highest among survivors of childhood cancer, and the excess risk was mainly for cancers characteristic of Li–Fraumeni syndrome, such as brain tumors and sarcomas. Patients with soft tissue sarcomas who develop an SPC are more likely to have a family history of cancer than those without one (15). The tumor types occurring in excess in family members are similar to those observed as SPCs, such as cancers of the breast, bone, joint, or soft tissue, thus indicating that the risk of SPCs is associated with a familial predisposition. Genetic predisposition also plays a significant role in increasing the risk of SPCs among patients receiving radiation therapy for hereditary retinoblastoma, with the risk increasing with increasing dosages of radiation (74). These studies suggest that germ-line mutations in tumor suppressor genes might interact with therapeutic exposures to increase the risk of SPCs.

Literature clearly supports the role of chemotherapy and radiation in the development of SPCs. However, interindividual variability exists, suggesting a role for genetic variation in susceptibility to genotoxic exposures. The risk of SPCs could potentially be modified by mutations in high-penetrance genes that lead to serious genetic diseases, for example, Li–Fraumeni syndrome (75) and Fanconi anemia (76–79).

However, the attributable risk is expected to be very small because of their extremely low prevalence. The interindividual variability in risk of therapy-related SPCs is more likely related to common polymorphisms in low-penetrance genes that regulate the availability of active drug metabolite, or those responsible for DNA repair. Genetic variation contributes 20–95% of the variability in cytotoxic drug disposition. Polymorphisms in genes involved in drug metabolism and transport are relevant in determining disease-free survival and drug toxicity (80). Variation in DNA repair plays a role in susceptibility to de novo cancer (81–85) and likely modifies SPC risk after exposure to DNA-damaging agents, such as radiation and chemotherapy. Gene–environment interactions may magnify subtle functional differences resulting from genetic variations.

Drug-Metabolizing Enzyme

Metabolism of genotoxic agents occurs in two phases. Phase I involves activation of substrates into highly reactive electrophilic intermediates that can damage DNA—a reaction principally performed by the CYP family of enzymes. Phase II enzymes (conjugation) function to inactivate genotoxic substrates. The phase II proteins comprise the glutathione S-transferase (GST), NAD(P)H:quinone oxidoreductase-1 (NQO1), and others. The balance between the two sets of enzymes is critical to the cellular response to xenobiotics; for example, high activity of phase I enzyme and low activity of a phase II enzyme can result in DNA damage from the excess of harmful substrates.

DNA Repair

DNA repair mechanisms protect somatic cells from mutations in tumor suppressor genes and oncogenes that can lead to cancer initiation and progression. An individual's DNA repair capacity appears to be genetically determined (86). A number of DNA repair genes contain polymorphic variants, resulting in large inter-individual variations in DNA repair capacity (87). Even subtle differences in an individual's DNA repair capacity may be important in the presence of large external influences such as chemotherapy or radiotherapy. Mismatch repair (MMR) functions to correct mismatched DNA base pairs that arise as a result of misincorporation errors that have avoided polymerase proofreading during DNA replication (88). Approximately, 50% of t-MDS/AML patients have microsatellite instability, associated with methylation of the MMR family member MLH1 (89,90), low expression of MSH2 (91), or polymorphisms in MSH2 (92). RAD51 is one of the central proteins in the homologous repair (HR) pathway, functioning to bind to DNA and promote ATP-dependent homologous pairing and strand transfer reactions (93).

RAD51-G135C polymorphism is significantly over-represented in patients with t-MDS/AML compared with controls (C allele: OR = 2.7) (94). Although XRCC3-Thr241Met was not associated with t-MDS/AML (OR = 1.4, 95%CI, 0.7–2.9), a synergistic effect resulting in an eightfold increased risk of t-MDS/AML (OR = 8.1, 95% CI, 2.2–29.7) was observed in the presence of XRCC3-241Met and RAD51-135C allele in patients with t-MDS/AML compared with controls (94). Base excision repair (BER) pathway corrects individually damaged bases occurring as a result of ionizing radiation and exogenous xenobiotic exposure. The XRCC1 protein plays a central role in the BER pathway and also in the repair of single strand breaks, by acting as a scaffold and recruiting other DNA repair proteins (86,95). The protein also has a BRCA1 C-terminus (BRCT) domain—a characteristic of proteins involved in DNA damage recognition and response. The presence of variant XRCC1-399Gln has been shown to be protective for t-MDS/AML (96) and basal cell carcinoma (97). Nucleotide excision repair (NER) removes structurally unrelated bulky damage induced by radiation and chemotherapy. The polymorphic Gln variant (ERCC2 Lys751Gln) of the NER pathway is associated with t-MDS/AML (98).

Previous studies have examined single gene polymorphisms in small samples, contributing to the largely inconclusive results (93,96–113). In the few studies where multiple SNPs were studied, individuals with more than one variant

were at higher risk (93,99,114). Furthermore, none of the previous studies have systematically examined gene–therapy interactions, because of the absence of detailed therapeutic exposure data collected by the previous studies and the small sample sizes. Researchers are currently systematically addressing these questions.

Pathogenesis of Second Primary Cancers

In the past decade, progress in discerning carcinogenesis has focused on the cumulative mutations that alter specific loci in DNA, leading to downstream alterations in the encoded proteins. Two general types of genes have been the target of interest for unraveling neoplastic transformation. The first is the proto-oncogene, which codes for cellular signaling components that play a role in controlling normal growth and differentiation. The ability of proto-oncogenes to participate in neoplastic transformation arises from the fact that the protein products of these genes are crucial relays in the elaborate biochemical circuitry that governs vertebrate cells (115).

There are several general categories of proto-oncogenes. These include growth factor receptors acting via a tyrosine-specific protein kinase pathway, glutamine triphosphate (GTP) binding proteins, membrane- and cytoskeletal-associated tyrosine-specific kinases, extracellular growth factors, serine- and threonine-specific protein kinases, and steroid-type growth factor receptors (Fig. 20.5). Therefore, products of the

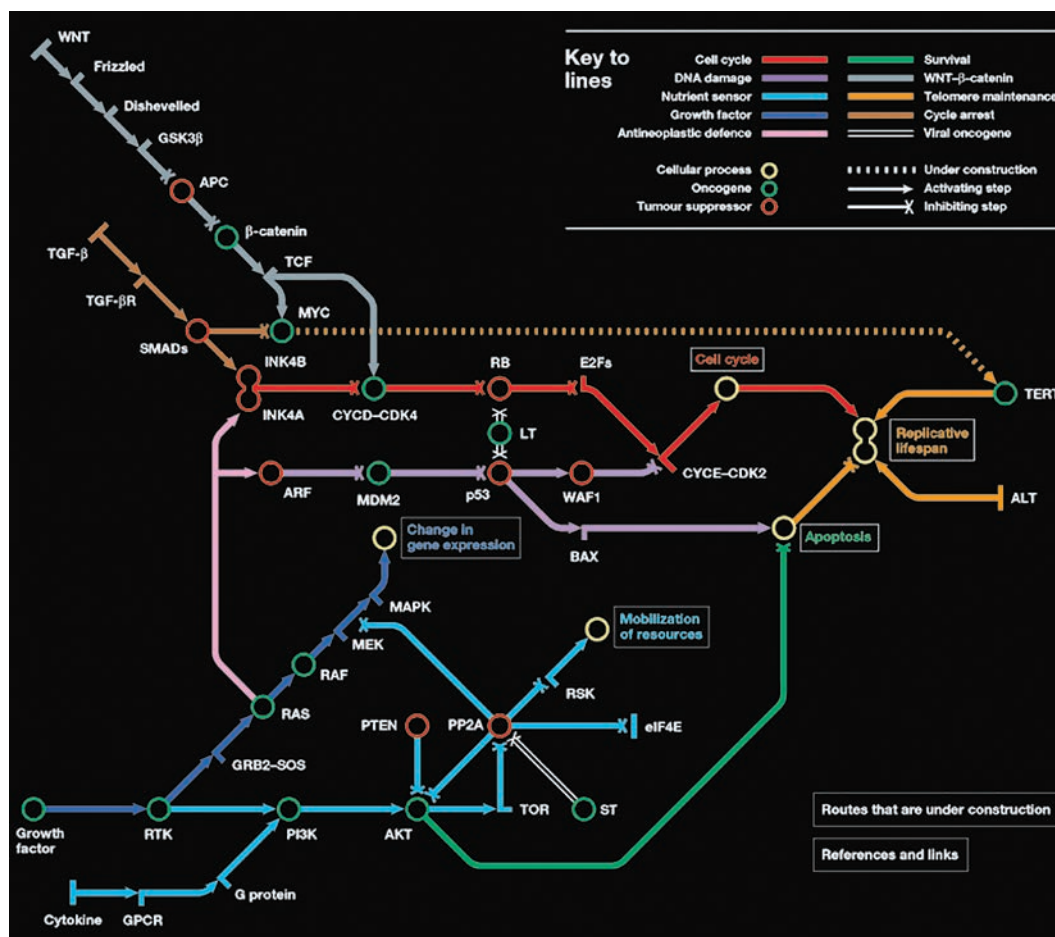


Figure 20.5 A subway map of cancer pathways. (Hahn WC, Weinberg RA. Modelling the molecular circuitry of cancer. *Nat Rev Cancer*. 2002;2(5):331–341, with permission.)

proto-oncogene may include polypeptide hormones acting on the cell surface, receptors for these hormones, proteins that convey signals from the cell surface to its depths, and chemicals that affect nuclear functions.

The second category of genes involved in carcinogenesis is called tumor suppressor genes (116). These genes restrain cell growth. Carcinogenesis could be the result of inactivation of a tumor suppressor gene, eliminating its growth-suppressing function. This could allow unbridled cell growth and neoplastic transformation.

There has been much interest in tumor suppressor genes in childhood cancer. This interest initially focused on the RB1 gene and its relationship to retinoblastoma and osteogenic sarcoma and is now expanding to a variety of other malignancies (74). In late G1 or early S phase the RB1 protein (pRB) becomes progressively more phosphorylated at multiple sites. The enzymes that carry out these phosphorylation reactions are cyclin-dependent kinases, which are activated by complex formation with cyclins A, D, and E and regulate cell cycle events. The level of pRB phosphorylation remains high until late in M phase, when a phosphatase removes these post-translational modifications. The pRB is again underphosphorylated in G0/G1. These periodic phosphorylation and dephosphorylation reactions are believed to modulate pRB's physical and functional interaction with a variety of cellular targets.

In resting cells (G0) or cells in early G1, pRB can be found in a complex with a cellular transcription factor called E2F. In general, transcription factors are proteins that, by binding to a specific DNA sequence adjacent to the genes they regulate, promote the expression of particular genes. E2F contributes to the activation of a constellation of genes encoding S-phase functions needed for DNA synthesis. When E2F is complexed to pRB, E2F gene-mediated transcriptional activation does not occur. Therefore, RB1 functions in part by its sequestration of E2F in G1 (117,118).

The p53 gene is another tumor suppressor gene that has provoked interest among those studying childhood cancer. p53 has been shown to be mutated in many histologic types of cancer (116–118). In various cell lines p53 has been shown to inhibit proliferation, promote differentiation, enable cells to arrest their growth after exposure to certain DNA damaging agents, and mediate apoptosis (117,118).

The mechanism through which p53 exerts its growth suppressive function is under vigorous investigation. Much of the available evidence suggests that p53 acts as a transcriptional activator or a transcription factor (117,118). Some sequence-specific DNA binding has shown that p53 may also function as a transcription factor by interacting with other DNA-bound proteins, thereby affecting their activity. Several transcriptional target genes for p53 have now been identified, with the assumption that such genes are likely to mediate the growth suppressive properties attributed to p53 (117,118).

p21 is one of the most important mediators of p53's actions. The suppression of cell growth by p53 may be related to activation of p21 expression. As a transcription factor, p53 induces p21, which in turn inhibits cyclin-dependent kinases. As an inhibitor of cyclin-dependent kinases, p21 prevents phosphorylation of pRB and hence the expression of genes needed for replication.

Apoptosis, or programmed cell death, is an important biological consequence of exposure to ionizing radiation and other DNA-damaging agents. Initial reports of radiation-

induced apoptosis emphasized the importance of p53 in this cellular response. Cell cycle arrest after irradiation at the G1 checkpoint requires the expression of p53 in some cell lines. In tumor cells that undergo p53-dependent apoptosis, it seems that one of the functions of p53 is to screen for damaged DNA. In the presence of damaged DNA, wild-type p53 facilitates cell cycle arrest and DNA repair. Therefore, it prevents the proliferation of cells with damaged DNA. One might speculate that p53-negative cells that sustain radiochemotherapeutic damage would exhibit a diminished capacity to detect and respond to such damage. Consequently, the damaged DNA could be duplicated. If a lethal mutation had occurred from radiochemotherapeutic damage, then the cell would die. However, if a sublethal mutation had occurred, it is possible that a lack of p53 might allow amplification of the injured DNA and result in a cancer (117,118).

A pervasive dogma in cancer research is that carcinogenesis is a multistage process. The classic description of this process involved the concepts of initiation, promotion, and progression. More recent models involve multiple chromosomal changes in a variety of genes as growth-stimulating oncogenes are activated and tumor suppressor genes inactivated. Is it possible that exposure to a course of therapeutic radiation can result in mutations at the multiplicity of genetic loci necessary to produce a secondary cancer?

One possibility is that a protracted course of radiation will induce sufficient mutations to produce all or most of the steps necessary to produce a second cancer. For this to be true, ionizing radiation would have to be capable of producing point mutations to activate proto-oncogenes and point mutations and deletions to inactivate tumor suppressor genes. Radiation would produce cancer by the instantaneous creation of initiated cells (119). Because radiation is ineffective at causing point mutations but extremely effective at causing large deletions, inactivation of tumor suppressor genes such as p53 is likely to be an important mechanism of radiation carcinogenesis. The cell initiated by radiation may undergo clonal expansion with subsequent promotion. Once a malignant cell is generated, it gives rise to a tumor after some lag period.

It is also possible that in addition to inactivating tumor suppressor genes, radiation may generate a malignant diathesis by other subtle mechanisms. For example, a mutation in the genes responsible for DNA mismatch repair could lead to defective repair phenotype. In this way, multiple mutations may derive from a radiation-induced mutation in a repair system. In this postulated mechanism, radiation causes persistent genomic instability, resulting in a high rate of spontaneous mutations including those associated with a malignant phenotype (120).

Despite the support for the aforementioned mechanisms of carcinogenesis, accumulating evidence has challenged some of these theories and provoked alternate hypotheses. These include theories hypothesizing that a breakdown in DNA duplication or repair leads to many thousands of random mutations in cells, that damage to a few "master" genes corrupts the genome, leading to deregulation, and that abnormal numbers of chromosomes may lead to the ensuing carcinogenic events (121–125).

Environmental and Lifestyle Factors

Environmental exposures and lifestyle factors such as tobacco, alcohol, diet, and hormonal factors and their association with SPCs have been most commonly studied in survivors of

adult-onset cancers. Smoking has been linked with lung cancer occurring as an SPC among survivors of Hodgkin lymphoma, with the risk increasing with increasing radiation dosages, suggesting a positive interaction on a multiplicative scale (126). Moreover, the increase in risk of lung cancer with increasing radiation dosage was much greater among the patients who smoked after the diagnosis of Hodgkin lymphoma than among those who refrained from smoking ($p = 0.04$) (126). Alcohol consumption has been shown to be a risk factor for oral, esophageal, and liver cancers occurring as SPCs (127). There are several anatomic sites, such as colon, breast, ovary, uterus, and prostate, where nutritional and hormonal factors play a role in carcinogenesis. Bidirectional associations across several hypothesized nutrition- and hormone-related cancers have been demonstrated across many registries. However, these studies are generally lacking in specific exposure information, and the support for a given etiologic hypothesis usually is indirect because the correlations between cancers hypothesized to share a common risk factor are examined without direct measurement of the putative common risk factors or potential confounders. Moreover, because the environmental exposures and lifestyle factors seem to be associated primarily with adult-onset cancers, a sufficiently large cohort of childhood cancer survivors must be followed until they reach the age at which they would be at risk for developing such cancers.

PRIMARY CANCERS ASSOCIATED WITH SECOND PRIMARY CANCERS

The next section focuses on certain primary cancers that are associated with a significantly greater risk of SPCs (e.g., retinoblastoma and Hodgkin lymphoma). It also focuses on primary cancers, with large, well-characterized cohorts of patients followed for sufficiently long periods of time to develop SPCs (e.g., ALL and the Wilms tumor).

Retinoblastoma

Children with hereditary retinoblastoma are at exceptionally high risk of developing multiple primary cancers, especially osteosarcoma and soft tissue sarcomas (relative risk [RR] = 30, 95% confidence interval [CI] 26–47) (14,128). On the other hand, patients with nonhereditary retinoblastoma appear not to be at greater risk for SPCs. The cumulative incidence of a second cancer at 50 years after diagnosis was reported to be 51% ($\pm 6.2\%$) for hereditary retinoblastoma and 5% ($\pm 3\%$) for nonhereditary retinoblastoma. The high risk of multiple primary cancers in patients with hereditary retinoblastoma is attributable primarily to germ-line mutations in the retinoblastoma tumor suppressor gene, *RB1*. For second primary soft tissue sarcomas, the relative risks showed stepwise increase for all dosage categories of radiation therapy and were statistically significant at 10–29.9 Gy and 30–59.9 Gy. Third and additional nonocular tumors (soft tissue sarcomas, bone tumors, and skin cancers) have been reported among patients with retinoblastoma who had developed a radiation-related SPC (129), with the 5- and 10-year incidence rates reported to be 11% and 22%, respectively. The cumulative probability of death from an SPC has been reported to be 26% at 40 years after bilateral retinoblastoma diagnosis (130). In an extended (beyond 40 years) analysis of data from this report, the standardized mortality ratio was 35, and included not only sarcomas, melanomas, and CNS neoplasms, but also uterine and lung cancer (131).

Radiotherapy for retinoblastoma further increased the risk of mortality from second cancers in this report. The risk for six subtypes of soft tissue sarcoma (fibrosarcoma, liposarcoma, histiocytoma, leiomyosarcoma, rhabdomyosarcoma, and others) was evaluated in a cohort of 963 on-year survivors of hereditary retinoblastoma (132). The study demonstrated elevated risk for all sarcomas combined (standardized incidence ratio [SIR] = 184, 95% CI, 143–233), and for individual subtypes. Leiomyosarcoma was the most frequent subtype (SIR = 390, 95% CI, 247–585), with 78% of the leiomyosarcomas diagnosed 30 or more years after the retinoblastoma diagnosis. Among patients treated with radiotherapy for retinoblastoma, there was a statistically significantly increased risk of soft tissue sarcomas in the field of radiation, as well as outside the field, indicating the role for genetic predisposition independent of radiation. The cumulative risk for any soft tissue sarcoma was 13.1% at 50 years (95% CI, 9.7–17%).

These studies indicate that genetic predisposition has a substantial impact on risk of subsequent cancers in patients with retinoblastoma, which is further increased by radiation therapy. Moreover, patients with retinoblastoma are at a higher risk for developing third and fourth tumors, although the location and other risk factors are similar to those described for SPCs.

Hodgkin Lymphoma

Reports from large, well-characterized cohorts of patients reveal that in survivors of Hodgkin lymphoma the risk of developing SPCs is 7–18 times higher than in the general population (Table 20.5) (6,11,53,54,133).

Metayer et al. (134) reported their analyses of 5925 patients with Hodgkin lymphoma diagnosed before 21 years of age and reported to 16 population-based cancer registries in North America and Europe between 1935 and 1994. A total of 157 solid (RR = 7.0, 95% CI 5.9–8.2) and 26 acute leukemias (RR = 27.4, 95% CI 17.9–40.2) were reported. The risk of solid tumors remained elevated among 20-year survivors (RR = 6.6) and persisted for 25 years (RR = 4.6). Temporal trends for cancers of thyroid, female breast, bone and connective tissue, stomach, and esophagus were consistent with the late effects of radiotherapy.

The risk of SPCs in a cohort of 1641 patients diagnosed before the age of 20 years in the five Nordic countries was described to be 7.7 times that of the general population (54). The overall cumulative risk of SPCs was 1.9% at 10 years, 6.9% at 20 years, and 18% at 30 years. High risks were observed for breast cancer (RR = 17, 95% CI 9.9–28), thyroid cancer (RR = 33, 95% CI 15–62), secondary leukemia (RR = 17, 95% CI 6.9–35), and the non-Hodgkin lymphoma (RR = 15, 95% CI 4.9–35).

A cohort of 694 children and adolescents followed for a median of 13 years for the development of SPCs revealed the relative risk of developing an SPC to be 15.4 (95% CI 10.6–21.5) for female and 10.6 (95% CI 6.6–16.0) for male patients (53). Breast cancer and soft tissue sarcomas were the most common solid tumors. The actuarial risk of SPC at 20 years of follow-up was 9.7% for men, 16.8% for women, and 9.2% for breast cancer.

The Late Effects Study Group followed a cohort of 1380 children with Hodgkin lymphoma diagnosed at a median age of 11 years (range: 0.3–16) in North America and Europe between 1955 and 1986 to determine the incidence of second

Table 20.5
Second Cancers after Childhood Hodgkin Lymphoma

Reference	Cohort Size	Time Period Studied	Number of Second Cancers	Cumulative Incidence (%) (Years)	Standardized Incidence Ratio
53	694	1960–1995	59	Males: 9.7 (20) Females: 16.8 (20)	Males: 10.6 Females: 15.4
54	1641	1940s to 1991	62	18 (30)	7.7
133	182	1960–1989	28	26.7 (30)	9.4
11	1380	1955–1986	135	31.2 (30)	17.9
134	5925	1935–1994	195	Solid tumors: 11.7 (25)	7.7
19	930	1960–1990	102	19 (25)	Males: 8.41 Females: 19.93

malignant neoplasms and associated risk factors (11). The cohort was recently updated to extend the median length of follow-up from 11 to 15.1 years (31). The median age at last follow-up was 27.8 years (3.5–52.7), and the median length of follow-up was 17.0 years (0.1–45). An additional 103 subsequent neoplasms were ascertained (total $n = 212$). The cohort's risk of developing SPCs was 18.5 times higher than that of the general population (SIR = 18.5, 95% CI 15.6–21.7). The cumulative incidence of any second malignancy was 10.6% (95% CI 8.6–12.7) at 20 years, increasing to 26.3% at 30 years; and of the cumulative incidence of solid malignancies was 7.3% (95% CI 5.5–9.1) at 20 years, increasing to 23.5% at 30 years. Breast cancer was the most common solid malignancy (SIR = 56.7, 95% CI 40.5–77.3). Other commonly occurring solid malignancies included thyroid (SIR = 36.4), bone (SIR = 37.1), colorectal (SIR = 36.4), lung (SIR = 27.3), and gastric (SIR = 63.9) cancers. Risk factors for solid tumors included young age at Hodgkin lymphoma and radiation-based therapy. Thirty-two patients developed third neoplasms, with the cumulative incidence approaching 21% at 10 years from diagnosis of second malignancy.

Constine et al. recently evaluated 930 children treated between 1960 and 1990. Treatment included radiation alone (43%), chemotherapy alone (9%), or both (48%). SPCs occurred in 102 (11%) patients, with a 25-year actuarial rate of 19%. As can be seen in Table 20.6, the earliest solid tumors occurred at 8 years, and continued to occur throughout the follow-up interval. The survival for all patients, stratified according to whether they developed a SPC, is shown in Fig. 20.6. Notably, the SIR for females, 19.93, was significantly greater than for males, 8.41 ($p < 0.0001$) (Fig. 20.7). After excluding breast cancer, the SIR for females was 15.4, still significantly greater than for males ($p = 0.0012$) (Fig. 20.8), primarily due to secondary thyroid cancer. Increasing radiation dose was associated with an increasing SIR ($p = 0.0085$). Overall, an increased risk was associated with female gender, increasing radiation dose, and age at treatment (12–16 years).

Follow-up of these large cohorts of survivors of childhood Hodgkin lymphoma for extended periods of time documents the increasing occurrence of radiation-associated solid tumors, especially breast and thyroid cancers and the emergence of other cancers common in the adult population, such

Table 20.6
Time from Diagnosis to Second Malignancies

SMN Site	Number	Time (Years)			SIR	AER
		Median	Minimum	Maximum		
Breast	29	17.2	9.4	36.1	37.25	18.62
Thyroid	14	14.4	8.5	23.0	25.14	8.87
Gastrointestinal	13	15.8	10.0	33.1	27.15	8.26
Leukemia	9	6.4	2.4	17.8 ^a	21.49	5.66
Soft tissue sarcoma	9	15.6	8.7	18.2	50.35	5.82
Bone	8	11.6	9.2	23.4	53.47	5.18
Lymphoma	6	15.3	1.4	23.9	5.20	3.20
Central nervous system	4	11.3	8.2	29.3	9.68	2.37
Head and neck	3	16.4	15.1	19.9	12.87	1.83
Lung	2	13.4	10.6	16.2	4.55	1.03
Other	5	11.5	0.03	24.9	1.78	1.45

^aTwo chronic leukemias occurred at 14.3 and 17.8 years, respectively. No acute leukemias occurred after 7 years.

From Constine LS, Tarbell N, Hudson MM, et al. Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose. *Int J Radiat Oncol Biol Phys*. 2008;72:24–33, with permission.

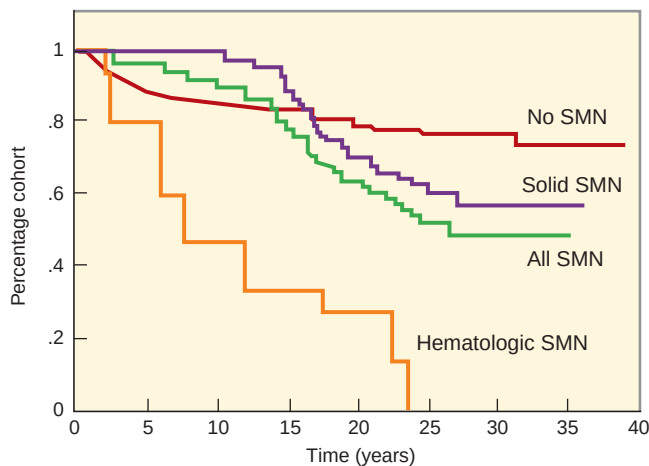


Figure 20.6 Overall survival of patients according to whether they developed no secondary malignancy, a solid secondary malignancy, a hematopoietic secondary malignancy, or any secondary malignancy. (From Constine LS, Tarbell N, Hudson MM, et al. Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose. *Int J Radiat Oncol Biol Phys*. 2008;72:24–33, with permission).

as colon and lung cancer, at a younger age than expected in the general population. It is notable that modern techniques that reduce the volume of irradiated tissue are associated with a decreased risk for breast cancer, and this may be expected to also occur for other SPCs (135).

Acute Leukemia

For survivors of childhood ALL, the estimated actuarial risk of developing an SPC has been reported to be 2.5–5% at 15 years from diagnosis (Table 20.7) (6,16,34,136–139),

demonstrating quite clearly that the risk of SPC in children with ALL treated with contemporary risk-based therapy remains low.

Among the SPCs observed after treatment of ALL, central nervous system (CNS) tumors in patients treated with cranial irradiation, acute myeloid leukemia, and thyroid cancer are most commonly reported. Children under 6 years of age at the time of radiation to the CNS are at a higher risk of developing second primary brain tumors (6,16). In a recent study that evaluated 16,540 survivors of any leukemia, the most frequent SPCs were CNS tumor (SIR 8.52), non-Hodgkin lymphoma (SIR 9.41), and thyroid cancer (SIR 18.8) (140).

The incidence and type of SPCs after Berlin–Frankfurt–Munster treatment in 5006 children with ALL diagnosed between 1979 and 1995 and followed for a median of 5.7 years were reported (139). This cohort's risk of developing an SPC was 14 times higher than that of the general population, and their risk of developing a brain tumor was 19 times higher. The cumulative risk of SPC was 3.5% at 15 years among patients treated with cranial irradiation but only 1.2% among nonirradiated patients.

A cohort of 8831 children diagnosed with ALL and enrolled on Children's Cancer Group therapeutic protocols between 1983 and 1995 revealed the cumulative incidence ($\pm$ SE) of any SPC to be $1.3 \pm 0.2\%$ (at 10 years), representing a risk of 7.9 times higher than in the general population. The risk was significantly higher for acute myeloid leukemia (RR = 52.3), the non-Hodgkin lymphoma (RR = 20.8), parotid gland tumors (RR = 33.4), thyroid cancer (RR = 13.3), brain tumors (RR = 10.1), and soft tissue sarcoma (RR = 9.1). Multivariate analysis revealed relapse of primary disease (RR = 3.5, 95% CI 2.1–5.8), female sex (RR = 1.8, 95% CI 1.1–2.8), and radiation to the craniospinal axis (RR = 1.6, 95% CI 1.0–2.6) to be independently associated with a higher

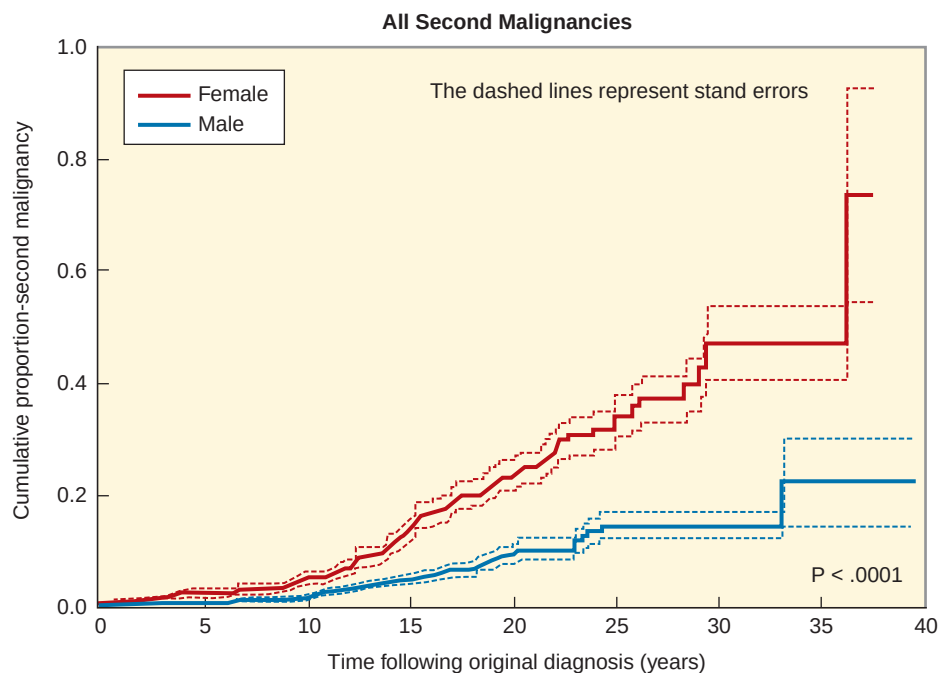


Figure 20.7 Cumulative proportion of second malignancies according to gender, with standard errors. (From Constine LS, Tarbell N, Hudson MM, et al. Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose. *Int J Radiat Oncol Biol Phys*. 2008;72:24–33, with permission).

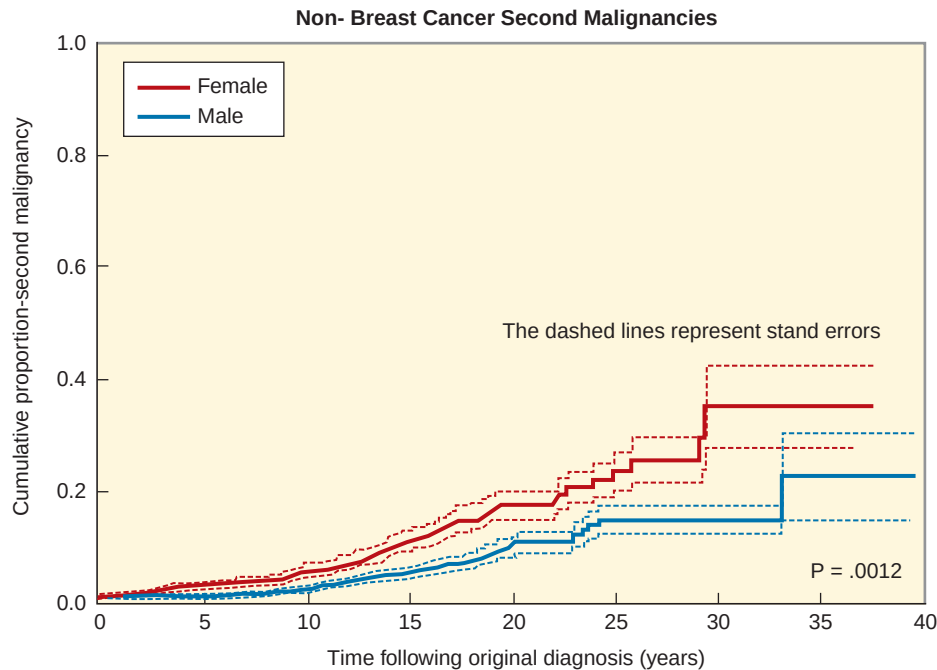


Figure 20.8 Cumulative proportion of second malignancies according to gender, with standard errors, after excluding breast cancer. (From Constine LS, Tarbell N, Hudson MM, et al. Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose. *Int J Radiat Oncol Biol Phys*. 2008;72:24–33, with permission).

risk of second neoplasms. Actuarial survival at 10 years from diagnosis of second neoplasms was 39%.

Wilms Tumors

Between 1969 and 1991, 5278 patients were enrolled in the National Wilms Tumor Study (NWTs) and by the end of 1993 had contributed 39,461 person-years of follow-up. Forty-three second neoplasms were observed, whereas only 5.1 were expected (RR = 8.4, 95% CI 6.1–11.4) (42). The cumulative incidence of an SPC was 1.6% after 15 years from diagnosis of Wilms tumor. Abdominal irradiation received as part of initial therapy was associated with a higher risk of an SPC (RR = 1.4 per 10 Gy, 95% CI 1.1–1.8). Doxorubicin potentiated the radiation effect. Treatment for relapse further increased the risk of SPCs. Of the 43 patients with SPCs, 7 were identified to have acute myeloid leukemia at a median of 3 years from diagnosis of Wilms tumor (141). All 7 patients had received chemotherapy regimens that included doxorubicin or etoposide, and 6 of the 7 patients had received

infradiaphragmatic irradiation. A report from the United Kingdom found a standardized incidence ratio of 6.7 for solid SPCs, and the cumulative incidence for all solid tumors was 2.3%, 6.8%, and 12.2% by ages 30, 40, and 50 years, respectively (142). In a recent report that updates data from NWTs and reviews 6185 patients, there were 27 deaths from SPCs among the almost 3000 5-year survivors, and primarily included CNS, GI, and lymphatic/hematopoietic neoplasms (143). These results demonstrate the importance of current efforts to limit the use of intensive chemotherapy and radiation therapy to patients with aggressive disease.

Bone Tumors

A recent report assessed the incidence of solid organ SPCs in survivors of bone tumors who were treated on legacy Children's Cancer Group/Pediatric Oncology Group protocols from 1976 to 2005, 2842 patients (1686 with osteosarcoma and 1156 with Ewing sarcoma). The standardized incidence ratio was 19 for patients treated for osteosarcoma, and

Table 20.7
Second Cancers after Childhood Acute Lymphoblastic Leukemia

Reference	Cohort Size	Time Period Studied	Number of Patients with Second Cancers	Cumulative Incidence (%) (Years)	Standardized Incidence Ratio
136	1597	1972–1995	13	2.7 (18)	— ^a
137	981	1958–1985	8	2.9 (20)	5.9
138	1815	1962–1988	20	5.0 (15)	— ^a
139	5006	1979–1995	52	3.3 (15)	— ^a
34	8831	1983–1995	70	1.3 (10)	7.0
16	9720	1972–1988	43	2.5 (15)	7.0

^aInformation not available.

5.0 for patients treated for Ewing sarcoma, and the 10-year cumulative incidence of solid organ SPCs for the entire cohort was 1.4% (144).

Non-Hodgkin Lymphoma

The incidence of SPC in children with non-Hodgkin lymphoma was recently assessed by Bluhm et al. (145) among 1082 5-year survivors in the Childhood Cancer Survivor Study cohort. Twenty-seven solid tumors developed with a 3% cumulative incidence between 5 and 20 years, and risk factors were female sex, mediastinal involvement with non-Hodgkin lymphoma, and irradiation exposure of the breast tissue and thyroid gland.

SECOND PRIMARY CANCER REGARDLESS OF PRIMARY MALIGNANCY

Certain radiation-related SPCs, such as breast, brain, and thyroid cancers, and musculoskeletal tumors, have been well characterized, especially in survivors of childhood cancer (Fig. 20.9). The next section is devoted to these SPCs, focusing on the magnitude of risk and risk factors associated with their development.

Musculoskeletal Tumors

Radiation-associated bone tumors and sarcomas demonstrate a clear association with radiation therapy (146,147). The secondary bone tumors develop in the radiation field, typically after a latency period of 10 years. Both bone tumors and sarcomas may be aggressive and respond poorly to therapy (13,43,44).

The estimated risk of subsequent bone tumors among 9170 2-year survivors of childhood cancer was reported to be 133 times that of the general population (95% CI 98–176), with an estimated 20-year cumulative risk of $2.8 = 0.7\%$ (44). As compared with matched controls who had survived cancer in childhood but not developed bone cancer later, the risk (95% CI 1–7.7) of developing a bone tumor was 2.7 times higher in patients who received radiation therapy, with a

sharp dose–response gradient, reaching 40 times higher after dosages to the bone of more than 60 Gy. After adjustment for radiation therapy, treatment with alkylating agents was also linked to bone cancer (RR = 4.7, 95% CI 1.0–22.3), with the risk increasing with cumulative drug exposure.

A report from the population-based National Registry of Childhood Tumours in Britain of a cohort of 13,175 3-year survivors of childhood cancer diagnosed between 1940 and 1983 revealed the cumulative probability to be 0.9% at 20 years, except after hereditary retinoblastoma (7.2%), Ewing sarcoma (5.4%), and other malignant bone tumors (2.4%) (43). The risk of bone cancer increased substantially with the cumulative dosage of radiation to the bone ($p = 0.001$, linear trend). At the highest level of exposure, the risk appeared to decline ($p = 0.065$, nonlinearity). The risk of bone cancer increased linearly ($p = 0.04$, one-tailed test) with the cumulative dosage of alkylating agents.

A cohort study of 4400 3-year survivors of a first solid cancer during childhood diagnosed in France and the United Kingdom between 1942 and 1986 revealed the risk of osteosarcoma to be a linear function of the local radiation dosage (13). Bilateral retinoblastoma, Ewing sarcoma and soft tissue sarcoma were found to be associated with a higher risk of a subsequent osteosarcoma.

A total of 108 patients with sarcomas were diagnosed in 14,372 long-term survivors of childhood cancer participating in the Childhood Cancer Survivor Study, a median of 11 years from diagnosis of childhood cancer. The risk of sarcoma was more than ninefold higher among childhood cancer survivors than among the general population (SIR = 9.02, 95% CI, 7.44–10.93). The excess absolute risk was 3.25 per 10,000 person-years. Higher risk was associated with primary sarcoma diagnosis (RR = 10.1, 95% CI, 4.7–21.8), radiation therapy (RR = 3.1, 95% CI, 1.5–6.2), with a history of other second neoplasms (RR = 2.2, 95% CI, 1.1–4.5), and with treatment with higher doses of anthracyclines (RR = 2.3, 95% CI, 1.2–4.3) or alkylating agents (RR = 2.2, 95% CI, 1.1–4.6) (147).

These studies demonstrate that the risk of second primary bone tumors and sarcomas is increased among certain specific tumor types, and that the risk is associated with the use of radiation therapy anthracyclines and alkylating agents. These studies therefore provide a rational basis for targeted surveillance and modification of therapeutic protocols in certain high-risk groups.

Breast Cancer

Breast cancer has been increasingly reported among patients receiving radiation for Hodgkin lymphoma. Results from several registries show that 10 or more years after radiation, the overall breast cancer risk is approximately 4 times higher (6,134,148–153), and can be 55–75 times higher, in girls exposed to radiation at puberty than in the general population (11,31). The risk of developing breast cancer remains elevated for many years (Table 20.8) (11,31). The risk is highest among patients diagnosed at a younger age, with the risk decreasing to that of the general population for patients receiving radiation for their primary cancer after the age of 30 years. Again, the risk appears to increase with radiation dosage, and the tumors typically develop in or at the edge of the radiation field (6,11,134,148,154,155). The risk of second breast cancer after chest radiation increases in a linear fashion with radiation dose (p for trend <0.001) (156,157).

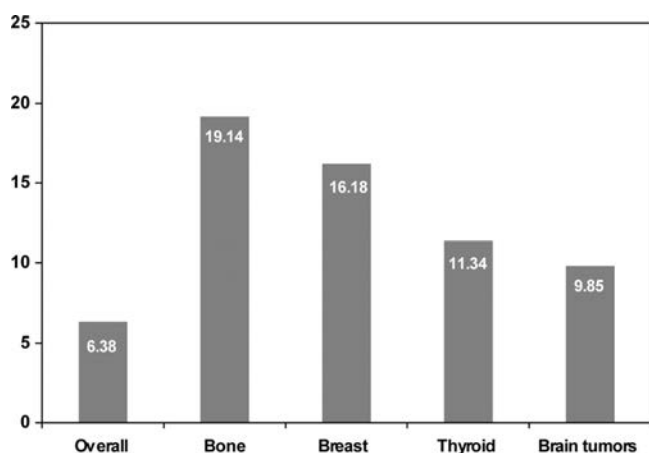


Figure 20.9 Standardized incidence ratio by type of second primary cancer (Adapted from Neglia JP, Friedman DL, Yutaka Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2001;93:618–629.).

Table 20.8
Risk of Breast Cancer in Hodgkin Lymphoma Survivors by Age and Latency

Reference	Size of Cohort	Length of Follow-Up	No. of BCs	Median Age at Diagnosis of HL/BC	Median Latency	Relative Risk	Risk Factors	Outcome (% Alive)
6	13,851	15.4 years	60	— ^a	— ^a	16	Radiation therapy	— ^a
158	3,817	— ^a	105	< 30 years	18 years	61	Radiation therapy Alkylating agents (decreased risk)	
11	483	11 years	17	11/32 years	19 years	75	10–16 years Radiation therapy	82%
148	885	10 years	26	28/40 years	15 years	13 (<15 years at diagnosis)	Age <30 years at Radiation therapy	73%
134	5,925	10.5 years	52	— ^a	— ^a	14	Radiation therapy	— ^a

^aInformation not available.

BC, breast cancer; HL, Hodgkin lymphoma.

Follow-up of a cohort of female Hodgkin lymphoma survivors diagnosed and treated before 16 years of age showed that the actuarial estimated cumulative probability of developing breast cancer approached 28% at 30 years from diagnosis (31). The median age at diagnosis of Hodgkin lymphoma was 14 years, and the median age at diagnosis of breast cancer was 32 years. The median latency between the diagnosis of Hodgkin lymphoma and the diagnosis of second primary breast cancer was 18 years (range 4–28 years). Of the 29 patients with breast cancer, 10 subsequently developed cancer in the contralateral breast. The estimated cumulative probability of developing breast cancer among women receiving irradiation approached 25% by 40 years of age.

The Childhood Cancer Survivor Study cohort has evaluated the risk of breast cancer among 13,581 5-year survivors of childhood cancer (6). Breast cancer was the most common SPC ($n = 60$), and the cohort had a risk of developing a second primary breast cancer 16.2 times higher than that of the general population. The majority of second primary breast cancers occurred among survivors of childhood Hodgkin disease. The median time to development of breast cancer was 15.7 years. The risk of developing a breast cancer appeared to remain elevated throughout the follow-up period ($RR = 10.1$ at 5–9 years of follow-up and 10.1 at 20–30 years of follow-up).

In an early report on secondary breast cancer among female survivors of Hodgkin lymphoma, van Leeuwen et al. (126) found that the risk increased with increasing radiation dosage up to at least 40 Gy. They explained the substantial risk reduction that was associated with chemotherapy as possibly reflecting its effect on menopausal age, suggesting that ovarian hormones promote tumorigenesis after radiation has produced an initiating event. These findings are similar to those of Travis et al. (158), who found that hormonal stimulation appears important for the development of radiation-induced breast cancer, as evidenced by the reduced risk associated with ovarian damage from alkylating agents or radiation. Recent

reports also show that ovarian hormonal suppression from pelvic irradiation decreases the risk for secondary breast cancer (135,150,159). Inskip et al. recently evaluated 6647 women who were 5 years survivors of childhood cancer and in the Childhood Cancer Survivor Study. The odds ratio for breast cancer increased linearly with RT dose, and reached 11-fold at 40 Gy (159). The high radiation-related risk, which does not diminish at the highest dosages or the longest follow-up, suggests the need for lifelong surveillance. For women treated after the age of 30, however, no excess breast cancers have occurred (148).

Thyroid Cancers

The risk of thyroid cancer has been described after radiation therapy for several primary cancers, including Hodgkin lymphoma, ALL, and brain tumors, and after total body irradiation for hematopoietic cell transplantation (6,11,16,31,32, 34,160–164). Risk factors include radiation therapy at a young age and female sex.

The long-term risk of developing a thyroid tumor in 4096 3-year survivors of childhood cancer treated between 1942 and 1985 in France and Britain was reported to increase with increasing dosage of radiation: A dosage of 0.5 Gy was associated with a risk of developing a thyroid cancer 35 times higher than in the general population, and the risk increased to 73 times when the exposure increased to 3.6 Gy (161). Radiation therapy at a young age has been identified as a risk factor for the development of secondary thyroid cancers (160). The risk of thyroid cancer was reported to be 18 times that of the general population among 1791 5-year survivors of Hodgkin lymphoma followed as part of the Childhood Cancer Survivor Study cohort (162). Thyroid cancer has also been reported among patients receiving radiation to the craniospinal axis for ALL (6,16,31). The Childhood Cancer Survivor Study utilized a nested case-control study design to describe the risk factors associated with secondary thyroid

cancer. The case series was derived from 69 cases of thyroid cancer (78% papillary, 15% follicular, 7% other/unspecified) and 265 controls from a cohort of 14,054 childhood cancer survivors. A dose–response relationship between thyroid cancer and radiation up to 20–29 Gy, but a downturn in the odds ratio from a peak of 9.8-fold at higher doses, demonstrating evidence for a cell kill effect. The excess relative risk per gray decreased with increasing age at childhood cancer diagnosis, from 4.45 for 0–1 year olds to 0.48 for 15–20 year olds (Fig. 20.3A) (165).

Brain Tumors

Brain tumors have been reported after cranial radiation for histologically distinct brain tumors or for prophylaxis or treatment of CNS disease among patients with ALL. Patients identified to be at greatest risk were those receiving radiation at age less than 6 years (6,16,34,136–139). A nested case-control study design was utilized by the Childhood Cancer Survivor Study to evaluate the risk factors for the occurrence of new primary neoplasms of the CNS (33). The report included 116 survivors who developed a subsequent CNS tumor, each compared to four individually matched control subjects. The median time between original cancer diagnosis and development of a subsequent glioma or subsequent meningioma was 9 and 17 years, respectively. Radiation exposure was statistically significantly associated with the risk of subsequent CNS tumors (odds ratio [OR] = 6.8 for glioma and OR = 9.9 for meningioma), with a linear dose–response pattern. However, the pattern differed substantially for glioma compared to meningioma, with slopes of 0.33 and 1.06 per Gy, respectively (Fig. 20.3B). Younger age at radiation exposure was an independent risk factor for a secondary glioma.

Other Carcinomas

Bassal et al. (166) analyzed the risk of secondary carcinomas in 13,136 childhood cancer survivors (>5 years) in the Childhood Cancer Survivor Study. Seventy-one carcinomas were diagnosed at a median age of 27 years and a median elapsed time of 15 years, and included genitourinary system (35%), head and neck (32%), gastrointestinal (23%), and other sites (10%). Fifty-nine percent developed the SPC in an irradiated field.

Prevention Strategies

The absolute risk of SPC is small, with fewer than two excess second cancers occurring per 1000 patient-years of follow-up (6). The ongoing efforts to improve survival after childhood cancer must not be overshadowed by the risk of SPC. However, of all possible late sequelae, SPC can be the most devastating. It is therefore imperative that patients and health care providers are aware of risk factors for SPC and the populations at greater risk for developing SPCs so that surveillance is focused and early prevention strategies can be implemented.

Examples of primary prevention strategies include use of gender-specific therapy for patients with Hodgkin lymphoma to reduce the risk of radiation-associated breast cancer among female survivors. Another example of a primary prevention strategy is tailoring therapy based on the identification of patient's heterozygous for drug-metabolizing enzymes before therapy is initiated for the primary cancer.

Secondary prevention measures currently under consideration include programs to educate clinicians and survivors

about the risk of SPC and about ways to decrease the risk of developing SPC by adopting healthful lifestyles. For example, both patients and health care providers need to be educated about the higher risk of breast cancer among the female survivors of childhood cancer. Patients must appreciate the importance of properly conducted self-examination as the foundation of breast cancer screening. In addition, clinical and mammographic screening should be instituted at a younger age and performed more frequently than recommended for the general population (167). Other measures include intervention programs for smoking cessation, screening for breast, lung, and cervical cancers, chemoprevention for specific cancers, and avoidance of unnecessary exposure to sunlight. The Children's Oncology Group (COG) has developed risk-based, exposure-related guidelines (Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers) (168) specifically designed to direct follow-up care for patients who have completed treatment for pediatric malignancies. These guidelines represent a set of comprehensive screening recommendations that can be used to standardize and direct the follow-up care for this group of cancer survivors. Ongoing monitoring facilitates early identification of and appropriate management of treatment-related complications in order to enhance the care of these patients. Specially tailored patient education materials, known as "Health Links," accompany the guidelines, offering detailed information on guideline-specific topics in order to enhance health promotion in this population with specialized healthcare needs. The Guidelines and the Health Links can be downloaded from <http://www.survivorshipguidelines.org>. An interactive Web-based version of a standardized summary form, designed to interface with an automated version of the COG Long-Term Follow-Up Guidelines to generate individualized follow-up recommendations, is currently under development and, when completed, will be available at <http://www.survivorshipguidelines.org>.

Since SMNs remain a significant threat to the health of cancer survivors, vigilant screening is important for those at risk. Risk for therapy-related myelodysplasia and acute myeloid leukemia usually manifests within 10 years following exposure. Recommendations include monitoring with annual complete blood count for 10 years after exposure to alkylating agents or topoisomerase II inhibitors. Most other SPCs are associated with radiation exposure. Screening recommendations include careful annual physical examination of the skin and soft tissues in the radiation field with radiographic or other cancer screening evaluations as indicated. Since outcome after breast cancer is closely linked to stage at diagnosis, close surveillance resulting in early diagnosis should confer survival advantage (169). Mammography, the most widely accepted screening tool for breast cancer in the general population, may not be the ideal screening tool by itself for radiation-related breast cancers occurring in relatively young women with dense breasts; hence the recommendations by the American Cancer Society include the use of adjunct screening with magnetic resonance imaging (170). Thus, specialized recommendations for females who received radiation with potential impact to the breast (i.e., radiation doses of 20 Gy or higher to the mantle, mediastinal, whole lung, and axillary fields) include monthly breast self-examination beginning at puberty, annual clinical breast examinations beginning at puberty until the age of 25 years, and then a clinical breast examination every 6 months, with annual mammograms and MRIs begin-

ning 8 years after radiation or at age 25 (whichever occurs later). Screening of those at risk for early-onset colorectal cancer (i.e., radiation doses of 30 Gy or higher to the abdomen, pelvis, or spine) should include colonoscopy every 5 years beginning at the age of 35 years or 10 years following radiation (whichever occurs last).

Future Directions

While the body of literature documenting the increased risk of SPCs is substantial, there still remain many unknowns about the very long-term effects. Ongoing surveillance will, with time, provide answers to these questions: (i) the magnitude of risk among survivors of adult-onset cancer; (ii) clearly defined associations with therapeutic exposures in these survivors of the adult-onset cancers; (iii) the nature and risk of SPCs in childhood cancer survivors followed for an extended period of time; (iv) impact of the prevention strategies on the reduction in risk of SPCs.

SPCs provide us with a unique opportunity to understand the etiology and pathogenesis of cancer. The exact timing and magnitude of the primary exposure (i.e., cancer therapy) are known, and following the patients closely may lead to a better understanding of the progression of events and perhaps the identification of biomarkers that would identify patients who ultimately develop SPCs (41). Several such studies that involve prospective, longitudinal follow-up of patients are being undertaken to elucidate the sequence of events that ultimately lead to the development of SPC.

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Anesthesia for External Beam Radiotherapy

Scott R. Schulman, Heather J. Frederick, and Edward C. Halperin

Considering the awesome aspect of the therapy machines together with the fact that no one may be with the patient during the period of irradiation, it is surprising that the great majority submit to the complete course of therapy with little or no restraint and no sedation.... In a small number of patients in the infant-to-toddler age group of 1½ to 5 years of age, patient cooperation may be impossible to obtain.... Complete immobility of the patient is absolutely essential for the accuracy and success of treatment.... Sedation of the patient becomes virtually a *sine qua non*.

Harrison and Bennet (1) made these observations more than 30 years ago. Their classic article, "Radiotherapy Without Tears," was the first published report describing anesthesia for radiotherapy in children. The problem of inadequate sedation prompted the authors to develop

the following simple method of anesthesia for radiotherapy of infants.... The method is applicable when the anesthetist remains outside the treatment room and consists of the insufflation of nitrous oxide, oxygen, and halothane through the sidearm of the oropharyngeal airway (1).

Forty years of progress in anesthesiology have validated not only Harrison and Bennet's observation but also their solution to the problem of providing anesthesia for radiotherapy. This chapter reviews issues in the sedation of children with an emphasis on monitoring the anesthetized child in the radiotherapy suite, develops a model of the ideal anesthetic for pediatric radiotherapy, explores anesthetic options for radiotherapy, and discusses the implications of the child's underlying disease that influence the anesthetic choice.

BEHAVIORAL TECHNIQUES TO AVOID ANESTHESIA

When possible, children should be irradiated without anesthesia. In some cases, a behavioral program to teach children how to cooperate with radiation treatment without sedation and anesthesia may be successful. Behavioral therapy techniques, called desensitization or exposure therapy, were originally developed for treating severe anxiety, fears, and phobias. The procedure involves inducing a relaxed state using music, cartoons, stories, or videos. Subsequently, one introduces the staff, equipment, and routines needed for radiation treatment.

A behavioral technique called differential positive reinforcement is used to strengthen cooperation and coping.

Incentives such as praise, stickers, toys, and prizes are provided when the child attempts to cooperate. These are used to shape the child's ability to inhibit movement when instructed to do so. Shaping is a behavioral psychology technique whereby the criteria for reinforcement are gradually altered as the child improves performance. At the beginning, an approximation of the desired behavior is acceptable. After a while, more challenging and rigid criteria are set for reinforcement.

Videotaped cartoons and movies may be used to provide relaxation, distractions, and ongoing positive reinforcement in training young children to cooperate with radiation therapy. A small television monitor can be suspended near the linear accelerator couch and connected to a VCR so that movies or cartoons may be played during radiotherapy while the child is in the treatment position. Slifer et al. (2–4) demonstrated the efficacy of this technique in children between the ages of 2½ and 7 years. Nine of 11 children were able to successfully undergo all of their radiation planning and treatment sessions without sedation.

The implementation of a psychoeducational intervention consisting of careful preparation of the patient for radiotherapy through the use of picture books, medical play, and reward systems reduced the need for anesthesia in a longitudinal study (5). After implementing the intervention, the percentage of children requiring anesthesia decreased from 21% to 9%. The authors concluded that the cost of implementation (median 6 hours of time by a qualified nurse, plus materials) was offset by the reduced requirement for anesthesia.

Many pediatric radiotherapy centers have thoughtful programs designed to provide the services described above. Music therapists, psychologists, play therapists, social workers, and radiation therapists throughout the world have created a variety of culturally appropriate tools that they are almost always willing to share with colleagues including radiation therapy "comic books," "coloring books," video education tools, "make your own movie about radiotherapy with you as the star," cheerful murals painted on the walls of the radiotherapy waiting room, and decorating stabilization devices with child-friendly themes. At meetings of professional societies these heart-warming ideas are freely shared with colleagues.

FREQUENCY OF ANESTHESIA FOR PEDIATRIC RADIOTHERAPY

When behavioral techniques to achieve patient cooperation and stability fail, anesthesia or sedation must be used. The frequency of anesthesia use as a function of patient age at the initiation of external beam radiation therapy in the Duke

Table 21.1
Need for Anesthesia in Children as a Function of Age at Initiation of Irradiation

Age (Years)	Total Number of Patients Receiving External Beam Radiation Therapy under Anesthesia	Total Number of Patients Receiving External Beam Radiation Therapy	Percentage of Patients Needs Anesthesia
0–<1	25	26	96%
1–<2	24	27	89%
2–<3	30	35	86%
3–<4	20	41	49%
4–<5	16	44	36%
5–<6	4	38	11%
6–<7	2	28	7%
7–16	2	273	0.7%
Total	123	512	

From Fortney JT, Halperin EC, Hertz CM, et al. Anesthesia for pediatric external beam radiation therapy. *Int J Radiat Oncol Phys.* 1999;44:587–591, with permission.

University Medical Center pediatric radiotherapy population is shown in Table 21.1. For very young children (≤ 3 years) anesthesia is almost always needed. After approximately 5 years of age, however, anesthesia is rarely needed.

GOALS OF ANESTHESIA FOR RADIOTHERAPY

To accomplish the twin goals of irradiating the treatment volume while sparing healthy tissue, control of patient movement must be precise and absolute. How are these goals achieved in children? The approach varies depending on the institutional resources. Conscious or deep sedation is used in some centers, whereas general anesthesia is used in others. Regardless of the institutional practice, there is no substitute for vigilant monitoring and prompt intervention by people skilled in detecting and managing complications associated with the administration of sedative drugs to infants and children.

Anesthesiologists are increasingly asked to provide care outside the traditional operating room setting, such as in the radiotherapy suite. This is appropriate because the specialty

has unique expertise in patient evaluation, selection, and monitoring and the ability to respond immediately to any complication of therapy. Expertise in drug selection and a comprehensive approach to the care of the child, which includes preanesthetic evaluation, postanesthetic care, and the provision of up-to-date feeding guidelines, are hallmarks of the anesthesiologist.

A prolonged fast before the induction of general anesthesia is no longer necessary. The American Society of Anesthesiology recommendations on preanesthetic fasting apply to all ages and are widely followed as standard of care (6). All patients can safely drink clear liquids (e.g., apple juice, water, popsicles) until 2 hours before induction. Breast milk is allowed up to 4 hours, and milk or formula until 6 hours before induction. A light breakfast, for example toast and milk, may be allowed up to 6 hours prior to anesthesia for afternoon cases, but typically solid foods are withheld after midnight, especially in older children.

The goals of anesthesia for pediatric radiotherapy are listed in Table 21.2. There are several options that, to varying degrees, accomplish the listed goals. There are no prospective,

Table 21.2
Goals for Ideal Anesthesia for Outpatient Pediatric Radiation Therapy

Patient immobility
Rapid and smooth onset of effect with sedation, hypnosis, amnesia, and analgesia adequate for nonpainful radiation therapy procedures, along with a sufficient degree of muscle relaxation
Brief duration of action
Painless administration
Prompt recovery without postprocedure side effects but with residual analgesia and antiemetic effects during recovery
Minimal interference with eating, drinking, and playing
Safety for repeated administration
Low risk of tolerance to the anesthetic agents (tachyphylaxis)
Maintenance of a patent airway in a variety of body positions
Absence of side effects such as cardiovascular instability, respiratory depression, spontaneous movements, and excitatory activity
Cost-effectiveness

Modified from Refs. 9 and 40, with permission.

randomized studies in the setting of pediatric radiotherapy that demonstrate the superiority of one technique of general anesthesia over another.

Several routes of drug administration are available for sedation of children. Each drug and drug combination has its own set of side effects and contraindications. Several general guidelines may be considered. First, the route of administration of the drug should be the least traumatic for the particular child. Oral administration, avoiding intramuscular or intravenous administration, should be considered when feasible. Second, it should be kept in mind that some children will develop a tolerance to certain drugs used for sedation. Over time, the amount of drug and time needed to achieve sedation may both increase.

INHALED ANESTHETICS

Several general anesthetic options exist for radiotherapy. The anesthesiologist individualizes therapy based on data obtained from the patient's history, physical and laboratory examination, and discussions with the child, parents, and radiation oncologist. The physical limitations of the radiotherapy suite (such as the presence of an air exhaust system so that volatile anesthetic agents can be used) are also important in devising the anesthetic plan.

General anesthesia is accomplished with either inhaled agents (Table 21.3) or intravenous agents (e.g., barbiturates, ketamine, propofol). The use of inhalational agents requires an anesthesia machine and, ideally, a waste scavenging system. The first report of anesthesia for pediatric radiotherapy used halothane. Halothane is a halogenated hydrocarbon volatile anesthetic first introduced for clinical use in 1956. Halothane has a long history of safe, effective use in pediatric patients. It rapidly produces an anesthetic state when inhaled, with minimal airway complications such as coughing and laryngospasm. Due to its tendency to depress cardiovascular function in a dose-dependent fashion and its arrhythmogenic potential, it has generally been replaced by sevoflurane for mask induction in children (7). Sevoflurane has minimal pungency compared with halothane and may be more readily tolerated by children. Its lower solubility permits a more precise control over the delivery of anesthesia and a more rapid induction of and recovery from anesthesia. Sevoflurane also seems to have a lower respiratory irritant capacity than halothane and produces less coughing and breath holding than some other inhaled agents (8–11) (Fig. 21.1).

A risk of inhalation anesthesia is upper airway obstruction, which is often exacerbated in radiation therapy by the position of the patient. Positioning often entails immobilization



Figure 21.1 Anesthesia for radiation therapy may be initiated with an intravenous drug and maintained by inhalation anesthesia; it may be initiated and maintained with an intravenous agent, or, as shown in this procedure, it may be initiated and maintained by an inhaled agent. The 2-year-old patient with Stage IV neuroblastoma is seated on a trusted caregiver's lap while the anesthesiologist administers the drug. A therapist is diverting the child by giving a "high five" because "you are being so cooperative." The child received twice-daily radiotherapy for 12 days.

of the child's head in a stabilization device (Fig. 21.2), which can impede airway patency (Fig. 21.3) when an insufflation technique is used. This obstruction is relieved with an oropharyngeal or nasopharyngeal airway or a laryngeal mask airway (LMA). Although endotracheal intubation may be necessary in a small proportion of patients presenting for radiotherapy, it is preferable to avoid this technique because repeated laryngoscopy and intubation carry the risk of airway edema and trauma to the laryngeal structures. Intensity-modulated radiotherapy and tomotherapy techniques often allow the radiation oncologist to use a supine rather than a prone position for irradiation of the craniospinal axis, for example. Management of the airway in a supine patient is far easier for the anesthesiologist. This is an example of how the anesthesiologist and pediatric radiation oncologist can collaborate to ease each others contribution to the care of the child.

An adjunct for airway management during pediatric radiotherapy is the LMA. The LMA (Fig. 21.4) is a silicone tube, the distal end of which has an elliptical-shaped cuff that, when correctly inserted and inflated, forms a low-pressure seal around the larynx and allows spontaneous ventilation in a variety of body positions without the need for endotracheal intubation. Therefore, the LMA provides many of the advantages of endotracheal intubation: a guaranteed patent airway without the disadvantages of repeated laryngoscopy and intubation. The LMA has been used for radiotherapy in children as young as 3 weeks of age. Grebenik et al. (12) reported the use of the LMA for pediatric radiotherapy in 25 children who received more than 300 anesthetics. They observed no complications directly related to the use of the LMA. Morris and Marjot (13) reported one case of posterior pharyngeal wall edema that corresponded to the area of contact between the posterior surface of the LMA and the oropharynx in a child repeatedly anesthetized with an LMA for radiotherapy. Moylan and Luce (14)

Table 21.3

Inhalation Anesthetic Agents Commonly Used in Pediatric Radiation Therapy

Sevoflurane ($\text{CFH}_2\text{--O--CH}(\text{CF}_3)_2$)
Nitrous oxide (N_2O)
Isoflurane ($\text{CF}_2\text{H--O--CClH--CF}_3$)
Enflurane ($\text{CF}_2\text{H--O--CFCl--CF}_2\text{H}$)
Halothane ($\text{CF}_3\text{--CClBrH}$)
Desflurane ($\text{CF}_3\text{H--O--CFH--CF}_3$)



Figure 21.2 **A:** Intensity-modulated radiotherapy delivered from multiple directions by a linear accelerator is facilitated in this anesthetized child with a thermoplastic head immobilization device combined with a polyurethane foam–customized head and neck support. The gas mask is incorporated into the head immobilization device, and the treating therapist has placed beam setup marks directly on the device. The capnometry monitor is entering the airway tubing at the top. **B:** This 35-month-old girl with recurrent medulloblastoma received craniospinal irradiation over a course of 37 days. This picture was taken on her final day of therapy during the primary tumor site boost.

reported more than 2500 anesthetics given to 145 children with an LMA over a 4-year period for radiotherapy. They raised the concern that a prone position for radiotherapy with the neck partially flexed can produce kinking of the LMA, with the possibility of airway obstruction. A reinforced LMA may help alleviate this problem (15).

In summary, general inhalation anesthesia has the following features that make it an attractive technique for pediatric radiotherapy: onset is rapid, depth is easily controllable, administration is not unpleasant, recovery is rapid, the incidence of nausea and vomiting is low, and airway patency is well preserved.

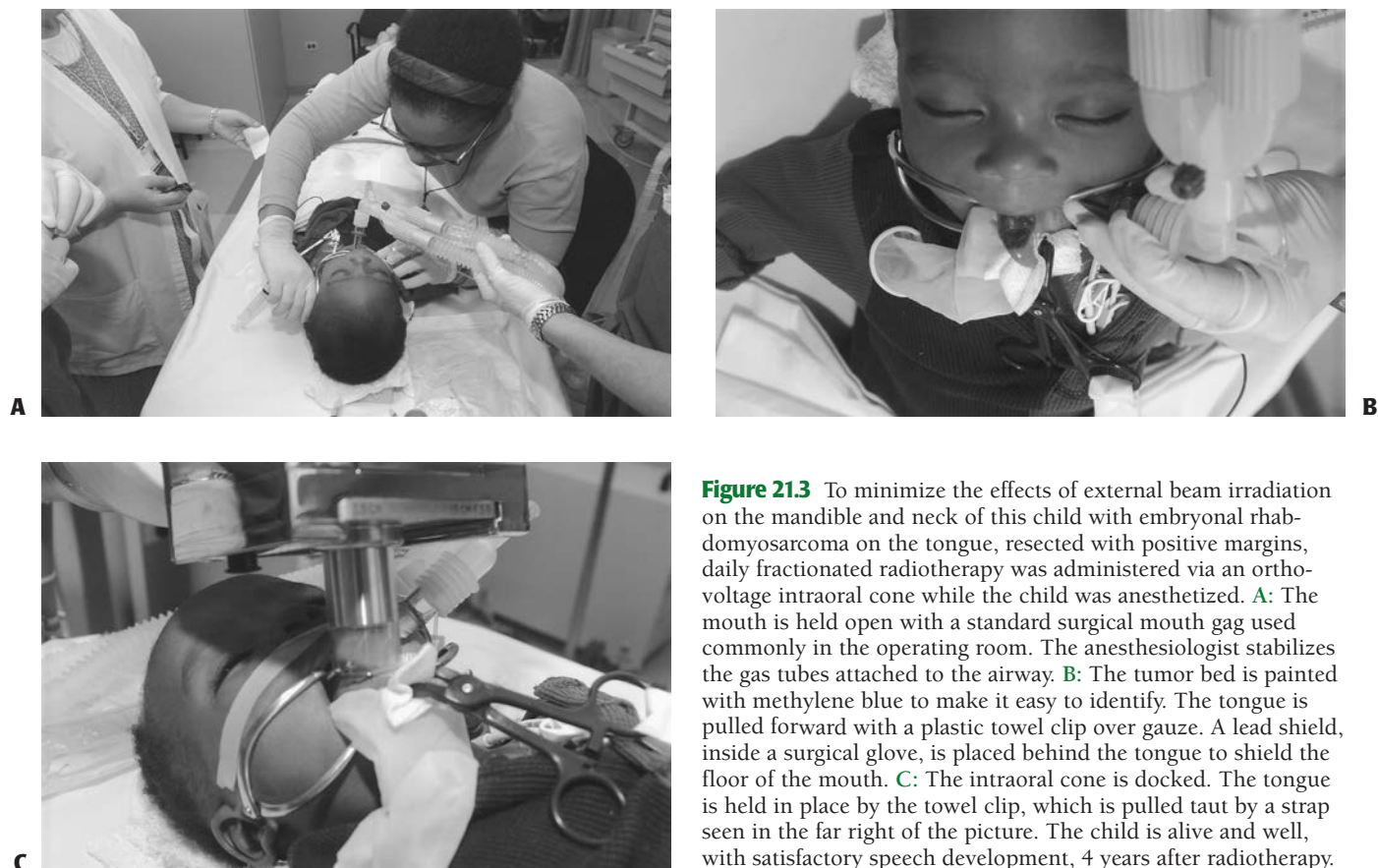


Figure 21.3 To minimize the effects of external beam irradiation on the mandible and neck of this child with embryonal rhabdomyosarcoma on the tongue, resected with positive margins, daily fractionated radiotherapy was administered via an orthovoltage intraoral cone while the child was anesthetized. **A:** The mouth is held open with a standard surgical mouth gag used commonly in the operating room. The anesthesiologist stabilizes the gas tubes attached to the airway. **B:** The tumor bed is painted with methylene blue to make it easy to identify. The tongue is pulled forward with a plastic towel clip over gauze. A lead shield, inside a surgical glove, is placed behind the tongue to shield the floor of the mouth. **C:** The intraoral cone is docked. The tongue is held in place by the towel clip, which is pulled taut by a strap seen in the far right of the picture. The child is alive and well, with satisfactory speech development, 4 years after radiotherapy.



Figure 21.4 A mobile anesthesia machine such as the Narkomed Mobile (Dräger) with a remote screen for data and alarms is suitable for the radiotherapy suite.

INTRAVENOUS ANESTHETICS

Intravenous anesthesia is also a popular and effective technique for pediatric radiotherapy. Intravenous anesthesia relies on either intermittent or continuous infusion of anesthetic agent into a peripheral or central vein in order to maintain a therapeutic concentration (16). Although it is not a new concept (sodium thiopental was administered by continuous drip as early as 1944), the advent of newer, short-acting anesthetic drugs, better equipment for infusing these drugs, and an improved understanding of pharmacokinetics in pediatric patients have led to a resurgence of interest in this technique. Postulated advantages of intravenous anesthesia include fewer peaks and troughs in serum concentration of drug, providing a steady-state serum concentration. Proponents of intravenous anesthesia contend that this steady-state concentration results in a more rapid induction of and emergence from anesthesia when compared with inhaled anesthetics. The time to emergence for short duration cases (less than 45 minutes) is likely to be rapid with either technique. With longer cases, the emergence with inhalational anesthesia may even be quicker, depending on the depth of anesthesia. The use of intravenous anesthesia does not require an anesthesia machine.

There is an extensive body of experience with ketamine in the radiotherapy suite (17–19). Since its release in the early 1970s, this dissociative anesthetic has been widely used for radiation therapy in children. Ketamine produces excellent analgesia and amnesia of short duration. Ketamine is easy to administer (it can be given intramuscularly if there is no intravenous access) (20), and is felt to preserve respiration and airway patency more effectively than inhaled anesthetics. One series described a child with a pharyngeal tumor who experienced airway obstruction with halothane anesthesia. When

ketamine was substituted for halothane, the patient had an uneventful anesthetic treatment, which resulted in satisfactory conditions for radiotherapy (21).

Ketamine and midazolam can be used to produce repetitive intravenous anesthesia for a child undergoing radiation therapy. Ketamine is a phencyclidine derivative that produces dissociative anesthesia, characterized by electroencephalographic evidence of dissociation between the thalamus and the limbic system. The drug has a rapid onset of action, a short duration, and high lipid solubility. It does not produce significant depression of ventilation. There is an increase in systemic and pulmonary arterial blood pressure, cardiac output, cardiac work, and myocardial oxygen needs. The drug is metabolized extensively by hepatic microsomal enzymes. There have been case reports of tolerance developing with repeat administration of ketamine (22).

Ketamine is not a panacea. There are several caveats to its use. Ketamine has ocular effects that have implications for radiotherapy. The onset of ketamine anesthesia often is accompanied by nystagmus (more commonly horizontal than vertical). Nystagmus with ketamine usually is transient; however, if it persists, it may be impossible to use a hanging lens block in an anterior field for the treatment of retinoblastoma. Ketamine can also produce involuntary movement of other muscle groups (jerkings), which is undesirable in pediatric radiotherapy. Ketamine raises blood pressure and heart rate. Its use in the setting of elevated intracranial pressure (ICP) is contraindicated because it causes ICP to increase. Although ketamine generally preserves respiratory drive and airway patency, apnea can occur after an intravenous bolus. In addition, it is a potent sialogogue, and copious secretions often accompany its use. Secretions can cause airway obstruction. Ketamine also sensitizes the airway to irritable stimuli, and reflex laryngeal closure (laryngospasm) often occurs. A drying agent such as atropine or glycopyrrolate should be given in conjunction with ketamine.

Finally, emergence from ketamine anesthesia often is characterized by hallucinations and nightmares. The incidence of emergence reactions ranges from 10% to 30% in adult patients. Emergence reactions are much less common in children. The reason for this difference is not known. Whatever the mechanism, the occurrence of these emergence reactions can be reduced if a benzodiazepine such as diazepam or midazolam is used.

Benzodiazepines are rarely used as the sole agents for radiotherapy in children. Diazepam (Valium) is painful to administer when given intravenously, and its duration of action exceeds the duration of most radiotherapy sessions. Midazolam (Versed) is a water-soluble benzodiazepine that is two to three times as potent as diazepam. It is short acting and not painful when given intravenously, but when used by itself it does not produce satisfactory sedation for radiotherapy. A plateau in sedative effect often accompanies its use, so additional dosing does not produce the desired clinical effect. In the event that a patient receives an overdose of benzodiazepine or demonstrates an exaggerated clinical effect, the drug can be displaced from its receptor by flumazenil, a benzodiazepine antagonist. Flumazenil should not be used in patients who chronically receive benzodiazepines, as it can precipitate acute withdrawal.

Barbiturates are sedative–hypnotic drugs that depress the activity of the central nervous system (CNS). These drugs

produce sleep within seconds of intravenous administration. Awakening is rapid and occurs by redistribution of the drug from the CNS. Barbiturates are given as an intravenous bolus or as a bolus followed by a continuous infusion. The short-acting barbiturates thiopental and methohexital have been used in pediatric radiotherapy (23,24). Side effects include apnea, hiccoughs, laryngospasm, and paradoxical CNS excitation. Some radiotherapists use droperidol, a butyrophenone derivative with pharmacologic actions similar to those of haloperidol and phenothiazines, generally followed by pentobarbital for intravenous anesthesia.

Narcotic analgesics produce sedation as a side effect. Potent synthetic opioids such as fentanyl, sufentanil, alfentanil, and remifentanyl may be used to supplement intravenous anesthesia, but their use is limited by their ability to depress respiration, cause chest wall rigidity, and produce tolerance. These side effects of narcotics make opiate anesthesia undesirable for radiotherapy. Radiotherapy is not a painful procedure; narcotics should not be necessary. Mixed opiate agonist-antagonists such as nalbuphine and butorphanol are touted as producing sedation and analgesia with less respiratory depression (plateau effect), and may be useful adjuncts in anesthesia for radiotherapy.

Propofol is an intravenous anesthetic that has hypnotic-sedative properties. The active ingredient, 2,6-diisopropylphenol, is formulated in an emulsion of soybean oil, glycerol, and egg lecithin. This formulation gives it a milky-white appearance. It is a highly lipid-soluble compound and therefore has a rapid distribution into the CNS and a rapid elimination, which has made it a popular anesthetic agent for day surgery and short procedures. It can be given via a central venous line or a peripheral intravenous catheter. When it is given peripherally, pain on injection is common. This pain can be reduced by administering the drug with lidocaine. Propofol has been increasingly used by anesthesiologists in pediatric radiotherapy and, at some centers, is the drug-of-choice. It is given as an intermittent bolus or as a bolus followed by continuous infusion. Awakening is rapid, and the incidence of side effects is low. When it is administered as a rapid intravenous bolus, apnea and hypotension are common. However, when the dosage is fractionated and administered slowly, spontaneous respiration and blood pressure are preserved. Propofol appears to possess antiemetic properties, which adds to its appeal.

Rapid and safe induction of anesthesia with propofol in children usually entails a loading dose of 2.5 mg/kg administered intravenously. The dosage is higher in nonpremedicated children. Maintenance of anesthesia is achieved by continuous infusion of 2.5 mg/kg/hr if it is supplemented by analgesics and nitrous oxide. Tachyphylaxis with propofol is rare (25,26). Fast awakening after the propofol infusion is stopped results from its short elimination half-life and the lack of substantial accumulation during administration over a long period. The elimination half-life after a single injection is even shorter in children than in adults. Respiratory depression during injection of propofol anesthesia can occur primarily through an overly rapid injection. Controlled administration of the induction dose, using an automatic pump, guarantees a slow and steady injection. Clinically significant respiratory depression during the maintenance phase of sedation can be avoided by stabilizing the infusion rate using an automatic pump (27).

Scheiber et al. (28), from the University Hospital of Essen in Germany, reported 155 propofol anesthetic sessions

performed on consecutive pediatric radiation therapy patients with a mean age of 30 months. The mean duration of anesthesia was 18 minutes. There were no clinically important complications involving respiration, circulation, or neurologic functions except for one transient episode of desaturation managed by suctioning and change in head position. Children awakened spontaneously at an average of 4 minutes after the propofol infusion was discontinued. No tachyphylaxis or unpleasant side effects were observed.

A lipid-based anesthetic agent such as propofol can support rapid microbial growth at room temperature. Bennett et al. (29) documented the association of propofol with postoperative infections. Eleven of 74 children receiving radiotherapy at Duke University Medical Center in the 1990s who had a central venous line developed proven sepsis (15%) with fever and a positive blood culture drawn through the central line. Of these 11 children, 8 had received prior chemotherapy (73%). Six of the 11 had been anesthetized with propofol (55%), 4 with a short-acting barbiturate induction plus inhalation anesthetic (36%), and one with inhalation anesthesia alone (9%). The pathogens cultivated from these 11 children included *Staphylococcus*, *Bacillus*, *Streptococcus*, *Enterobacter*, and *Candida* (30). These cases occurred prior to the addition of antimicrobial preservatives to propofol, which were added by the manufacturer in response to such reports. One formulation of the drug (Diprivan) contains EDTA; newer generic versions contain sodium metabisulfite or benzyl alcohol. Since the addition of preservatives, there have been no documented postoperative infections attributed to propofol. When infections do occur, they appear to be associated with a lapse in aseptic technique.

There are four potential sources of central venous access colonization producing sepsis: the skin insertion site, the catheter hub, hematogenous seeding of the catheter, and infusate contamination such as might be caused by propofol (31). In the setting of anesthesia for pediatric external beam radiotherapy, one is concerned about the possible contamination of the catheter through repeated use by the anesthesiologist. It is well known that there is a high incidence of central venous line sepsis in a variety of high-risk settings including patients receiving chemotherapy or total parenteral nutrition, burn unit patients, and those in the intensive care unit (30,31). The risk of sepsis with repeated catheter use in such settings ranges from 5% to 29%. Therefore, though catheter infections should be minimized by strict adherence to aseptic technique, there is always the potential for sepsis in the child whose central venous line is accessed repeatedly, regardless of the anesthetic technique. The pediatric radiation oncologist must work closely with the anesthesia team to be sure that the appropriate equipment is provided in the radiation treatment area to assure an aseptic process for drug administration.

Dexmedetomidine has become a popular agent for intravenous sedation and anesthesia in pediatric patients. It is a highly specific alpha-2 adrenergic receptor agonist that provides sedation with less respiratory depression than narcotics. Although apnea is possible, it generally preserves minute ventilation and is considered a safer agent for sedation in patients with potential respiratory compromise. The most common hemodynamic effect in children is bradycardia, which may require pharmacologic therapy with an anticholinergic agent such as atropine or glycopyrrolate (32). Though no studies have yet evaluated the safety of daily exposure to dexmedetomidine in children or adults, a case report describes the

successful use of dexmedetomidine as the sole sedative for 9 of 12 treatments in a 21-month old undergoing radiotherapy for a posterior fossa tumor (33).

SEDATION OR ANESTHESIA?

Conscious sedation as a medically controlled state of depressed consciousness allows protective reflexes to be maintained, retains the patient's ability to maintain a patent airway independently and continually, and permits appropriate response by the patient to physical stimulation or verbal commands (e.g., "open your eyes"). General anesthesia is a medical state of unconsciousness, usually accompanied by a loss of protective reflexes, including the inability to maintain a patent airway independently and to respond to physical stimulation or verbal commands.

The drugs commonly used for sedating young children in radiation therapy include chloral hydrate, which is administered by an oral or rectal route; phenobarbital, which may be administered orally, rectally, or intravenously; fentanyl, which is available for administration orally, intramuscularly, or intravenously; midazolam, for intramuscular or intravenous use; meperidine, which may be administered orally, rectally, or intramuscularly; promethazine, which is a sedative agent administered orally or intramuscularly; chlorpromazine, which may be administered orally or intramuscularly; or droperidol, which may be administered intramuscularly or intravenously. Chloral hydrate has principally a sedative effect. Pentobarbital has both sedative and hypnotic effects. Fentanyl has analgesic and amnesic effects. Meperidine is primarily an analgesic. Promethazine and chlorpromazine have principally sedative effects, whereas droperidol has both tranquilizing and sedative effects.

Some institutions first attempt to sedate a child for radiation before using general anesthesia. For physicians who first use chloral hydrate, the dosage is 75–100 mg orally or rectally. If adequate sedation is not achieved in 20 minutes, a second dose of 25 mg/kg can be given if the lesser dose of 75 mg/kg was used initially. The maximum dosage should not exceed 2000 mg. An alternative is midazolam 0.05–0.2 mg/kg given by slow intravenous push over 3–5 minutes and titrated to effect. It is generally recommended to give oxygen by mask during the procedure. Some physicians prefer meperidine 0.5–1 mg/kg, with a maximum of 20 mg, to be given by slow intravenous push over 3–5 minutes. If sedation fails, general anesthesia is administered by an anesthetist. The criteria for consulting an anesthesiologist include the need for a regular boosting of chloral hydrate, unsatisfactory sedation, or unsatisfactory radiation therapy caused by patient motion.

A retrospective review of the clinical experience with sedation and anesthesia for pediatric radiation therapy published by investigators from the King Faisal Specialist Hospital and Research Center of Riyadh, Saudi Arabia (27) demonstrated a high rate of unsatisfactory conditions with sedation alone. They attempted to sedate children and, if that failed, then moved to general anesthesia. In a series of 1033 consecutive treatments, 86% included general anesthesia, and 14% were performed with conscious sedation. With the use of general anesthesia, satisfactory control of motion for radiotherapy was achieved in 97% of cases. Conscious sedation gave a satisfactory result in only 68% of cases ($p = 0.0001$). The highest success rate was achieved with propofol anesthesia in 837 procedures. Only 7% of these procedures had at least one complication, and satisfactory treatment was achieved in 98% of cases.

Although the authors of this study argue that, except for retinoblastoma cases, physicians should use conscious sedation with midazolam before moving to general anesthesia, the data may not support this view. Conscious sedation often does not achieve a sufficiently stable child for precision radiation therapy, the uncertain duration of times to achieve anesthesia may make it difficult to operate a radiation therapy department on schedule, and the significant incidence of complications all may argue for a policy of moving directly to anesthesia under the direction of an anesthetist rather than conscious sedation administered by a radiation oncologist in an attempt to avoid anesthesia. Because anesthesia is almost always needed anyway, especially for younger children, the attempt to use conscious sedation may create unnecessary delays.

A retrospective review of 3833 procedures at St. Jude's Children's Research Hospital further confirmed the safety and reliability of general anesthesia for radiotherapy in children. All children received propofol anesthetics, some with adjuncts such as benzodiazepines, opioids, and/or ketamine. The median age was 3½ years (range 5 months–21 years). The complication rate was low (1.3%) and most were considered minor airway complications such as oxygen desaturation, cough, or apnea; none required advanced airway interventions (34).

It is crucial to have adequate monitoring capabilities when either sedating or anesthetizing children for radiation therapy. A daily evaluation process should include checking presedation vital signs and evaluating any contraindications such as presence of an upper respiratory tract infection, acute pulmonary problems, allergy, or other problems that may alter the appropriate drug dosage. The child is monitored during therapy with a closed-circuit television monitor that is clearly visible outside the radiation therapy room. A display of the pulse oximeter should be visible. Emergency equipment including a pediatric emergency cart, suction machine, Ambu bag, face mask, defibrillator, oral airway, and emergency drug box should be readily available. After each daily sedation, the child should be kept in the radiation therapy department until it is evident that the effects of sedation have worn off and the child is able to take fluids and has stable vital signs. Meticulous chart documentation is essential (35–37).

ANESTHESIA MONITORING

Unrecognized hypoventilation is the primary cause of morbidity and mortality in pediatric anesthesia (35). The respiratory depressant effects of many anesthetic agents combined with the propensity for airway obstruction as a consequence of positioning for radiotherapy make anesthesia for pediatric radiotherapy a risky proposition. The need to be physically removed from the patient during radiation delivery adds to the challenge of adequate monitoring.

What constitutes appropriate monitoring for children receiving sedatives and general anesthetics? The American Academy of Pediatrics Section on Anesthesiology and the American Society of Anesthesiologists have published guidelines (35,38). The standards for basic intraoperative monitoring of the American Society of Anesthesiologists state,

during all anesthetics, the patient's oxygenation, ventilation, circulation, and temperature shall be continually evaluated. Qualified anesthesia personnel shall be present in the room throughout the conduct of all general anesthetics, regional anesthetics, and monitored anesthesia

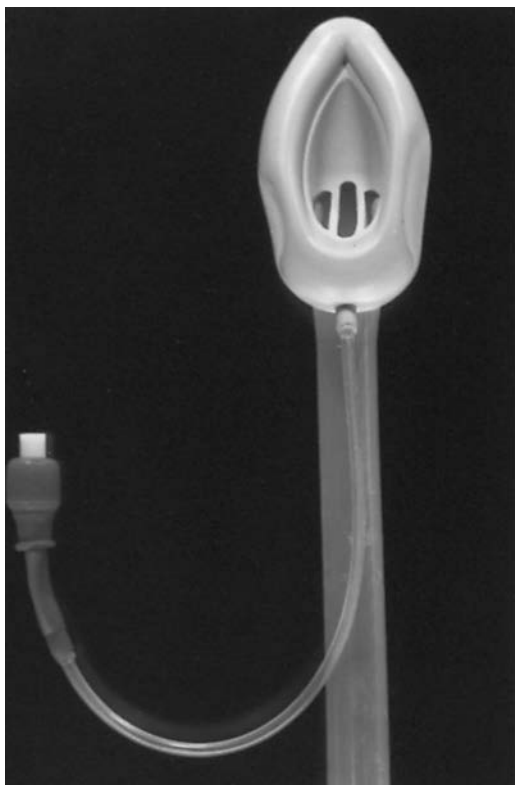
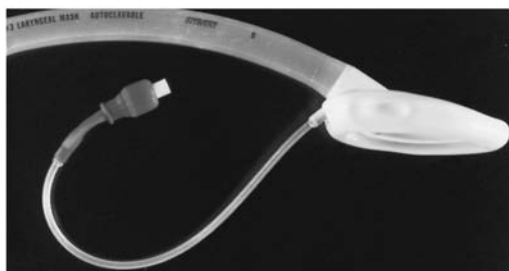


Figure 21.5 The laryngeal mask airway is a silicon tube. The distal end of the tube has an elliptical-shaped cuff that, when correctly inserted and inflated, forms a low-pressure seal around the larynx and allows spontaneous ventilation without the need for endotracheal intubation. (Photographed by permission of Gensia, Inc., San Diego, CA.)



care. In the event there is a direct known hazard, for example, radiation, to the anesthesia personnel that might require intermittent remote observation of the patient, some provision for monitoring the patient must be made.

The minimum monitoring standards for all patients undergoing anesthesia in any setting are continuous display of the electrocardiogram (ECG), arterial blood pressure and heart rate determined and evaluated at least every 5 minutes, pulse oximetry, capnometry, and monitoring of the fraction inspired oxygen in the breathing circuit.

Provisions made for monitoring in radiotherapy suites include closed-circuit television screens on which are displayed

the patient and the oxygenation, ventilation, circulation, and temperature monitors and leaded glass windows through which the patient and monitors can be viewed while the radiation treatment is delivered (Fig. 21.5).

Early reports of anesthesia for radiotherapy relied on visual inspection of patient color as a monitor of adequacy of oxygenation. However, the unreliability of direct observation for detecting cyanosis is known (39). Pulse oximetry is an accurate, noninvasive, continuous measure of arterial oxygen saturation. A pulse oximeter is an optical sensor that measures the concentration of oxyhemoglobin by transmitting red and infrared light through tissue beds such as a finger, earlobe, or nose. The use of a pulse oximeter is mandatory for any patient receiving sedative or anesthetic drugs. The Oxisensor (Nellcor, Inc.), a disposable pediatric digit oxygen transducer, can be used for these children. It is an expensive device, but with proper handling it can be reused from day to day (37). The pediatric pulse oximeter using Masimo Signal Extraction Technology (Masimo Corporation, Irvine, CA) may be more sensitive than conventional pulse oximeters in detecting hypoxic events (40) (Fig. 21.6).

It is important to emphasize that in patients receiving supplemental oxygen that decreasing oxygen saturation as measured by a pulse oximeter is a late sign of hypoventilation. How is ventilation best monitored? The first report of anesthesia for radiotherapy used continual visual observation of the thorax and abdomen combined with a wisp of cotton placed over the mouth. The cotton fibers moved in and out with inspiration and expiration, respectively, amplifying air movement. Amplifiers are used because the anesthesiologist cannot be physically present while radiation therapy is being delivered. While the anesthesiologist will rely on the oximeter, ECG, capnometry (vide infra), and a video monitor tracing of respiration, several amplifiers of ventilation were described for



Figure 21.6 The anesthetized child is monitored, in the accelerator vault, with the electrocardiogram, pulse oximetry, and capnometry. Notice that the gas delivery mask is well integrated into the radiotherapy head stabilization device.



Figure 21.7 **A:** The face mask is secured with straps and provides a stable, unobstructed airway. End-tidal CO_2 is monitored via side-stream capnography. The pediatric pulse oximetry probe fits most children and is reusable. **B:** The entire body is stabilized in a polyurethane custom foam mold.

use in radiotherapy prior to the era of remote electronic monitoring. These amplifiers may still be used, in conjunction with modern monitoring, to good effect. Visual amplifier methods include attaching a cotton-tipped applicator to the thorax and observing via a closed-circuit television monitor the excursions of the cotton tip with inspiration and expiration and placing a small light box on the patient's abdomen or chest and observing on the television monitor the movement of the lightbulb with each respiratory cycle. Aural amplifiers allow the anesthesiologist to hear the patient's breath sounds from outside the treatment area. An esophageal or precordial stethoscope can be connected to an audio amplifier, and the output can be heard on a speaker or earphone.

Observation of the movements of the reservoir breathing bag by the anesthesiologist is an excellent monitor of gas exchange. This technique is applicable to patients anesthetized with inhalational agents whose tracheas are intubated, those who have an LMA in place, or those who have a simple face mask applied over the nose and mouth. If the breathing bag cannot easily be seen on the closed-circuit monitor or through the leaded glass window, its movements can be amplified by a stick made of tongue blades. One end of the stick is attached to the neck of the breathing bag with a piece of tape, and a flag of white paper is placed at the opposite end of the stick. This long lever arm greatly accentuates the movements of the breathing bag and serves as an amplifier of ventilation.

The gold standard for assessing ventilation is capnometry. Capnometry is the quantitative measurement of the partial pressure of CO_2 produced by the patient during the ventilatory cycle. Capnography is the continuous graphic display of CO_2 concentration as a function of time. End-tidal CO_2 analysis is a mean of assessing alveolar ventilation, airway patency, and the functioning of the breathing circuit and ventilator. End-tidal CO_2 monitoring has been shown to be an effective monitor in pediatric anesthesia, capable of the early detection of many potentially life-threatening events such as apnea, bronchospasm, and disconnections in the breathing circuit (41).

The adequacy of circulatory function during the administration of anesthesia is assessed by continuous display of the

ECG and by measurement of blood pressure. Noninvasive, automated oscillometric blood pressure determination (DINAMAP, Criti Kom, Inc., Tampa, FL) is readily available and uniquely suited for remote monitoring of blood pressure. The ECG and DINAMAP displays are viewed indirectly on the closed-circuit monitor or directly through a leaded glass window if the radiotherapy suite is so equipped.

No matter how rigorous the adherence to recommendations and guidelines intended to promote high-quality care, it is impossible to guarantee specific patient outcomes. The provision of anesthesia for radiotherapy carries with it the additional challenge of remote monitoring of patients whose airways may be compromised not only by their underlying disease but also by the constraints of positioning for the procedure (Figs. 21.7 and 21.8).



Figure 21.8 Monitoring from immediately outside the treatment room is accomplished with a video screen displaying the child, an intercom system for audio, and a video monitor displaying the electrocardiogram, respiratory wave, and fraction of inspired oxygen. An additional camera allows viewing of the patient simultaneously.

ANESTHETIC IMPLICATIONS OF UNDERLYING DISEASE

Radiotherapy is used to treat several different pediatric malignancies. In the Duke series, the diagnoses leading to treatment with external beam radiotherapy under anesthesia were primary CNS tumor (28%), retinoblastoma (26%), neuroblastoma (18%), acute leukemia (9%), rhabdomyosarcoma (7%), Wilms tumor (5%), Langerhans cell histiocytosis (4%), and other (3%) (Fig. 21.9). It is not surprising that the diagnoses leading to radiotherapy under anesthesia differ somewhat from the most common diagnoses of cancer in childhood. Leukemia is an uncommon indication for radiotherapy under anesthesia because it is, in general, a malignancy of older children, and the role of radiation therapy is limited. Diseases associated with younger children in which radiotherapy is more frequently used dominate the list (30). Many of these malignancies have implications for the pediatric anesthesiologist. Children with supratentorial brain tumors can have elevated ICP. Management of anesthesia for patients with elevated ICP includes the avoidance of drugs that can raise ICP, such as ketamine. Anesthetic techniques that result in elevations in arterial CO₂ tension can produce intracranial hypertension by increasing cerebral blood flow.

Some neuroblastomas secrete catecholamines and cause systemic hypertension. Blood pressure elevations are associated with abdominal palpation. This problem is rare in pediatric radiotherapy because the tumor is not manipulated—the most common indications for radiotherapy in neuroblastoma are treatment of the tumor bed as part of a high-dose chemotherapy/marrow rescue procedure for advanced disease or for the palliative treatment of metastases.

Wilms tumors often are massive and can impair ventilation by increasing intra-abdominal pressure. An occasional child with a Wilms tumor will undergo endotracheal intubation for respiratory failure before presenting to the radiation oncologist for radiotherapy. These tumors can also extend into the inferior vena cava and renal vein, producing renovascular distortion and systemic hypertension.

Children with Hodgkin disease, non-Hodgkin lymphomas, and T-cell acute lymphoblastic leukemia can present with anterior mediastinal masses. These masses can produce tracheal compression and impair ventilation. They can also produce superior vena cava syndrome by compressing the great veins. Some patients with anterior mediastinal masses are referred to the pediatric radiation oncologist for external beam therapy before tissue biopsy. Radiation therapy before tissue biopsy is recommended in some of these patients because the induction of anesthesia for surgery in some patients with anterior mediastinal masses can be fatal. Death on induction of general anesthesia in these patients is caused by either the inability to ventilate because of airway compression or the inability of the heart to circulate blood because of tumor encroachment on the right heart or pulmonary circulation (42). Prospective identification of children with anterior mediastinal masses who are at risk for cardiorespiratory collapse on induction of general anesthesia involves a thorough history and physical examination aimed at eliciting signs and symptoms of airway and cardiovascular impairment. Laboratory studies useful in assessing preanesthetic risk include a chest radiograph, computed tomography scan, and upright and supine



A



B



C

Figure 21.9 A–C: The nurse is at the bedside in the recovery area in the radiotherapy department. Oxygen, suction, and pulse oximetry monitoring are immediately available.

flow-volume loops. The pediatric radiotherapist may treat patients with anterior mediastinal masses for whom the risks of general anesthesia are felt to outweigh the benefits of obtaining tissue before the institution of therapy. These patients should not receive anesthesia or sedation.

In addition to these considerations, the pediatric anesthesiologist must consider the associated implications of treating malignancy in children. These implications include the cardiac, hematologic, pulmonary, immunologic, and neurologic impairments caused by chemotherapy (41).

Anemia is one of the most common problems in children with cancer. Anemia decreases oxygen delivery to the tissues. Oxygen delivery is the product of the arterial oxygen content and the cardiac index. If oxygen delivery to the tissues is inadequate, organ system failure occurs. The minimum acceptable hemoglobin value in anesthetized children is unknown. Hemoglobin values as low as 7 g/dL may be adequate if the patient has normal cardiovascular compensatory mechanisms. However, many patients cannot compensate for low levels of hemoglobin because they have chemotherapy-induced myocardial dysfunction.

Cardiac toxicity is most notably caused by the anthracycline antibiotic chemotherapeutic agents doxorubicin and daunorubicin. These drugs have both an acute and a chronic effect. Acute toxicity manifests as rhythm and conduction disturbances such as supraventricular tachycardia, ventricular ectopic beats, and heart block. Chronic toxicity manifests as a cardiomyopathy, which can progress to left ventricular failure in 2–10% of patients. Factors that increase the risk of anthracycline cardiotoxicity include dosages greater than 550 mg/m², age younger than 1 year, concurrent use of other chemotherapeutic agents such as cyclophosphamide and cisplatin, and a history of mediastinal irradiation.

Pulmonary toxicity occurs in 5–10% of patients treated with the antibiotic chemotherapeutic agent bleomycin.

Bleomycin produces interstitial pulmonary fibrosis, which results in restrictive lung disease. The damage is thought to be produced by oxygen free radical formation. The role of exogenous oxygen in promoting the pulmonary toxicity of bleomycin is controversial. However, it is prudent to avoid inspired oxygen concentrations greater than 28% when anesthetizing patients who have been treated with bleomycin, provided that they maintain satisfactory levels of arterial oxygen tension.

On rare occasions, the child undergoing anesthesia for radiotherapy has received a prior course of irradiation to the head and neck or lungs. The anesthesiologist should be aware that these children may be at higher risk for laryngeal edema after instrumentation of the airway and for difficulty in maintaining oxygenation (43–46).

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Stabilization and Immobilization Devices

Kim L. Light and Edward C. Halperin

The management of pediatric radiotherapy patients is complex. The goal in radiation therapy is to achieve the desired tumor control while minimizing morbidity. This is especially important in children where late effects of the radiation treatments may include second malignancies and developmental delays. Even a small variation in dose can significantly influence the chance of tumor control and the risk of complications. Variations in dose to normal tissues have been greatly minimized by recent advances in diagnostic imaging, which accurately delineate the target volume. For example, the precise location of the target volume can be determined with computed tomography (CT), magnetic resonance imaging (MRI), and more recently, with positron emission tomography (PET) (1). There have also been great advances in radiation treatment planning over the years, which allow more accurate delivery of the prescribed dose to the target area. Treatment techniques used for adult and pediatric patients include three-dimensional conformal therapy, intensity-modulated radiation therapy (IMRT), proton radiation therapy (PRT), carbon ion therapy, stereotactic radiation therapy (SRT), and image guided radiation therapy (IGRT) (2–7). However, all of these technological advances in imaging, planning, and treatment will not be effective unless the patient holds still or is immobilized in a reproducible and comfortable position for each treatment session. The need for daily reproducibility is very important in pediatric patients because of the small margins that are used with the high-dose conformal techniques described. For the youngest patients, anesthesia may also be necessary to hold these patients still (a topic we reviewed in Chapter 21). In this chapter, we will consider psychological, educational, and mechanical aids for patient immobilization.

PSYCHOLOGICAL PREPARATION AND PATIENT AND FAMILY EDUCATION

Before beginning radiotherapy, many children have undergone multiple venipunctures, lumbar punctures, bone marrow biopsies, surgery, and chemotherapy. Therefore, they may fear medical personnel as well as any attempt to be immobilized for the radiation treatments. One important key to the child's cooperation is the parents' calm confidence. Because the child will sense their parents' positive or negative attitude, it is important that the child's parents feel comfortable with the treatment plan and express their confidence in the presence of the child. This confidence is gained by thoroughly informing the parents about the planning procedures and the daily treatment process.

In order to build the parents' comfort level, the therapy team should give them a tour of the radiotherapy department and introduce them to the personnel involved in their child's case. The parents should be given a chance to see and touch the equipment. Most important of all, the parents should be given an unhurried time to ask questions and have them answered. It is often advisable to conduct this initial visit without the child present so that conversation is not inhibited. The parents can also communicate ideas to the staff about making the child more comfortable. During the initial tour, the parents should be shown the type of immobilization device that will be used for the child. It is sometimes helpful for the parents to take home a picture of the device or a sample device to work with the child in their home setting. Later, the child must also be given a tour of the department and meet everyone involved in his or her case prior to starting the planning. The child should be encouraged to bring a favorite doll or stuffed toy animal for "treatment," and the radiation therapist should be willing to demonstrate the simulation and treatment procedure on the toy (8). An unhurried atmosphere, pleasant background music, patience, and positive reinforcement are all important to ensuring the child's cooperation.

Many pediatric inpatient services benefit from the expertise of trained play (or recreation) therapists. Because these therapists are often valuable allies in making a child more at ease in the treatment area, they should be made familiar with the routines of pediatric radiotherapy. Play therapists employ various techniques to prepare a child for treatment such as using special "toy" radiotherapy machines, art activities, and acting through the planned treatment. More specific behavioral techniques to improve patient cooperation with radiotherapy are discussed in Chapter 21.

Most children and parents are accustomed to receiving information from television. To meet this need, the physician may turn to specially prepared and commercially available videotapes/CDs that describe external-beam radiotherapy. Some of these videotapes/CDs are specifically targeted at a pediatric audience and use animation and professional actors designed to appeal to young children. Such videotapes/CDs can convey a significant amount of information in a short time and may be watched numerous times by the child and family, if necessary. Some clinics make it a routine to show such instructional films to children and families. In addition, some clinics use video systems during the radiation treatment to help relax and distract the child (9).

Music may also be a powerful tool. The radiotherapy department should have an audio system to play selections from a departmental library of children's music and stories or be

prepared to play selections of the child's choosing. Some children prefer a parent/sibling/grandparent to read aloud from a storybook during treatments.

ERRORS IN FIELD PLACEMENT

A field misalignment can result in a miss of some part of the tumor volume. With the use of conformal radiation fields, a setup error may result in a significant decrease in tumor control probability because of steep dose–response curve models. Furthermore, poor patient immobilization necessitates greater tumor margins. Improper immobilization will therefore result in treatment setup errors and increase the risk of normal tissue complications and compromised target coverage. To improve tumor control probability and reduce normal tissue complications, it is important to reduce setup error. Reducing setup errors can be facilitated by the proper use of immobilization devices.

Geometric misalignment of the patient relative to the incident beam can result from setup errors. These errors may persist throughout the course of treatment (systematic errors) or they may vary unpredictably around a mean value (random errors). A systematic error is probably of greater clinical significance than treatment-to-treatment variability or random error. The implicit conclusion is that errors in treatment delivery, including unsatisfactory immobilization, may be a significant cause of marginal recurrence of tumor after treatment (10–12).

No matter what precautions are taken, however, there will always be some uncertainties in the planning and delivery of external beam radiation therapy. The following discussion will explain some of these uncertainties. We are indebted to the well-known author and dosimetrist, Gunilla Bentel (1936–2000), for characterizing various treatment and delivery uncertainties (12).

In broad terms, treatment and delivery uncertainties are of two general types. The first are uncertainties related to the delivery of radiation. These include inhomogeneities in the beam, problems related to dosage calculations, variables in radiation machine output, instability of the beam-monitoring technique, and problems related to beam flatness. The second type of uncertainties in the delivery of radiation therapy can be divided into those related to mechanical inaccuracies in the equipment and those related to the patient. Mechanical uncertainties include errors in field size settings and rotational settings, errors in the crosshair alignment, errors in the arc rotation system (if one is used), deviations in the position of the isocenter, incongruence of the light beam with the actual beam, problems with the alignment system, couch-top difficulties, and errors in constructing the beam-shaping blocks or application of the multileaf collimator system. Patient-related uncertainties include uncertainty in target delineation, organ motion, movement of skin marks, day-to-day problems in repositioning, and patient motion. To reduce the detrimental impact of these uncertainties, effective immobilization techniques are essential.

To the authors' knowledge, there are no large-scale mathematical evaluations of the effectiveness of immobilization in pediatric radiation oncology. This is not surprising because of the small number of pediatric cases and the wide variety of sites treated; it would be difficult to generate a large series of pediatric patient data. Fortunately, however, there are

reports in the literature of the value of adult and pediatric immobilization and comparisons of various types of immobilization devices (13–21). It would be reasonable to conclude that using immobilization in the treatment of childhood cancers would show improvements in setup reproducibility that are similar to adult cases. Even with the use of anesthesia for daily treatments, immobilization of pediatric patients is worthwhile. One cannot be assured that the anesthetized child is placed in the same position every day. Only a customized immobilization device, adapted to the needs of the anesthesiologist, can minimize patient-related treatment uncertainties.

THE IDEAL MECHANICAL AID

Mechanical immobilization of the pediatric radiotherapy patient is an adjunct to patient education and psychological preparation, not a substitute for it. Patient positioning aids can range from simple to complex. The ideal mechanical aid to patient positioning will meet the following goals:

- The child must feel comfortable and secure; there must be no danger of falling.
- The device must satisfy the radiotherapy treatment plan regarding patient position for correct geographic irradiation.
- The body part treated should be rendered immobile.
- The position of the body part should be reproducible for daily treatment.
- The stabilization device should not adversely affect beam buildup and backscatter characteristics.
- The system should be economical.
- If anesthesia is used, the device must not interfere with the establishment of a secure airway, intravenous access, and the use of monitoring equipment.

STANDARD ACCESSORY DEVICES

There are a large number of commercially available radiotherapy accessories for patient stabilization. For example, a plastic head sponge may be used to provide stability for the head when the patient is supine. Plexiglas, plastic, or wooden sheets or boards may be used to widen the couch since many treatment couches are narrow and do not provide a comfortable resting place for a child's arms or legs. These boards may be anchored by placing them, in part, under the child's body (12). All of these devices have the advantage of being inexpensive and reusable. However, they cannot be customized to fit the individual patient.

AQUAPLAST AND POSICAST

A custom-made contoured thermal plastic mask (WFR Aquaplast, Inc., Avondale, PA) provides very effective immobilization for supine pediatric brain patients and is available from many vendors (22,23). These masks can be used with a customized head sponge or one of the standard head sponges. The plastic comes in various thicknesses of perforated sheets that soften and become malleable when heated to 160–180°F (70–80°C) in a hot water bath. The material's stickiness and elasticity hold it in place during the molding process. To customize the face mask to the patient, the softened thermoplastic sheet is draped over the patient's face from the hairline to



Figure 22.1 This personalized head sponge and thermoplastic mask is used to immobilize a pediatric patient receiving brain irradiation. Marks can be drawn on the mask to aid in setup and treatment reproducibility.

below the chin. The material is pressed closely to the bridge of the nose and chin to ensure a reproducible fit. In addition, Aquaplast may be clamped to a carbon fiber baseplate that can then be inserted into or on top of the treatment couch. The Aquaplast may also be attached to the BrainLAB (BrainLAB, Westchester, IL) frameless radiosurgery device that is used for SRT. The perforations in the Aquaplast mask allow air circulation and a partial view of the patient's anatomy. Setup marks and radiation field marks may be drawn directly onto the immobilization mask to assist in daily setup of the patient (Fig. 22.1). If anesthesia is necessary for daily treatments, the Aquaplast can also be stretched to accommodate the anesthesia mask (Fig. 22.2). However, stretched thermoplastic causes a slight increase in the radiation surface dosage, which will vary depending on how much the mask is stretched and how large the holes are in the mask (24).



Figure 22.2 A thermoplastic mask is used with anesthesia to stabilize a child receiving external beam stereotactic radiotherapy (SRT) for retinoblastoma.



Figure 22.3 This personalized prone immobilization is used for brain and spine treatment for a patient with medulloblastoma.

When treating a pediatric patient's brain and spine, the treatment is usually delivered with the patient lying in the prone position. There are several commercially available systems used for this type of treatment. For example, Aquaplast offers a prone base-plate device that can be tilted for optimal head extension. Aquaplast is first used to make a customized face support, and then an additional sheet of Aquaplast is draped over the posterior aspect of the head. The patient's body is positioned on a cushion of suitable height in order to make the patient as comfortable as possible (Fig. 22.3).

For pediatric patients who require extremity treatment, Civco (Civco Medical Solutions, Inc., Kalona, Iowa) offers a casting material that can be contoured to the patient's anatomy. The affected extremity is first placed in the desired position. Then, a softened sheet of Posicast is stretched over the patient's extremity above and below the treatment area and locked into place on the multifix baseplate. This type of immobilization device keeps the extremity stabilized in the desired rotation angle for each treatment. The unaffected extremity may be moved out of the way or locked down to keep it out of the radiation field. Setup and treatment marks may be drawn directly onto the cast for ease in daily alignment and setup (Figs. 22.4 and 22.5).

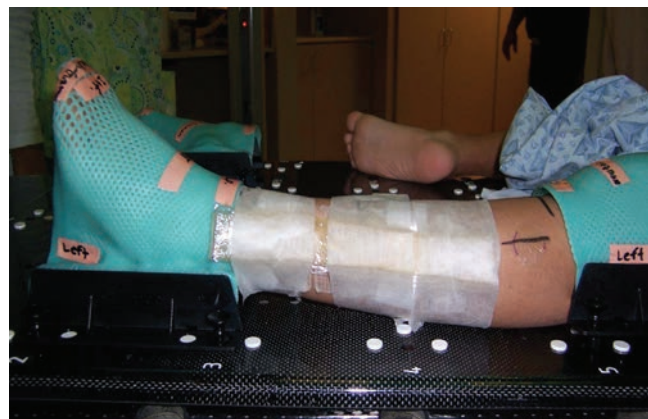


Figure 22.4 Extremity immobilization for a pediatric patient receiving radiation treatments for rhabdomyosarcoma.



Figure 22.5 Extremity immobilization showing the unaffected leg moved out of the way and locked in place.

POLYURETHANE FOAMS

The Alpha Cradle and Alpha Cradle Mold Maker (Smithers Medical Products, Inc., Akron, OH) are commercially available systems that are commonly used to create customized polyurethane molds for immobilizing both adult and pediatric radiotherapy patients (10,12,17,20,21). To form an Alpha Cradle mold, the pediatric patient is first placed on top of a polystyrene bag. Inside the bag are chemical materials that, when activated, cause the polyurethane foam to expand. To further stabilize and strengthen the device, Styrofoam sheets, 0.75–1 in. thick, may also be placed inside the bag. In addition, various commercially available frames may be used with this system to specifically immobilize the thorax, abdomen, or extremities. When the chemical reaction is activated, the expanding foam fills the bag and molds itself around the patient's body and the stabilization material. Once the chemical reaction is initiated, the patient must be positioned within 5 minutes. Then the child must remain motionless for approximately 15 minutes as the immobilizer hardens and cools. While the exothermic chemical reaction generates temperatures that do not exceed 105.7°F, this degree of heat may be uncomfortable for some children. Placing a sheet of paper or a pillowcase on the bag usually allows enough heat displacement for comfort without interfering with the molding process. After the mold hardens, marks can be drawn directly onto the cradle for setup purposes (Fig. 22.6).

It should be noted that the presence of an Alpha Cradle increases the surface dosage slightly for ^{60}Co , 6-MV, and 18-MV photon beams. The magnitude of the increase is a function of the thickness of the transited cradle and the energy of the beam (25). The authors of this book have occasionally noticed an increase in skin reactions in the area irradiated through an Alpha Cradle. Therefore, the Alpha Cradle should be kept as thin as possible without compromising patient positioning.



Figure 22.6 Alpha Cradle Immobilization with daily anesthesia for a pediatric patient being treated for neuroblastoma.

VACUUM BAGS

Many institutions use vacuum bags or pillows for immobilization (Civco Medical Solutions, Inc., Kalona, IA). These bags are popular because they can be customized for individual patients and still be reused multiple times if properly cleaned, sanitized, and stored carefully. The vacuum bag is filled with tiny polystyrene beads. The patient lies on the bag in the treatment position and then air is evacuated from the bag through a valve. The evacuation of air from the bag forces the polystyrene beads and the plastic bag against the body to provide a rigid, comfortable positioning device. The body shape is retained throughout the course of treatment as long as the bag is not punctured or damaged. A vacuum bag immobilizer can be created in a few minutes, it can easily be adjusted after forming, and it can be reused for several patients. However, the surface dosage is slightly higher for a beam passing through the bag (25).

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Cancer Pain Management in Children

Pesach Shvartzman

In spite of the advancement in the knowledge and skills in treating cancer pain in children, many patients still receive suboptimal treatment. No physician, nurse, technician, or parent likes to see a child in pain. However, we still witness many barriers to treatment. For many parents the words *morphine* or *methadone* mean the situation is serious or terminal, we are giving up, addiction, and/or concern that when there will be a need for stronger pain medications it will not be effective. Amongst many medical teams morphine and methadone mean addiction, risk of shortening life, respiratory depression, confusion, tolerance, side effects, and fear of pain medications. Unfortunately, many physicians and nurses do not receive structured training in pain management.

One of the reasons treating children with pain is difficult is that evaluating the pain level in children is complex. As pain is a subjective feeling, children above the age of 5 years will know to report pain on an imaginary scale of 0–10 VAS (visual analogue scale). In children under the age of 5 years, a Faces Pain Scale can be used to report the level of pain. In younger children, evaluation tools that integrate observation of behavior may be used, such as facial expressions, restless legs, level of activity, crying and consolability.

Pain in the child with cancer can be due to the illness itself (e.g., a brain tumor causing increased intracranial pressure), a diagnostic procedure (such as bone marrow aspiration or lumbar puncture), or treatment (surgery, mucositis after chemotherapy, or radiation).

The pathophysiologic classification has important practical implications since for each category a specific treatment is recommended. Neuropathic pain is caused by an injury to the transmission system: peripheral nonmyelinated type C fibers, and type A myelinated nerve fibers, or injury to the spinal cord or the brain. The injury may be a result of the tumor infiltration, chemotherapy, radiation, mechanical reasons (i.e., surgery), or infection (i.e., herpes zoster). Nociceptive pain derives from stimulation of peripheral receptors as in a fracture or bone tumor. Pain can be treated by both pharmacologic and nonpharmacologic methods. At our disposal there are many pain killers: acetaminophen, nonsteroidal anti-inflammatories (NSAIDs), opioids, tramadol, anticonvulsants, and antidepressants.

HOW DO WE CHOOSE WHICH MEDICATION TO GIVE FIRST AND WHEN?

A useful tool to assist in this predicament is the World Health Organization (WHO) ladder. The severity of pain, on a scale of 1–10, determines the type and dose of medication prescribed.

For mild pain (1–4) administer nonopioids, for moderate pain (5–7)—low dose opioids $\pm$ adjuvants, and for severe pain (8–10)—opioids $\pm$ adjuvants. However, like a step ladder, a patient with severe pain is initially prescribed nonopioids, effectiveness is assessed, and if pain management is not achieved, only then the next stage up the ladder is taken.

In our latest recommendations, published by the Israeli Cancer Association and the Israeli Medical Association, we recommended the elevator model rather than the WHO ladder. In this model, medications are prescribed in accordance with the patient's pain level. Thus, a child reporting a pain intensity of 8/10 would receive an opioid rather than an NSAID or acetaminophen, and if a child reports pain intensity of 4/10, an NSAID or acetaminophen would be prescribed (Fig. 23.1).

In each stage, if the patient has neuropathic pain a medication for neuropathic pain should also be prescribed. For

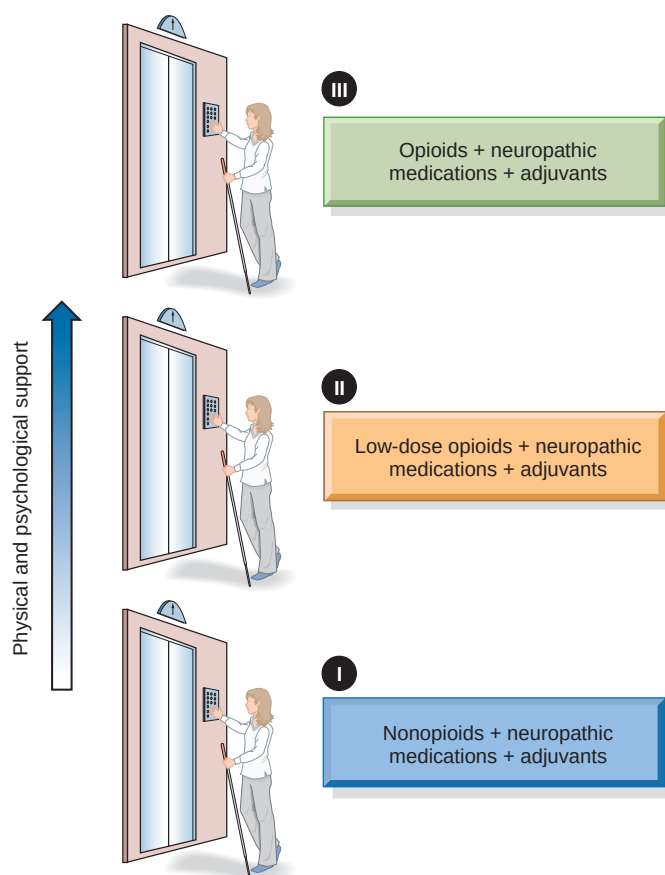


Figure 23.1 The elevator model.

Table 23.1**Opioids Available for Children**

Drug	PO	Transdermal	IV
Fentanyl	N/A	12 mcg/hr every 3 days	Initial dose: 12 mcg/h Basal: 0.5–1.5 mcg/kg/hr 0.5–1 mcg/kg q15–30 minutes
Hydromorphone	0.03–0.06 mg/kg/dose q3–4 hours > 50 kg: 1–2 mg q3–4 hours		Initial dose: 0.003 mg/kg/dose; Basal: 0.003–0.005 mg/kg/hr 0.015 mg/kg/dose q3–4 hours
Morphine	6 months: 0.3 mg/kg/dose q3–4 hours > 50kg: 10–15 mg q3–4 hours		Initial dose: 0.01–0.02 mg/kg/dose Basal: 0.01–0.03 mg/kg/hr 0.05–0.1 mg/kg/dose q3–4 hours > 50kg: 2.5 mg/dose to 5 mg/dose q3–4 hours
Oxycodone	–0.2 mg/kg q4 hours Adults: 5–10 mg q4 hours	N/A	N/A

PO, oral; IV, intravenous; N/A, not applicable.

mild pain (1–4) with a neuropathic component the patient will receive nonopioids and antidepressants, anticonvulsants, steroids, or NMDA antagonist. If the patient suffers from moderate pain (5–7) with a neuropathic component, he or she will receive low-dose opioids and neuropathic pain medications. For severe pain (8–10) with a neuropathic component, the patient will receive opioids and neuropathic pain medications (Tables 23.1 and 23.2).

HOW IS NEUROPATHIC PAIN DIAGNOSED?

The main tool for diagnosing neuropathic pain is the patient's history. The patient may report a change in sensation (hypoalgesia or allodynia), paresthesia, tingling, or a burning or freezing sensation specific to an anatomic region. There is no need for an EMG, EEG, MRI, or CT to make the diagnosis.

HOW IS PAIN SEVERITY EVALUATED?

Children aged 5 years and older will know how to relate to the VAS of 0–10. Younger children, 3–5 years old, will relate to the faces pain scale. For children who cannot express themselves we rely on observation or other commonly used tools such as the FLACC by observing facial expressions, leg movements, activity, crying, and consolability.

OPIOIDS (TABLES 23.1, 23.2, AND 23.3)

Opioids are a mainstay for the treatment of pain. They bind to five types of receptors (μ , κ , σ , δ , ϵ) of the peripheral or spinal nerve systems. Opioids modify the transmission signal and decrease pain perception. In addition, at the supraspinal level, opioids send inhibitory signals and affect the limbic system to modify the emotional response to pain.

Table 23.2**Neuropathic Pain Medications**

Drug	PO
Amitriptyline	0.2 mg/kg to a maximum of 1–2 mg/kg/day over 2–3 weeks 10 mg PO at night to a maximum of 50–100 mg/day over 2–3 weeks
Baclofen	2–7 years, PO: start 10 mg/day, increase by 5–15 mg/day every 3 days as needed divided three times a day
Carbamazepine	>8 years: as above to a maximum of 60 mg/day divided three times a day 40 mg/kg/day
Clonazepam	0.01 mg/kg/day divided up to four times a day, increase to effect, maximum of 0.2 mg/kg/day divided three times a day or 20 mg/day
Dexamethasone	Antiemetic, 10 mg/m ² IV or orally daily; maximum dose 20 mg daily, maximum dose of 40 mg/day
Gabapentin	2–5 mg/kg/dose q2–3 weeks, after b.i.d. after t.i.d. increase for 2–4 weeks, maximum 10–20 mg/kg t.i.d.
Ketamine (low dose)	PO 0.2–0.4 mg/kg/dose PO t.i.d. and PRN
Midazolam	0.2–0.75 mg/kg up to 20 mg

PO, oral; IV, intravenous; PRN, pro re nata (when necessary).

Table 23.3**Opioids Conversion**

Oral/Rectal Dose (mg)	Analgesic	Parenteral Dose (mg)
300	Propoxyphene	—
90	Tramadol	—
^a	Fentanyl	0.1
7	Hydromorphone	1.4
	^b	Methadone
30	Morphine	10
20	Oxycodone	—

Oral Morphine vs. Fentanyl Patch

Oral Morphine (mg/24 hrs)	Fentanyl Patch (μg/hr/72 hrs)
50	25
100	50
150	75
200	100

Conversion of Morphine to Methadone

Oral Morphine Dose (mg)	Morphine/Methadone Ratio
<100	3:1
100–300	5:1
300–600	10:1
600–800	12:1

^aAs conversion is dose dependent, it should be preformed with caution if no prior experience exists.

^bConversion ratios noted above are based on estimates and could change from patient to patient and in different pain conditions. One should monitor carefully the level of pain relief and side effects for the days following conversion.

Each opioid has different effects on individual receptors at different levels, such that there is great variability in response between children. These differences are specific and individual for each child. Thus, there is no correlation in the analgesic sensitivity to the different opioids and in the side effects for individuals. A patient can develop significant sedation with morphine and no sedation with oxycodone. One patient will need minimal doses of an opioid to achieve an analgesic effect and another with the same pathology will need very high doses. Another interesting aspect of opioids is that there is no ceiling effect; there is no maximal dose for any opioid.

Opioids can be divided into two groups: immediate release (IR) and extended release (ER) medications. IR opioids are morphine, codeine, oxycodone, hydromorphone, hydrocodone, and fentanyl.

Morphine is the most widely used opioid. Taken orally (PO), activity begins within 30 minutes and peaks within an hour, ending after about 4 hours. Administered subcutaneously (SC) the peak activity is reached within 30 minutes, and intravenously (IV) within 5–10 minutes. Hydromorphone and oxycodone pharmacokinetics are similar; however, there is no parenteral oxycodone. Oxycodone is 1.5–2.0 times

more potent than morphine with similar pharmacokinetics. Oxycodone has two metabolites: noroxycodone which is partly active and oxymorphone which is active though its quantity is minimal. It clears in children very quickly and can be used in high doses.

Morphine metabolizes in the liver to M-6-glucuronide (an active potent metabolite) and to M-3-glucuronide that is probably a nonactive metabolite, but suspected of causing increasing neurotoxicity, such as hyperalgesia, allodynia, or myoclonus.

Hydromorphone is 100 times more potent than morphine and a little more lipophilic. It has an active metabolite (hydromorphone-3-G) and there are anecdotal reports in children of higher neurotoxicity in high doses.

Fentanyl is a very potent lipophilic opioid, 80–100 times more potent than morphine in adults but only 13–20 times in children. Fentanyl activity is quicker and it is active for a shorter time than morphine given parenterally. It does not have any active metabolites. Pharmacokinetics in children is similar to that in adults.

In our opinion, codeine is not appropriate for pain management as 15–20% of the population are slow metabolizers and do not form the active metabolite.

From the analgesic point of view there is no preference for one opioid over another. In patients with kidney function problems there is an advantage for fentanyl and methadone that do not have active metabolites.

Methadone is an opioid with unique characteristics. There are two isomers that bind to the mu and NMDA receptors. Methadone does not have active metabolites and has a very long half-life (12–200 hours) that cannot be predetermined. Clinical conversion from one opioid to methadone depends on the metabolism of the patient and the previous dose of the opioid received. There are little data on the pharmacokinetics of methadone in children, though from our experience and of other authors it is an excellent opioid to use for pediatric palliative care—with careful and rational use. Methadone for single dose use is available in an IR form and in an ER form for chronic use.

Morphine conversion to methadone is 1:5 for morphine doses up to 100 mg and 1:10–20 for higher morphine doses.

Morphine, oxycodone, and hydromorphone have ER preparations, given every 8–12 hours. In children with usually relatively quick metabolism they should be administered every 8 hours. Fentanyl is provided as a patch that releases regular doses for 48–72 hours. This is a very convenient preparation for children as it increases compliance rate dramatically.

INITIATION OF OPIOID ANALGESIA

Since there is no analgesic advantage of one opioid over another, the clinician should prescribe the most convenient opioid. In children, fentanyl patches are definitely a good option. In children suffering from kidney function problems choose fentanyl or methadone. Start with the lowest recommended dose. In case a child or a parent is worried about taking opioids, start with an IR opioid every 4 hours. In a family without concerns an ER can initially be used. Provide regular around-the-clock care and add a rescue dose (also called “breakthrough”) as necessary. The rescue dose is always given only as IR opioids. This dose may be repeated every hour if

administered PO, every 30 minutes if administered SC, and every 5–10 minutes if administered IV. The rescue dose is calculated at 10–20% of the total ER opioids dose in 24 hours. It is recommended that the total regular dose should be given as the sum of ER opioids doses and the rescue doses as IR of the same opioid.

SIDE EFFECTS OF OPIOIDS (TABLE 23.4)

The most common side effects are sedation, nausea, vomiting, and constipation. Development of addiction and tolerance are very rare. There is no tolerance to the analgesic effect and the constipation. Tolerance is developed for other side effects such as sedation (within 5–7 days) or nausea/vomiting (within approximately 2 weeks).

If a side effect is intolerable or does not dissipate in a reasonable time frame, opioids may be changed (opioid rotation), as there is no overlap between the different opioids in their side effects profile in a specific patient. Additional medications can be used to treat the side effects while continuing the opioids. Thus, antiemetics can be prescribed for vomiting or nausea, Ritalin for sedation, clonazepam for myoclonus, and stool softeners for constipation.

Respiratory depression is very rare during the appropriate use of opioids in children with cancer. Respiratory depression, if it does occur, is never a sudden cessation in breathing but rather a gradual depression that is always preceded by a decrease in conscious state.

Table 23.4
Common Opioids Side Effects

Side Effect	Management
Constipation	Stool softener Stimulant laxative Low-dose naloxone
Nausea/Vomiting	Opioid rotation Antiemetics Antihistamines
Pruritis	Antihistamines Hydroxyzine
Fatigue	Opioid rotation psychostimulant trial
Confusion	Opioid rotation; methylphenidate dose reduction
Myoclonus	Opioid rotation Benzodiazepine Muscle relaxant
Urinary retention	Opioid rotation External bladder pressure Bethanechol
Respiratory depression	Oxygen Repositioning Use opioid receptor antagonists with caution

TREATMENT OF COMMON PAIN SITUATIONS

Neuropathic pain is common in children with cancer. The reasons for neuropathic pain can be infiltrating tumor, post-surgical neuropathies, phantom pain, and postchemotherapy such as neuropathy after treatment with vinca alkaloid.

There are no randomized control studies in the pediatric literature regarding the medical treatment of children with neuropathic pain due to cancer. We extrapolate from studies in adults. Effective medications in neuropathic pain management are opioids (NNT-2.5), antidepressants, tricyclics (NNT-2.6), SSRI (NNT-6.7), gabapentin (NNT-4.1), duloxetine, and pregabalin (Table 23.2).

For severe mucositis, opioids are indicated. For bone pain, steroids, bisphosphonates, and radiation therapy play important roles. Pain relief from radiation may take up to 10 days.

For pain stemming from bowel obstruction, anticholinergics and octreotide are effective (e.g., in children suffering from malignant bowel obstruction that cannot be operated upon or with a short life expectancy).

RADIOTHERAPY AND PAIN

Radiotherapy is often used to treat pain caused by bone, spinal cord, or neural plexus infiltration or by brain tumors causing increased intracranial pressure. However, there are some conditions in which radiotherapy is the cause for pain in the child with cancer.

Most patients can tolerate the radiotherapy procedure, but occasionally a patient may not tolerate proper positioning secondary to pain. Providing a proper analgesic before radiation by giving a rescue dose as an IR opioid might be needed. If the IR opioid is given PO, it should be given 1 hour before the procedure. If the IR opioid is given SC, it should be given 30 minutes before the procedure, and if the IR opioid is given IV, it should be given 10 minutes before the procedure. Sometimes appropriate sedation should also be provided.

There are some conditions related to radiotherapy causing pain in childhood cancer, such as mucosal injury. When such injury occurs in the oral cavity, as commonly seen in patients irradiated to the head and neck area or before bone marrow transplantation with total body irradiation, it is called mucositis. When the injury occurs in nonoral alimentary tract mucosa, it presents as esophagitis, gastritis, enteritis, colitis, or proctitis. These injuries manifest as pain, dysphagia, odynophagia, nausea, vomiting, and diarrhea. The main principles for controlling these painful conditions, discussed previously, should be applied.

Plexopathy is extremely rare; however, it can cause a significant neuropathic pain months to years after radiotherapy. Treatments involve early physical and occupational therapy, and multimodality pain regimens using opioids and neuropathic pain medications as previously discussed. Rarely, invasive procedures such as neural blocks, neurolytic procedures, or neuromodulation may be needed.

In this chapter we emphasized the pharmacologic treatments for pain. Alternative/complementary modalities include relaxation, behavioral, and distraction techniques.

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Blood Count Depression in the Child with Cancer

Myriam Weyl Ben Arush

INTRODUCTION

The organ most consistently and frequently affected by conventional cancer treatment is the bone marrow and secondarily the peripheral blood cells. The suppression of the stem cell in the marrow or the interference with the active proliferation of a particular cell line is predictable, based on the therapy modalities, chemotherapeutic agents, and radiotherapy modalities.

The depression of red blood cells, giving rise to anemia, occurs much more slowly than drug-induced leukopenia because of the differences in the half lives of the mature cells of these two cell lines. When one compares the half life of the red cell (~120 days) with the half life of platelets (~5–7 days) and with the half life of granulocytes (~ 6–8 hours), it is evident why the latter two are more frequently involved in earlier and more severe suppression by chemotherapy and radiotherapy.

HEMATOLOGIC COMPLICATIONS OF CANCER CHEMOTHERAPY

If a particular agent predominantly affects the stem cells rather than cells in specific phases of the cell cycle, then all cell lines will be suppressed. Very few classes of chemotherapeutic agents selectively depress the stem cell. Examples of these agents are the general group of nitrosoureas (lomustine, carmustine). Other classes of agents, mainly the cell-cycle agents that are not specifically phase selective (such as the anthracyclines and certain alkylating agents like busulfan), may cause delayed suppression of bone marrow cells and longer recoveries than phase-specific agents like the antimetabolites and vinca alkaloids (Tables 24.1 and 24.2).

The degree of cytopenia is influenced by the age of the patient (children have a much more cellular marrow with a decreased percent of fat), stage of the disease, previous treatments,

Table 24.1

Drug Class or Compound and Degree and Duration of Myelosuppression

Myelosuppression: Nadir and Duration			
Drug or Drug Class	Degree of Suppression ^a	Nadir of Myelosuppression (Days)	Duration of Marrow Recovery (Days)
Anthracycline	III	6–13	21–24
Vinca alkaloids	I–II	4–9	7–21
Mustard alkylator			
Nitrogen mustard	III	7–14	28
Antifolates	III	7–14	14–21
Antipyrimidines	III	7–14	22–24
Antipurines	II	7–14	14–21
Podophyllotoxin	II	5–15	22–28
Alkylators	II	10–21	18–40
Nitrosoureas	III	26–60	35–85
Miscellaneous ^b			
Busulfan	III	11–30	24–54
Carboplatin	III	16	21–25
Cisplatin	II	14	21
Dacarbazine	III	21–28	28–35
Hydroxyurea	II	7	14–21
Mithramycin	I	5–10	10–18
Mitomycin	II	28–42	42–56
Procarbazine	II	25–36	35–50
Razoxane (ICRF)	II	11–16	12–25

^aI, mild; II, moderate; III, severe (based on common dose schedules).

^bAgents differing from their class of compounds.

and the ability of the liver and kidney to metabolize and/or excrete the cytotoxic compound.

Nitrosoureas typically produce a late and often severe thrombocytopenia that occurs 4–6 weeks after the administration of the agent. Thrombocytopenia may occur after recovery from leukopenia and may persist for 1–2 weeks after the nadir occurs. Severe bone marrow hypoplasia may be seen after the administration of busulfan, which is used for conditioning in autologous bone marrow transplantation in pediatric solid tumors. Thrombocytopenia may persist long after the granulocyte count has returned to near normal values and is the last to recover. In leukemia, Cytosar causes severe aplasia with a transient blastema with circulating myeloblasts for a period of 1–7 days.

Generally, agents that are specifically cell-cycle active and phase-specific produce a rapid cytopenia (Table 24.2). Recovery is quicker, especially from agents that are active in S and M phases. Agents that tend to be non-cycle active or exert their effect in cells in G_0 have the greatest delay myelosuppression and affect the stem cells before specific delineation in erythropoiesis, granulopoiesis, or megakaryopoiesis.

Very few cancer chemotherapy drugs are truly nonmyelosuppressive. Bleomycin, vincristine, and L-asparaginase generally do not cause significant bone marrow suppression.

HEMATOLOGICAL COMPLICATIONS OF RADIOTHERAPY

In adults, the head, cervical, thoracic, lumbar, and sacral spines account for approximately 13%, 3%, 14%, 11%, and 14% of the active bone marrow, respectively (1). In children, these values are different, reflecting the age-dependent distribution of functioning marrow. The long bones (femur, tibia), ribs, and skull, are hematopoietically more important in children than in adults.

Total body irradiation produces drastic decreases in leukocyte, erythrocyte, and platelet counts (1). The decrease in peripheral leukocyte count, especially lymphocyte count, following radiotherapy has been extensively reported in adult patients (2–5). Plowman reported that lymphocyte counts remain depressed years after the radiation therapy (6). The decrease in erythrocytes is less spectacular and the erythropoietic system effectively compensates by proliferating upon demand (7). These effects of radiation on the hematopoietic system depend on several factors: pretreatment blood indices, stage of the cancer, the field location of treatment, surface area treated, the cumulative dose administered, as well as any other concurrent therapy received by the patient, especially chemotherapy (1,2,7–9).

Hematopoietic stem cells replicate and differentiate along lymphoid or myeloid lineages regulated by a network of hematopoietic growth factors and cellular interactions. Families of colony-stimulating factors have been identified that control the process of replication and differentiation. The hematopoietic system is also dependent on the microenvironment that consists of endothelial cells, adventitial cells, fibroblasts, macrophages, and fat cells (10).

The in vivo effects of localized single exposure to 250 kVp x-rays on the femoral bone marrow of rats demonstrated that doses of 10 Gy have transient effects on stromal function, and this is rapidly repaired (11). In contrast, doses of 20–100 Gy

Table 24.2

Cell-Cycle Activity of Chemotherapeutic Agents

I. Cycle-Active Phase-Specific Agents	II. Cycle-Active Phase-Nonspecific Agents
G_1 -phase specific	Alkylating agents
Steroids	Busulfan
L-Asparaginase	Chlorambucil
Diglycolaldehyde	Cyclophosphamide
S-phase specific	Nitrogen mustard
Antimetabolites	Phenylalanine mustard (L-PAM)
Antifolates	Ifosfamide
Methotrexate	Antibiotic-type agents
Baker's antifol (triazinate)	Anthracyclines
Antipyrimidines	Daunorubicin
Azacytidine	Doxorubicin (adriamycin)
Cytarabine	Rubidazole
Fluorouracil	Dactinomycin
Antipurines	Mithramycin
Mercaptopurine	Mitomycin C (mutamycin)
Thioguanine	Nitrosoureas
Steroids(?)	Carmustine (BCNU)
Cyclophosphamide(?)	Lomustine (CCNU)
Miscellaneous	Semustine (methyl-CCNU)
Hydroxyurea	Miscellaneous
Procarbazine	Cisplatin
Diglycolaldehyde	Dacarbazine (DTIC)
G_2 -phase specific	Streptozotocin
Bleomycin	Carboplatin
M-AMSA	
Razoxane (ICRF)	
M-phase specific	
Vinca alkaloids	
Vincristine	
Vinblastine	
Epipodophyllotoxins	
Etoposide (VP-16-213)	
Teniposide (VM-26)	
G_{α} -phase specific	
Alkylators (mustard-type)	
Busulfan	
Nitrogen mustard	
Phenylalanine mustard (L-PAM)	

M-AMSA, M-Amsacrine; BCNU, Bis-chloronitrosourea; CCNU, Cyclin U; DTIC, Deticene.

result in aplasia of the femur associated with extensive sinusoidal injury. Regeneration of bone marrow is performed by circulating pluripotent hematopoietic stem cells that disseminate to the locally aplastic segments of marrow and renew hematopoiesis. Some studies demonstrate that single-fraction doses of 5–10 Gy or fractionated irradiation to conventional fields such as mantle or pelvis delivering 1.8–2 Gy/day to 55–70 Gy at conventional dose rate produce decreased proliferative capacity of explanted stromal cells (12,13).

Acute Toxicity from Radiation Therapy

Peripheral blood cells acutely respond to radiotherapy by progressively decreasing in number caused by the destruction

of both mature and precursor cells. The sequence and rate of decline is similar to that caused by the majority of chemotherapeutic drugs, which reflects the kinetics of bone marrow cell production, maturation, and longevity. Lymphopenia occurs almost immediately after low dose radiation because these cells are exquisitely sensitive and die in interphase. After 30–40 Gy to large bone marrow volumes, neutropenia occurs in the first 10 days, followed by thrombocytopenia in 2–3 weeks, and anemia in 2–3 months.

The hematopoietic recovery of peripheral counts has been attributed to the increased hematopoietic production in shielded marrow sites, expansion of bone marrow space, and infield regeneration of bone marrow (8). Yang et al. (2) found that the most dramatic decline in leukocytes occurred during the first week of radiotherapy (16% from pretreatment to week 1 level). The fall in counts was at a rate of 3% per week during the rest of the treatment period.

Zachariah et al.'s study (14) documented the effect of fractionated regional external beam radiotherapy on white blood cell (WBC) count in 299 adult cancer patients treated by conventional radiotherapy and found that the greatest weekly interval change in counts occurred during the first week of treatment for all groups of patients. The same authors showed that lymphocyte counts had the greatest decline (between 51% and 67%) during therapy, confirming that lymphocytes are the most sensitive peripheral blood cell to radiotherapy. Other investigators (2,4,5) reported a similar observation.

The Nadir

In the study of Zachariah et al. (14), the nadir for all counts occurred during the middle to end of radiation treatment (between day 16 and 30) for all sites. This finding is consistent with the expected cumulative effect of radiotherapy. Sutz et al. (3) reported that over 90% of the drop in the average WBC count had taken place by day 15 and suggested that the WBC level reaches a new equilibrium by that day and only minor changes occurred thereafter. Yang et al. (2) showed that initial complete blood count (CBC) values were predictive of patients at lower nadir; if the patients started radiotherapy with a WBC count lower than $6000/\text{mm}^3$, 33% had a risk of WBC decrease below $3000/\text{mm}^3$ during their treatment; in 44% of the patients with hemoglobin under 12 g/dL at the beginning of radiation therapy, it dropped below 10 g/dL.

Radiobiological and clinical studies suggest that overall treatment time may be an important predictor for the efficacy of radiation (2). Therefore, treatment interruption may be therapeutically disadvantageous and should be avoided.

Chronic Toxicity from Radiation Therapy

When small radiotherapy fields comprise only 10–15% of the bone marrow, the unexposed bone marrow responds by increasing its population of progenitor cells. A better understanding of this phenomenon is provided by studies of the effects of irradiation on the release of growth factors from the stroma. Release of these factors may cause a direct radioprotective effect or be indirectly radioprotective by increasing hematopoiesis in surviving stem cells or in cells outside the radiation field (15).

When larger fields of more than 25% of the bone marrow are irradiated, permanent ablation or hypoplasia occurs at similar dose levels as for small fields. The unexposed marrow

segments will have stimulated hematopoietic activity followed by extension of functioning marrow into previously quiescent areas, such as the femoris. Count recovery occurred in 1–2 months after completion of therapy in most of the patients; bone marrow regeneration and recovery required a longer time (15). Irreversible damage after more than 50 Gy is a consequence of irreparable injury to the microvasculature manifested by bone marrow fibrosis (11).

PEDIATRIC PROTOCOLS GUIDELINES

Craniospinal Radiotherapy in Brain Tumors

Hematologic toxicity is common among patients receiving craniospinal irradiation (CSI) following chemotherapy. The percent of functioning bone marrow within a typical CSI field is approximately 55% (13,14). Exposure to chemotherapy may alter the bone marrow's sensitivity and the capabilities of repair following radiation therapy. Marks et al. (16) identified 20 children who received prior chemotherapy and 17 who did not, 47% of those pretreated with chemotherapy had to stop CSI for hematological toxicity versus 5% of those who did not. In this study there was a statistically significant increased rate of decline in WBCs, platelets, and hematocrit among the patients who received chemotherapy prior radiotherapy. Jefferies et al. (17) described 114 children treated by CSI for treatment of primary CNS tumors, 63 received chemotherapy before radiotherapy. A young age, prior chemotherapy, and a higher radiation dose to the tumor were associated with severe hematological toxicity. Chemotherapy during radiotherapy with vincristine was not associated with more toxicity; 33% of the patients developed grades 3 and 4 hematological toxicity, with a higher risk (69%) if they received prior chemotherapy. Chang et al. (18) performed a retrospective study on 79 patients treated by electron or photon therapy CSI. Younger patient age and the sequence of chemotherapy before radiotherapy were associated with increased acute hematologic toxicity. The incidence of leukocyte depression to grade 3 to 4 toxicity was 62% in the electron group and 32% in the photon group ($p=0.018$). The incidence of grade 3 to 4 platelet toxicity was higher with electrons (21%) than with photons (4%).

The ongoing protocol of the Children's Oncology group (ACNS0331) in children diagnosed with standard risk medulloblastoma includes CSI with vincristine once weekly. The hematologic guidelines are the following: if the absolute neutrophil count (ANC) falls to less than $500/\mu\text{L}$, a treatment break may be considered; another option is to irradiate only the posterior fossa. CSI may be resumed when the ANC has risen over 10% on two consecutive tests, or is above $750/\mu\text{L}$. A break is instituted if the patient is febrile or ANC is less than $1000/\text{mL}$. Platelets transfusions are indicated when counts are under $30,000/\mu\text{L}$, and CSI is reinstituted when the count is above $50,000/\mu\text{L}$ or have risen above 10% of the count on two consecutive tests. Blood transfusions are recommended when hemoglobin falls below 9 g/dL.

Radiotherapy in Sarcoma

Sherbourne et al. (19) described the blood transfusion requirements in 26 adult patients diagnosed with sarcoma and treated by combined chemotherapy and radiotherapy; 69% required a transfusion during treatment, although there was

variation in transfusion need according to the chemotherapy schedule, the use of more than three drugs, or a regimen containing cis-platinum. The authors recommend transfusing patients 48 hours prior to radiotherapy and to maintain hemoglobin levels at 10 g/dL during radiotherapy.

Radiotherapy in the *Ewing sarcoma* is usually delivered concurrently with chemotherapy (protocol POG 9354, CCG 7942); therefore low counts are usual, and treatment interruption is not considered necessary for low blood counts unless there is significant mucosal breakdown or if radiotherapy is delivered to a large pelvic mass. Most of the guidelines recommend maintaining hemoglobin >10 g/dL.

The Euro-Ewing protocol recommends modifying or withholding chemotherapy, if the blood count is low, until the end of the radiotherapy course. During radiotherapy, blood cell counts are obtained weekly. Hemoglobin or hematocrit levels should be recorded on the daily treatment record.

Guidelines regarding *rhabdomyosarcoma* are similar to other sarcomas (ARST0531); low blood counts are commonly related to chemotherapy. Treatment cessation is recommended only if there is uncontrolled infection or bleeding, ANC <750/mm³, or platelets <75,000/mm³.

Hodgkin Disease

Peiffert et al. (20) studied the immediate hematologic toxicity during total nodal irradiation (TNI) for the Hodgkin disease in a series of 72 patients with stage IIB or III who received three courses or more of chemotherapy before radiotherapy. The blood cell count at the beginning of the treatment was crucial; only 16% of the patients had interruption of TNI when the blood cell count was normal. The recommendations of the authors for the patients receiving mantle and inverted Y fields are to wait for the absolute normalization of blood cell count before beginning irradiation and start irradiation by mantle field (rather than inverted Y field). These two measures are able to reduce the number of interruptions of irradiation due to hematotoxicity. Rubin et al. (8) found that 17 of 27 patients treated with extended field radiotherapy in the Hodgkin disease had WBC depression below 2500 cells/mm³; only 7 of 27 had platelet depression under 50,000/mm³.

Usually, in pediatric Hodgkin disease, radiotherapy is delivered after chemotherapy. The guidelines of the Children's Oncology Group for Hodgkin patients treated according to the Phase III Group wide Study (Dose-Intensive Response-Based Chemotherapy and Radiation Therapy for Children and Adolescents with Newly Diagnosed Intermediate Risk Hodgkin Disease AHOD0031) are the following: start of radiotherapy (without correlation with the location of the field and the dose) is recommended when ANC > 1000/mm³ and platelets >100,000/mm³. Radiation should be held if the ANC is <500/mm³ or platelets <25,000/mm³, and resumed when the ANC is >1000 mm³ and platelets >75,000 mm³.

Neuroblastoma

In high-risk neuroblastoma, radiotherapy to the primary tumor bed is delivered after autologous bone marrow transplantation and should start no sooner than 28 days post transplant, ANC > 1000/mm³ is required to start radiotherapy in the protocol ANBL0532 (COG). The European protocol HR-NBL-1/ESIOP recommends starting radiotherapy at least 60 days from the transplantation due to the risk of busulfan-enhanced radiotoxicity.

Wilms Tumor

Radiotherapy (AREN 0532) is indicated in standard and high risk. The hematologic recommendations of the Children's Oncology Group are not dependent on the field (flank irradiation or whole abdomen irradiation; lung, liver, lymph nodes, brain) or the total dose: once radiotherapy is started, it is not recommended to stop treatment for anemia, leukopenia, or thrombocytopenia unless it is life threatening. Blood product support should be instituted according to institutional/protocol guidelines. If severe hematologic toxicity (ANC <300/μL or platelets <40,000/μL in standard risk; ANC <250/μL or platelets <10,000/μL in high risk) occurs during the course of treatment, radiation therapy is delayed until counts have recovered.

Guidelines in radiotherapy for children with *leukemia* are identical to others. Cranial radiotherapy is delivered especially to children with CNS involvement and patients not undergoing TBI can start radiation unless the absolute granulocyte count <750/μL, the platelet count <75,000/μL, or there is evidence of sepsis. Cranial radiation begins on day 29 (week 5) of Delayed Intensification II and Standard Risk B-precursor Acute Lymphoblastic Leukemia (COG, AALL0331).

COLONY-STIMULATING FACTORS

The value of *granulocyte colony-stimulating factor* (G-CSF) in radiotherapy-induced neutropenia is well documented in clinical and laboratory studies. MacManus et al. (21) described three patients with the Hodgkin lymphoma and one with the non-Hodgkin lymphoma, previously treated by chemotherapy, who developed neutropenia during CSI, and eight treated by G-CSF for brain tumors. G-CSF was administered only when the WBC count falls below a threshold level, unlike Marks and Halperin (22) who advised daily G-CSF injections. Knox et al. (23) reported the effect of G-CSF on Hodgkin lymphoma patients irradiated with by mantle fields. G-CSF increased WBC count and ANC and was well tolerated. Schmidberger et al. (24) reported 11 patients with isolated leukopenia during fractionated radiotherapy, treated with G-CSF: 4 patients received radiotherapy alone, and 7 patients received concomitant chemotherapy. G-CSF treatment was initiated upon the occurrence of leukopenia and maintained for the duration of radiotherapy. Side effects observed during G-CSF treatment consisted of mild bone pain in only one patient.

In summary, G-CSF may have a role in the management of leukopenia during radiotherapy, although it would not be expected that the drug would improve the underlying bone marrow fragility or its reserve, but could maintain the neutrophil count above a critical value, and allow the completion of radiotherapy within a specified prescription time.

The Value of Recombinant Erythropoietin for Treatment of Anemia

Anemia and hypoxia worsen the response of tumors to radiotherapy (25) and chemotherapy (26). There are evidences from randomized trials that recombinant human erythropoietin (EPO) can improve hemoglobin levels in patients receiving chemotherapy and radiotherapy for leukemia and solid tumors (27,28). Frommhold et al. (29) described anemic patients undergoing radiotherapy treated with erythropoietin.

A weekly increment in hemoglobin content of 0.7 g/dL was documented without any major side effects; in addition, the authors remarked that patients reacting sufficiently to recombinant EPO (Rh EPO) stimulation can expect better regional tumor control. Preclinical and clinical studies are necessary to ascertain not only the effect of EPO therapy on tumor biology and chemoradiation responsiveness, but also clinical outcomes such as tumor response, progression-free survival, and overall survival (30). Two randomized trials in adults reported negative outcomes with Rh EPO, as patients in the Rh EPO arm fared worse than their placebo-treated counterparts with respect to progression-free survival. The expression of erythropoietin receptor (EPO-R) in cancer cells has raised the possibility that exogenous EPO-R may exert direct effects on tumor cells associated with the potential for stimulation of proliferation, inhibition of apoptosis, or modulation of sensitivity to chemoradiation therapy (31). Further trials have to be designed in order to guarantee the safety of EPO therapy.

The Value of Thrombopoietic Agents for Treatment of Thrombocytopenia

Despite extensive efforts in the clinical development of thrombopoietic agents in the past decade, recombinant interleukin-11 (IL-11) is the only agent currently approved by the US Food and Drug Administration for thrombocytopenia induced by chemotherapy. The use of this agent is limited due to its narrow therapeutic index. Second-generation platelet-stimulating agents like romiplostim and eltrombopag are currently in clinical development in the aim of optimizing their dose and schedule in ameliorating chemotherapy-induced thrombocytopenia (32).

In conclusion, it is important to define the frequency and severity of myelotoxicity of irradiation and identify groups of patients where treatment itself and the outcome may be compromised by radiation-induced myelosuppression. Almost in all the clinical trials and international protocols, guidelines have been defined in order to avoid discontinuation of radiotherapy and/or avoid severe toxicity, especially in the heavily pretreated patients.

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Nutritional Problems in the Child with Cancer

Jerry Stein

INTRODUCTION

We often associate well-being with good nourishment. We eat comfort foods, follow the growth curves of our children, and espouse the importance of eating right for ourselves, for our families, and for our patients. Notwithstanding the current bout of epidemic obesity (1), we are still a culture that values a healthy diet.

Lay people and medical professionals often picture the child with cancer as a hairless, emaciated, hollow-eyed shadow of normal health, an image that contributes to a common perception that most patients on a pediatric oncology service are severely malnourished. Malnutrition is a common comorbidity in the pediatric cancer ward, and understanding the causes of this problem and the many modalities that are available for its treatment are important components of total care for children with cancer (2). This chapter highlights recent studies on nutritional support for children with cancer, with an emphasis on the specific effects of radiation therapy on the nutritional status of children.

NUTRITIONAL ASSESSMENT OF THE CHILD WITH CANCER

Nutritional status is measured as deviation from population norms by use of a standardized statistic known as the *z*-score. The *z*-score measures the number of standard deviations that a measure deviates from the population mean. Because children are dynamically growing organisms whose anthropomorphic characteristics change during the course of development, age-related standards have been generated from population studies. Commonly used anthropomorphic measures of nutritional status include height, weight, body mass index (BMI, weight divided by height squared), weight for height, mid-upper arm circumference, and triceps skinfold thickness. The last two of these measures seem to provide the most reliable indication of malnutrition in children with cancer. BMI is an unreliable tool in the assessment of children with leukemia at risk for malnutrition (3).

In addition to anthropomorphic measures, biochemical markers of nutritional status are often evaluated in children with chronic disease in general and cancer in particular. The ideal biochemical marker should be sensitive, easy to measure, and should have a short half-life so it can reflect recent changes in nutritional status. As opposed to serum albumin, which has a long half-life, prealbumin is an excellent nutritional biomarker. It has a short half-life (2 days as opposed to 3 weeks for albumin), is not an acute phase reactant,

and is easily measurable using commercially available kits. Prealbumin is a sensitive tool for measuring the recent nutritional status of children with cancer both at diagnosis and during the course of their treatment (4).

Additional nonanthropomorphic measures of nutritional status in children include determination of whole-body potassium (5), bioimpedance analysis (6), dual energy x-ray absorption (7), and imaging techniques such as MRI (8). Although these techniques are very sensitive, they require specialized equipment and are not available in every center caring for children with cancer. It is not clear if these more sophisticated techniques are substantially better than more universally applicable anthropomorphic measures.

ARE CHILDREN WITH CANCER MALNOURISHED AT THE TIME OF DIAGNOSIS?

Parents of children with cancer express concern about their child's nutritional status (9), and children with cancer often show signs of nutritional depletion. A survey of more than 400 children from Central and South America used anthropomorphic parameters to measure malnutrition in children with cancer at diagnosis. The different parameters used in this study identified malnutrition in 16–24% of patients (10). Weir studied 1025 children with acute lymphoblastic leukemia (ALL) in Scotland and found that 35% had a BMI > 0.5 standard deviations below age-adjusted means at diagnosis (11). Other studies have shown variable rates of malnutrition in children diagnosed with cancer, but have not always compared these children with age and socioeconomically matched healthy peers.

CAUSES OF MALNUTRITION IN CHILDREN WITH CANCER

Disease-related Causes of Malnutrition in Children with Cancer

Nutritional status is a reflection of net protein-calorie intake and utilization. Decreased dietary intake is seen in children with cancer at diagnosis, and occurs frequently in the course of therapy. Parents of infants and toddlers often report a decrease in appetite in the days and weeks prior to diagnosis. Space-occupying lesions in the abdomen can cause decreased appetite or early satiety due to physical pressure on the gastrointestinal system, while space-occupying lesions of the central nervous system can lead to decreased appetite and recurrent vomiting (particularly on awakening).

Rapidly proliferating tumor cells have metabolic needs greater than those of normal tissues, and tumors consume substantial amounts of energy both at the time of diagnosis and at the time of relapse (12). The increased metabolic demands of tumor cells are reflected by their avidity for glucose, a phenomenon exploited in positron emission tomography (PET) (13).

On the level of the “whole child,” metabolism is measured as resting energy expenditure (REE), a function of the ratio of oxygen consumption to carbon dioxide generation in patients at rest. The results of REE evaluation in children with cancer are not consistent between studies. Children with high tumor burden (high circulating blast cell counts and organomegaly) at the time of diagnosis of ALL were shown to have high REE values (14), but patients with stage IV metastatic neuroblastoma had surprisingly normal levels of REE despite evidence of malnutrition (15), albeit in a small number of patients who were studied. Another study suggested that children with a variety of solid tumors are in a hypermetabolic state (16). Children in the maintenance phase of therapy for ALL (when tumor burden is low to nearly absent), have REE similar to healthy controls (17), suggesting that chemotherapy of mild intensity does not substantially alter the metabolic needs of children so treated. REE values fall significantly during the first several weeks following stem cell transplantation in children (18). A normal metabolic rate in these children suggests that provision of an adequate caloric intake should restore them to nutritional equilibrium.

If intrinsic rates of tumor metabolism are not to blame for malnutrition among children with cancer, why is malnutrition common in this population? Several theories have been proposed. Tumors often secrete cytokines and hormones that influence metabolism and appetite. In an elegant experiment, Norton and colleagues first demonstrated that a soluble factor was responsible for changes in weight and appetite in response to tumors. In these experiments, circulatory anastomoses were created between pairs of rats where one rat harbored nonmetastasizing tumors, while the other member of the parabiotic pair was a non-tumor-bearing rat. The “healthy” member of the pair subsequently ate less and lost weight. These effects were reversed when the pairs were surgically separated (19). Administration of tumor necrosis factor (TNF) leads to cachexia and other signs of chronic illness in laboratory animals (20). By contrast, injection of TNF did not induce weight loss in humans in one study (21), while administration of TNF in patients described in other studies resulted in symptoms of acute inflammation (22).

Other hormones and cytokines that have been implicated in the cachexia associated with tumors include interleukins 1, 2, and 6, and interferon gamma. These cytokines can cause symptoms of inflammation in animals that are reminiscent of the B symptoms (weight loss, fever, night sweats) experienced by some patients with Hodgkin lymphoma. Although it is reasonable to conclude that these mediators may be responsible for weight loss in patients with Hodgkin lymphoma, studies that have attempted to correlate blood cytokine levels in patients with the presence of B symptoms have shown conflicting results (23).

Elhasid and colleagues demonstrated that although many children have signs of malnutrition at the time of the diagnosis of cancer, nutritional status improves during the

course of successful therapy, perhaps in parallel with disappearance of the tumor. This group also demonstrated that the nutritional status of younger children improves more rapidly after the start of therapy as compared with that of older children, reaffirming the notion that younger patients tend to “bounce back” more rapidly than their adolescent counterparts (4).

An unusual cause of malnutrition in children with tumors of the central nervous system (adjacent to the hypothalamus) is the diencephalic syndrome. First described in 1951 by Russell (24), this syndrome consists of severe emaciation, preserved linear growth, together with normal or precocious social and intellectual development. Although classically associated with hypervigilance, euphoria, hyperkinesis, and nystagmus, these findings need not be present to establish the diagnosis, and indeed were absent in a more modern series of patients with this syndrome. The diencephalic syndrome may be the result of acquired growth hormone resistance in patients so affected (25).

Treatment-related Causes of Malnutrition in Children with Cancer

Antineoplastic therapy has dramatic effects on the nutritional status of children. Specifically, radiation and chemotherapy can cause oral and gastrointestinal mucositis, alterations of sense of taste, nausea and vomiting, diarrhea, and infections of the gastrointestinal tract that independently or collectively affect caloric intake and utilization.

Changes in taste and smell perception are reported by many patients during the course of treatment (26). Children have impaired ability to differentiate sour and bitter tastes following total body irradiation (TBI) (27), which may contribute to dysgeusia and aversion for specific foods leading to decreased appetite following stem cell transplantation. Younger children may refuse to eat if their sense of taste is blunted, although older children and adolescents can often be coaxed into eating even if the taste of their food is not “quite right.”

Food aversion is common among children receiving chemotherapy. Pioneering work by Bernstein in the 1970s demonstrated that food aversion develops for specific foods that are ingested prior to the administration of emetogenic chemotherapy. Specifically, children demonstrated an aversion to maple-walnut ice cream 2–4 weeks after they had received chemotherapy only if ice cream of this flavor had been eaten in the hours preceding therapy (28). Food aversion can be easily demonstrated on the pediatric oncology ward as the food cart makes its mealtime appearance and many children immediately cover their noses so as to avoid the “hospital-food smell.” To many children, the odors that they associate with the hospital can elicit feelings of nausea and can decrease appetite.

Oral and gastrointestinal mucositis are frequent side effects of chemotherapy and radiotherapy. Therapy-induced apoptosis of mucosal epithelial cells and the basal cells that contribute to the constant regeneration of this tissue, results in the local release of intracellular (e.g., NF- κ B) and intercellular (e.g., interleukin 1 and TNF) mediators that contribute to inflammation of the mucosa (reviewed in Ref. 29). The resultant inflammation results in ulceration, local bacterial proliferation, a painful mouth, and the

inability to eat. Additionally, antineoplastic therapy causes immune suppression, leading to an increased susceptibility to herpetic oral infection (30), while the antibiotics that children with cancer often receive can predispose to superficial fungal infections of the mouth and esophagus. Blood levels of certain growth factors (e.g., epidermal growth factor) in the saliva of patients receiving radiation therapy to the oral cavity correlate with the severity of radiation-induced mucositis, suggesting a role for cytokine modulation in the evolution and possibly in the treatment of this complication (31).

Infection of the esophagus with cytomegalovirus, herpes simplex virus (32), or *Candida* can cause severe dysphagia and chest pain in children with compromised immune systems, and can in turn affect their ability to eat properly. Endoscopy is often required to establish a diagnosis of specific infectious agents that can cause esophagitis (33). Radiation therapy to the mediastinum can induce acute inflammation and of the esophageal mucosa, while esophageal strictures can occur either during therapy or as a late adverse event leading to dysphagia and swallowing dysfunction. This phenomenon can be aggravated by drugs that enhance radiation recall sensitivity such as anthracyclines (34). The cumulative effects of therapy-related mucosal complications result in a child for whom eating (or even the swallowing of saliva) is a painful and unpleasant experience.

Vomiting and nausea are frequent complications of cancer therapy in children, and obviously present a significant obstacle to effective nutrition. Acute abdominal syndromes including severe nausea, vomiting, and diarrhea developed in the majority of children treated with abdominal radiation therapy in the era before effective antiemetics were widely available. The emetogenic effects of abdominal irradiation are probably mediated by local damage to the gastrointestinal mucosa (35). By contrast, chemotherapy causes vomiting in children treated for cancer via stimulation of neurons in the area postrema, the nucleus tractus solitarius, and the dorsal motor neuron of the vagus nerve. Substance P (and its cognate receptor, NK-1) and stimulation of 5-hydroxytryptamine receptors are the dominant biochemical mediators of chemotherapy-induced vomiting.

Other causes of treatment-mediated nausea and vomiting include anticipatory or conditioned nausea, and increased intracranial pressure caused by solid tumors of the central nervous system. Recurrent vomiting results in irritation of the esophagus, and can lead to ulceration and Mallory Weiss tears, exacerbating nutritional problems in children and adolescents.

Radiation and chemotherapy can cause diarrhea either directly (e.g., abdominal radiation or drugs used infrequently in first-line pediatric protocols such as CPT-11) or secondarily (immunosuppression causing gastrointestinal infections and frequent antibiotic use causing overgrowth of gastrointestinal pathogens). Persistent untreated diarrhea that is not successfully treated can lead to malnutrition (36).

Many of the drugs used in cancer therapy induce nutritional deficits as part of their intrinsic mechanism of action. Antimetabolite medications used frequently in the treatment of children with ALL cause depletion of purine nucleotides that are needed for DNA synthesis (37). Asparaginase, a cornerstone of the treatment of lymphoblastic leukemia, causes depletion of asparagine, an amino acid that is needed for the

synthesis for many proteins (including insulin and albumin). Corticosteroids induce catabolism, and despite the concomitant hyperphagia that is often seen in children receiving this class of drugs, nutritional status is not improved (38). Corticosteroid use has additional unfavorable effects on calcium deposition in growing bones (39).

DOES NUTRITIONAL STATUS AFFECT TREATMENT TOLERANCE AND OUTCOME OF CANCER THERAPY IN CHILDREN?

There are no large-scale studies of treatment tolerance and nutritional status in children receiving chemotherapy. *Pneumocystis carinii* (now *jeveonii*) susceptibility, a benchmark infection that reflects the immune-suppressed state of children receiving intense antineoplastic therapy, is enhanced in malnourished laboratory animals (40) and in malnourished children with leukemia (41) suggesting a direct connection between immune function and nutritional status. Children with advanced cancer and malnutrition do not mount immune responses when challenged with recall antigens, but reactivity is restored following several weeks of intravenous alimentation (42). The presence of severe infections hinders the timely administration of scheduled antineoplastic therapy (possibly compromising its efficacy), and of course can endanger the life of the patient (43).

Improved nutritional status may facilitate the administration of dose-intense antineoplastic therapy, as was demonstrated in children receiving a high-risk (more intense) leukemia protocol (44). Several small prospective studies have demonstrated less treatment delays (45) and infections (46) in children with advanced solid tumors who received intravenous hyperalimentation concomitant to their chemoradiotherapy. Studies of dose intensity and nutritional status in children receiving contemporary therapy using high-risk leukemia and solid tumor protocols should be encouraged to explore the role of intense nutritional support in facilitating dose intensity on state-of-the-art protocols.

Nutritional status affects disease-free survival of children with cancer in some but not all studies. A study of children treated in El Salvador and Brazil found no correlation between nutritional status at diagnosis of leukemia or a solid tumor and the outcome of treatment (47). Similarly, no correlation between survival and nutritional status at diagnosis was found in a large cohort of children treated for ALL in the United Kingdom (11). By contrast, studies of children with advanced solid tumors demonstrated improved survival when nutritional interventions such as parenteral hyperalimentation were applied to patients with poor nutritional status at diagnosis (45,46). Surprisingly, children with BMIs at opposite ends of the spectrum (underweight and overweight) suffered an excess of treatment-related mortality and relapse incidence in a recently completed trial involving 768 children with acute myelogenous leukemia, although dose intensity was not affected by BMI (48). By contrast, a study of more than 600 children with ALL enrolled at a single institution on four consecutive treatment protocols did not demonstrate a correlation of BMI and survival. This latter study included extensive

pharmacologic monitoring of systemic exposure to the chemotherapeutic drugs administered throughout therapy, and BMI was not correlated with drug levels (49).

The effect of nutritional status on the quality of life of children with cancer is a current area of interest for many investigators. Issues relating to poor nutrition were common in children and adults with advanced cancer, but issues related to quality of life and nutritional status have not been extensively investigated in children at earlier (and hopefully more successful) phases of antineoplastic therapy (50–52). A six-item questionnaire that explores the patient feelings regarding anorexia/cachexia has been designed and validated in children with cancer aged 10–17 years (53). Notwithstanding the relative paucity of extant literature, many parents and some children associate dietary intake with overall well-being, and issues regarding anorexia/cachexia often consume substantial amounts of time and emotional resources in the oncology clinic. Parents can sometimes focus excessively on their child's dietary intake, leading to stress and conflict between themselves and their child. Clinicians should be alert to this potential flash point and should be prepared to provide the requisite counseling to relieve this source of potential strife.

NUTRITIONAL INTERVENTIONS FOR CHILDREN WITH CANCER

Does Feeding the Child with Cancer Feed the Tumor or Feed the Patient?

Van Eys (46) invokes the term “thermodynamic death” (usually used by cell biologists to describe the process that occurs when cells are starved of essential nutrients) to describe what may happen to children who do not receive adequate nutrition during the course of antineoplastic therapy. This potent analogy notwithstanding, Van Eys stresses that nutritional interventions should be aimed not at the cells of the child but rather on the child himself within the context of the family. Despite this commonsense approach, many pediatric oncologists were taught that nutritional interventions in children with cancer feed the tumor and not the patient. There is no convincing evidence in the literature of modern pediatric oncology to support this contention. As such, children with cancer should receive the full attention of the nutrition assessment and intervention team at the cancer center where they receive their antineoplastic treatment.

While the presence of a viable tumor mass may prevent full utilization of caloric intake for normal homeostasis due to the secretion of cytokines as outlined above, caloric support for children with cancer may positively affect their quality of life, their ability to tolerate therapy, and possibly the outcome of their treatment. In the absence of large, multi-institutional-controlled clinical trials to support specific nutritional interventions, nutritional assessment is not routinely performed in many centers caring for children with cancer, and the lack of evidence-based guidelines for nutritional interventions results in spotty implementation of nutritional therapy (54). An international consensus conference convened in 1998 to discuss nutrition in children with cancer strongly advocated supportive nutritional therapy by any route for these children in an effort to maintain normal nutritional status and growth (55).

SPECIFIC NUTRITIONAL INTERVENTIONS FOR CHILDREN WITH CANCER

Caloric Intake

Parenteral nutrition in children was first reported by Wilmore and Dudrick in 1968 (56,57). The use of intravenous hyperalimentation in children receiving antineoplastic therapy was studied intensively in the 1970s and 1980s. Van Eys showed that parenteral nutrition could be effectively delivered to children with cancer with limited adverse effects, which were themselves often attributed to the patients' depleted nutritional status at the time this treatment was initiated (46). Donaldson (58) demonstrated that the weight of children receiving abdominal radiation therapy could be maintained using parenteral nutrition, but that the benefits of this therapy were short-lived. Excitement for this alternative nutritional modality was tempered by analysis of pooled data from reported clinical trials of parenteral nutrition in patients (mostly adults) with cancer showed a highly significant increase in the infection rate in patients so treated (59). A meta-analysis performed by McGeer et al. (60) confirmed that the use of parenteral nutrition in cancer patients (again, mostly adults) was associated with increased rates of infection and poorer tumor response. A study performed in children demonstrated a nearly 10-fold increase in infections on days when parenteral nutrition was administered (61). Additionally, parenteral nutrition solutions often demand special preparation and are extraordinarily expensive. As such, parenteral nutrition is justifiably considered the nutritional route of last resort in many pediatric oncology centers.

Use of the patient's gastrointestinal tract for nutritional support during periods of disease or treatment-related anorexia is the most physiological and logical route for supplementation of caloric intake. Bakish and colleagues demonstrated that although nutritional counseling to promote weight gain in children with tumors of the central nervous system was not effective, use of invasive methods of enteral nutrition lead to lasting improvements in nutritional status as assessed by weight gain (62). Despite the notion that dietary counseling is futile in children suffering from anorexia during cancer treatment, some patients nonetheless respond well to this benign therapy, and its vigorous use is to be encouraged. Improving mealtime ambience can improve nutritional intake in cancer patients, and patients should be encouraged to participate in family mealtime on a regular basis (63,64).

As mentioned above, food aversion is a conditioned response that develops when specific tastes or odors are associated with the unpleasant effects of chemotherapy. Conversely, conditioned taste aversion (association between ingestion of a coconut or root beer-flavored Lifesaver candy chewed just before therapy) can be used as a “scapegoat” to avoid the food avoidance associated with antineoplastic treatment in children (64). Counseling children to avoid foods with a strong taste or odor in the hours before and after radiation or chemotherapy can also ameliorate this phenomenon.

The use of appetite stimulants has been explored in adults and in children. Cyproheptadine hydrochloride, an antihistamine, and megestrol, a progesterone-like hormone, are effective in some children with anorexia due to cancer therapy, but the former often causes unpleasant sedation, while

the long-term effects of the latter in children are unknown (65). Because suppression of adrenal corticosteroid secretion is common in children receiving megestrol, patients so treated should be carefully monitored by an endocrinologist at frequent intervals (66). Multi-institutional, prospective, randomized trials of appetite stimulants in children have not been reported.

The use of nasogastric and gastrostomy gavage feedings for children with cancer is increasingly utilized in children. Percutaneous placement of a gastric feeding tube is a minimally invasive procedure performed on an outpatient basis in most centers (67,68). Although local irritation/infection and mechanical problems (mostly leakage of gastric contents around the tube) can occur, gastrostomy feeding is a safe and efficient means of providing calories to children with treatment-induced anorexia. Nasogastric tube placement is useful for short-term nutritional support in these patients, and a trial of nasogastric feeding can serve as a useful test of the integrity of the gastrointestinal tract prior to placement of a surgical gastrostomy. Parents can easily learn to administer gavage feedings at home (69). Parents of young children are often reluctant to agree to nasogastric or gastrostomy tube placement, while adolescents and older children already afflicted by the stigma of their disease may recoil at the change in body image induced by placement of a tube. Gentle persuasion by the clinical team, including psychosocial support as needed, will usually help patients and their families deal with the emotional burden of these alternative forms of enteral nutrition. Patients usually adapt rapidly to the presence of feeding tubes, and the improvement in their quality of life after adequate nutritional homeostasis has been established often elicits comments from our patients and their families such as “why did we wait so long to place the tube?”. An added benefit of nasogastric tube or gastrostomy placement is the ease with which patients can receive the many oral medications that children with cancer often require, sparing parents of young children the endless struggle of trying to get their frequently stubborn progeny to swallow unpalatable but life-saving treatments.

A wide variety of oral formulas that can be used to supplement caloric intake is available in most centers. Some of these supplements come in flavors that children find acceptable. Consultation and close cooperation with a dietician combined with a flexible approach to the use of these supplements should be the standard of care.

Diarrhea

The administration of enteral nutrition in children with cancer is often hampered by the presence of diarrhea. Diarrhea in children with cancer can be caused by mucosal injury to the gastrointestinal tract but also by infection. Patients with diarrhea should be screened for a wide range of pathogens. Common “suspects” such as rotavirus should be sought, but stool specimens should also be tested for parasitic infections (such as cryptosporidium *Entamoeba histolytica* and *Giardia lamblia*), for the presence of *Clostridium difficile*, and for signs of bacterial and fungal overgrowth due to the repeated administration of broad-spectrum antibiotics. Profound immune suppression caused by antineoplastic therapy can sometimes lead to enteral infections with cytomegalovirus and adenovirus for which specific therapies exist. Specific treatment for infections should be administered as indicated by laboratory evaluations, keeping in mind that the presence of a pathogen

in a stool sample does not always indicate a true tissue infection. Pediatric oncology patients who suffer from chronic diarrhea should be evaluated by a gastroenterologist. Endoscopic visualization and biopsy of the intestinal mucosa is occasionally required in these children.

Diarrhea caused by radiation and chemotherapy can impair the absorption of nutrients. Stool samples should be tested for the presence of carbohydrate malabsorption by assay of reducing sugars using easily performed bedside tests (70); evaluations of protein and fat malabsorption are somewhat more cumbersome. Lactase deficiency occurs in the context of antineoplastic therapy in children, and consideration should be given to a diet free of lactose in symptomatic patients (71). In the presence of malabsorption, consideration should be given to the administration of an elemental or partially elemental proprietary formula, although controlled studies of this intervention have not been reported.

Many different agents have been proposed for the treatment of diarrhea in oncology patients (72,73). Probiotics should be used cautiously in children with depressed immunity as they can potentially gain access to the bloodstream and cause systemic infections (74). The use of bismuth and pectin preparation have not been systematically studied in children with cancer and persistent diarrhea, but care should be exercised in the administration of bismuth salicylate-containing preparations in small children with low platelet counts because of the theoretical possibility that the absorbed drug might promote bleeding or signs of aspirin intoxication (75). Chemotherapy-associated diarrhea, particularly that associated with the administration of irinotecan, may respond to coadministration of oral cephalosporins (76). Loperamide has been shown to be safe for use in children but should be used carefully in patients concurrently receiving opiates or vinca alkaloids lest signs of ileus develop. Octreotide may ameliorate diarrhea in adults with radiation-induced diarrhea and a long-acting formulation of the drug is available for use in adults (77–79). Octreotide has not been extensively studied in children, and the long-acting formulation is not suitable for use in small children.

Mucositis

The prevention and treatment of mucositis in patients receiving radiation and chemotherapy have been reviewed recently in a practice guideline issued by the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (80) and in a Cochrane review (81). The latter review analyzed the results of treatment using 33 different interventions, and readers interested in all possible and available treatments are referred to this comprehensive treatise. It is important to emphasize that the multitude of available treatments and the plethora of controlled clinical trials exploring their use attest to the reality that there is no consensus as to the best therapy for mucositis and that there is no one treatment that will be effective in all, or even most, patients. Nonetheless, there are many effective ways to prevent or treat mucositis in children receiving antineoplastic therapy, some of which are outlined below.

Mucosal injury can be caused by direct treatment effects or by secondary infection of the mucosa, as outlined above. Radiation to the oral mucosa should be avoided as much as possible by the use of intensity-modulated radiation therapy, or by the use of blocks to minimize the exposure of as much mucosa as is possible. Despite the best efforts of the therapist

to prevent radiation exposure to the oral cavity in children with its attendant short- and long-term effects, administration of significant radiation doses are often required to the oral cavity, particularly in the treatment of rhabdomyosarcomas and nasopharyngeal carcinoma. Cranial radiation usually spares the oral mucosa, while careful planning of radiation ports during the treatment of Hodgkin lymphoma involving cervical or mediastinal nodes can often prevent substantial mucosal damage to the mouth and esophagus.

It is intuitively obvious that good oral hygiene will attenuate the mucositis-causing effects of radiation. A prospective randomized trial performed among children receiving chemotherapy demonstrated significant improvements in mucositis scores in children allocated to a comprehensive oral care protocol consisting of tooth brushing and rinses with chlorhexidine and normal saline as compared to children allocated to a control arm (82). By contrast, an expert panel recommended against the routine use of chlorhexidine for the prevention of mucositis in (adult) patients receiving radiation therapy to fields that include the oral mucosa (80).

Benzylamine is a topical orally administered anti-inflammatory agent with antibacterial and analgesic properties that has shown great promise in the prevention of radiation-induced stomatitis following radiation therapy in doses as high as 50 Gy in at least one large randomized, placebo-controlled study (83). The results of a multicenter study comparing this drug to placebo have yet to be published. Only recently released for use in the United States, benzylamine is available on most continents and was given a grade A recommendation based on the expert panel of the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology based on a high "level of evidence." The Cochrane review cites additional useful agents that include amifostine, glutamine (84), ice chips (primarily for use together with 5-fluorouracil), and local laser therapy (85) among others. Most of these treatments have not been extensively explored in pediatric studies.

Keratinocyte growth factor (KGF) is a new, but still very expensive, agent that is effective for the prevention of mucositis. KGF administered prior to stem cell transplantation reduced the incidence of mucositis and reduced mucositis severity scores as compared to placebo if TBI was administered as part of the pretransplant preparative regimen (86). Controlled trials of the use of KGF in patients receiving irradiation of the oral mucosa for treatment of solid tumors have not been reported.

Our group has reported dramatic success with the use of Traumeel S, a homeopathic remedy widely used in many European countries, for the prevention of oral (but not esophageal) mucositis in children undergoing stem cell transplant (including patients who received TBI). This inexpensive and nontoxic formulation is useful only in patients who are old enough to retain the solution in their mouth for at least 1 minute, and it did not affect the incidence of odynophagia in study patients (87).

Mucositis can be very painful, and it behooves the medical team to strive to alleviate pain in young patients suffering from oral and esophageal pain. Patients with severe mucositis benefit from appropriate and aggressive pain control. The use of analgesics in children is explored fully in this textbook.

Nausea and Vomiting

The past 20 years have seen a revolution in the treatment of therapy-related nausea and vomiting. The reader is referred to an excellent review (88) and a guideline statement (89) on this topic. Where pediatric oncology wards were once dominated by scenes of children slumped over emesis basins as they suffered through their therapy, it is now not uncommon to encounter the pizza delivery man making rounds through the pediatric oncology ward as patients receive highly emetogenic treatments.

5-Hydroxytryptamine blockers and NK-1 inhibitors, together with adjuvants such as corticosteroids, have made once nearly intolerable treatments bearable for most patients. The 5-hydroxytryptamine blockers have impressive therapeutic indices, and are available in oral and intravenous forms, permitting flexibility in dosing. Different agents vary with regard to duration of action, with palonosetron having a half-life of nearly 2 days, while ondansetron has a half-life of 4–6 hours. Dosing intervals are dictated by the differing pharmacokinetic profiles of these agents. Although many 5-hydroxytryptamine blockers have been evaluated in children, studies exploring some of these agents (such as palonosetron (90)) have been reported only in abstract form. Tables 25.1 and 25.2 suggest doses, dosing routes, and administration intervals for some of these agents.

Even the best antiemetics administered in highly regulated clinical trials do not result in complete symptom control for all patients. A relatively small but still substantial percentage of patients continue to suffer from nausea and vomiting despite the administration of high doses of 5-hydroxytryptamine blockers. The use of adjuvant modalities in these patients has been evaluated, but the results of these treatments are variable at best.

In order to anticipate the antiemetic needs of a specific patient, it is important to be able to predict the emetogenicity of the specific treatments that the patient is about to receive. For practical purposes, antineoplastic treatments are classically divided by their emetogenicity risk into minimal (e.g., vinblastine, busulfan), low (e.g., methotrexate, topotecan), moderate (e.g., carboplatinum, and moderate dose cyclophosphamide), and high (e.g., cis-platinum). Radiation therapy to the abdomen is usually of low to moderate emetogenicity, while TBI is associated with more nausea and vomiting. Additional and important considerations for the clinician planning antiemetic therapy are the patient's past experiences with similar antineoplastic therapy with regard to nausea and vomiting, and the patient's expectations for the current course of therapy. It is important to propose realistic expectations to the patients regarding their chances of remaining completely nausea free during and after treatment.

The unique pharmacologic profiles of different 5-hydroxytryptamine blockers can be exploited for the patient's benefit. Because the emetogenic effects of chemotherapy that are specifically mediated via 5HT-3 receptors are usually short-lived, the longer-acting antiemetics are principally useful in patients receiving chemotherapy by prolonged continuous infusion and/or on consecutive days. Oral versus intravenous administration of antiemetics can also be tailored to a particular patient's needs. For example, children can receive an oral dose of a 5HT-3 antagonist on their way to the radiation oncology clinic to both ameliorate anticipatory

Table 25.1**First-Line Medications for Prevention and Treatment of Chemotherapy-induced and Radiation Therapy-induced Nausea and Vomiting**

Name	Oral Formulation	Intravenous Dose	Oral Dose	Adverse Effects
Ondansetron (Zofran)	4 and 8 mg tablets 4 mg/5 ml solution	0.15 mg/kg $\times$ 3 Maximum 32 mg/day	Age < 1 year: 1 mg $\times$ 3 2–4 years: 2 mg $\times$ 3 4–11 years: 4 mg $\times$ 3 $\geq$ 12 years: 8 mg $\times$ 3	Headache, fatigue, diarrhea, constipation
Granisetron (Kytril)	1 mg tablet 1 mg/5 ml solution	10–40 microgram/kg/day	<25 kg: 0.25 mg $\times$ 1–2/day 25–50 kg: 0.5 mg $\times$ 1–2/day >50 kg: 1–2 mg $\times$ 1–2/day	Headache, somnolence, diarrhea
Palonosetron (Aloxi)	0.5 mg capsule	3–10 microgram/kg/day Maximum 0.25 mg/day	No recommendation	Fever, agitation
Dexamethasone (Decadron)	Tablets and elixir	8 mg/m ² $\times$ 2 Maximum 20 mg/dose	8 mg/m ² $\times$ 2 Maximum 20 mg/dose	Mood swings, gastric irritation, hyperglycemia, hypertension
Aprepitant (Emend)	125, 40, and 80 mg capsules	115 mg on Day 1	125 mg on Day 1, 80 mg on Days 2 and 3; no pediatric dose	CYP3A4 interaction

Administer first dose of antiemetic 30 minutes before chemotherapy and 1 hour before radiation therapy.

nausea and to prevent vomiting following radiation therapy to the abdomen or to the central nervous system. 5HT-3 blockers have extraordinarily high therapeutic indices, and cause few ill effects. As such, there is a tendency to use high doses of these drugs (ampoules of granisetron contain 3 mg and ampoules of ondansetron contain 8 mg) than may be required, although smaller doses may be equally effective and more cost effective (91).

Although there is no evidence that one 5HT-3 antagonist is superior to another, many patients have their own opinions about which drug works best for them. Elaborate pharmacological debates with patients and their parents are often of little utility under these circumstances.

The addition of high-dose dexamethasone to an antiemetic regimen increases the number of patients who are nausea and emesis free, but high-dose steroids can have unfavorable effects

Table 25.2**Antiemetics with Lower Therapeutic Indices**

Name	Oral Formulation	Intravenous Dose	Oral Dose	Adverse Effects
Metoclopramide (Reglan, Pramin)	5 and 10 mg tablets 1 mg/mL syrup	Up to 1 mg/kg every 6 hours	Up to 1 mg/kg every 6 hours	Extrapyramidal syndrome, sedation, anxiety; consider coadministration of antihistamine
Droperidol	—	0.075 mg/kg every 6 hours	—	Extrapyramidal syndrome, dysphoria, anxiety, <i>Arrhythmia</i>
Tetrahydrocannabinol (Dronabinol)	2.5–10 mg capsules	—	5 mg/m ² with titration	Mood changes, hallucinations, shared hypersensitivity with sesame oil, addiction
Prochlorperazine (Compazine)	5–25 mg tablets 1 mg/mL syrup	Not recommended	0.1 mg/kg/dose $\times$ 3	Extrapyramidal syndrome, dystonia, sedation
Promethazine (Phenergan)	12.5–50 mg tablets 25 mg/5 mL syrup (suppository 12.5–50 mg)	0.25–1 mg/kg/ dose $\times$ 4 Up to 25 mg	0.25–1 mg/kg/ dose $\times$ 4 Up to 25 mg	Extrapyramidal syndrome, dystonia, sedation

These medications are more likely to cause adverse effects than those listed in Table 25.1; their use should be carefully monitored by physicians and nurses experienced in their use.

on mood and long-term health in children. Corticosteroids can also influence the penetration of some antineoplastic medications through the blood–brain barrier (92). The mechanism by which corticosteroids exert an antiemetic effect is not fully elucidated.

Although 5-hydroxytryptamine blockers are effective in the control of vomiting that occurs during and soon after the administration of radiation or chemotherapy, they are ineffective in controlling the delayed nausea and vomiting that are frequently seen following the administration of *cis*-platinum and other highly emetogenic agents. NK-1 receptor inhibitors have been found to be potent agents for the control of late-postchemotherapy vomiting, and have attained widespread use for this indication. NK-1 receptor inhibitors should be used in conjunction with 5HT-3 inhibitors. The use of NK-1 receptor inhibitors in children has been described (93), but large prospective studies have not been reported.

Other agents that have antiemetic effects in children include metoclopramide, phenothiazines, benzodiazepines, and cannabinoids. Use of these agents is frequently associated with unpleasant side effects, and they are generally less effective than 5HT-3 blockers. Because high doses of metoclopramide and phenothiazines can cause extrapyramidal reactions in children and adolescents, they are often administered together with antihistamines. The resultant sedation is occasionally a welcome relief from intractable vomiting that is seen in occasional patients despite the use of contemporary 5HT-3 blockers. Surprisingly, phenothiazines can occasionally exacerbate nausea and vomiting in children receiving chemotherapy (94).

The use of nonpharmacologic antiemetics such as acupuncture (95,96) or hypnosis (97) can be effective in the

prevention or treatment of therapy-associated nausea and vomiting, and the use of these and other nonpharmacological therapies should be explored prospectively in children and adolescents. Unfortunately, because these modalities are often operator dependent, it is difficult to design well-controlled multi-institutional trials exploring their use.

Anticipatory nausea is a common problem with children who are receiving antineoplastic therapy. A “bad experience” with the first cycle of therapy can induce a conditioned response in the patient. On subsequent clinic visits, or even as the patient wakes up on the day of a scheduled visit, nausea and vomiting may occur. Self-hypnosis and cognitive-distraction therapy may be helpful in ameliorating this troubling symptom (98–100).

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The full list of References for this chapter can be found online at the book’s website. Listed here are References particularly recommended for further reading.

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Psychosocial Aspects of Radiotherapy for the Child and Family with Cancer

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As cure can be achieved in a large majority of pediatric cancer patients, long-term effects and quality of life of the survivors are nowadays the principal challenges to pediatric oncologists. In recent years, it has become increasingly clear that the psychosocial effects of a treatment are an integral part of the treatment and should be considered when evaluating its overall effect and its impact on the patient's quality of life.

In this chapter, we will first present a literature review of what is known about the psychosocial effects of pediatric radiotherapy (RT) and then describe the results of an initial survey with children and parents we have conducted in two pediatric oncology centers in Israel about the psychosocial effects of RT.

LITERATURE REVIEW

In recent years there have been an increasing number of pediatric cancer survivors. The rate of survival has reached about 80% and is increasing. Additionally, the health professionals as well as the parents and the children themselves are increasingly becoming aware and conscious of the effects of the treatments, including RT. Hence, there is a growing body of studies of the psychosocial correlates and effects of pediatric cancer treatments in general and of RT specifically. Some of the effects are direct, others indirect and result from a variety of effects of radiation on physical functions.

Cognitive Effects of Radiotherapy

A large number of studies deal with investigating and assessing the cognitive effects of RT. As could be expected, the greatest bulk of the studies focus on the cognitive effects of cranial radiotherapy (CRT), since it is in this domain that cognitive effects are likely to be most easily detectable. Up to 40% of childhood cancer survivors who were exposed to CRT may experience neurocognitive impairment in one or more specific domains (1). Recent years have witnessed a remarkable advancement in the number and quality of studies focusing on cognitive effects following CRT (2). This surge of interest has led to an increase in information about the kind of cognitive effects of RT as well as the relations between these effects and various characteristics of RT. Nevertheless, the findings need to be considered with caution for two main reasons. First, although in the present review special care was taken to include only studies that refer directly to the effects

of RT per se, it is likely that many of the children participating in these studies did not undergo exclusively RT but often also surgery and chemotherapy that could have also impacted cognition in unspecified ways. Second, many of the children treated with RT got the treatment as a cure for brain tumors, which could have affected cognition independently of the RT.

The effects of radiation on the brain are usually described in terms of three stages: the acute phase, often associated with a sudden neurological deterioration, the subacute phase (or early delayed, 2–6 weeks after radiotherapy) when the “somnolence syndrome” may occur attended by fatigue and a transient exaggeration of the neurological signs, and finally the late phase in which various gradual neurocognitive deficits show up (3,4). Thus, most of the reported findings refer to the third phase.

Effects of RT on Intelligence

A large number of studies report the effects of RT on intelligence (Table 26.1). The studies vary greatly in the characteristics of the samples and the administered doses of RT. However, the majority support the general conclusion that CRT brings about a decline of about 5–20 points in IQ, which according to many studies, but not all, tends to be more pronounced if the RT dose has been higher and the child who got RT is younger. The decline in IQ persists over time, even to over 10 years after RT. There is evidence that the decline in IQ may be due at least partly to a decreased rate of acquiring new information (23).

Effects of RT on Specific Cognitive Functions

Several studies focused on identifying the effects of CRT on more specific cognitive functions than overall intelligence. Deficits in cognitive functioning following CRT are evident in attention, executive functioning, processing speed, working memory, and memory, all of which contribute to declines in intellectual and academic abilities (10,24). Monje (25) reported that CRT is associated with a progressive decline in cognitive function, prominently memory function, whereby impairment of hippocampal neurogenesis is thought to be an important mechanism. Children with acute lymphoblastic leukemia (ALL), who had been treated with RT, were compared in cognitive functioning with ALL patients who had been treated only with chemotherapy and with healthy controls (8). The comparison showed that the group who got RT had deficits in working memory and processing speed relative to

Table 26.1
Studies about the Effects of RT on IQ Scores

Descriptive Characteristics of Study	Findings Concerning IQ
A Japanese sample of 30 children aged 3–16 at diagnosis (5)	IQ level was almost 20 points lower than in healthy controls. The decline increases with time since diagnosis even when there is no tumor recurrence or hydrocephalus
A review of 18 studies (6)	In 12 of the 18 studies, patients who got RT had IQ levels 12–14 points lower than those who did not get RT (see also Ref. 7)
Children diagnosed with ALL who had been treated with RT were compared with two groups: ALL patients who had been treated only with chemotherapy and healthy controls (8)	The group who got RT showed deficits in IQ that were at least partly independent of other cognitive impairments
A comparison of children diagnosed with medulloblastoma who were treated with CRT and those treated only with surgery (9)	The decline in IQ is more severe in those treated with CRT than in those who got only surgery
Verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ) were assessed in 64 survivors diagnosed with ALL, about 20 years after diagnosis. 44 survivors got CRT, 20 only chemotherapy. The control group consisted of 45 healthy young adults. Earlier neuropsychological test results of 45 of the survivors were available (10)	Mean VIQ test scores were 91, 100, and 109 ($p < 0.001$), and the mean PIQ test scores 100, 111, and 118 ($p < 0.001$) for the irradiated survivors, nonirradiated survivors, and controls, respectively. There was a significant decline in PIQ and VIQ test scores in the irradiated group during the follow-up period, but only in VIQ in the nonirradiated group
Study dealt with trend in IQ as a function of time since diagnosis. Fifty children diagnosed with medulloblastoma completed 188 psychological evaluations using the Wechsler Intelligence Scales for Children over a 7-year study period following 35–40 Gy postoperative CRT (11)	Decrease in IQ in children treated with CRT. There was a delay prior to decline in performance for older patients, whereas in younger patients the decline starts earlier (already in the first year), reaches a plateau at approximately 6 years postdiagnosis, and increases more as time from treatment increases. A steeper decline was found for those with higher baseline performance
Children with malignant brain tumors who had been treated from 1986 to 1993 in Finland and were alive and tumor free 5 years later (12)	The mean full scale IQ was 85 (range 45–138), 24% had an IQ value less than 70, and only 36% more than 90
64 patients with posterior fossa tumors, including those treated with either surgery and CRT ($n = 32$) or surgery without RT ($n = 32$). Ten patients treated for non-CNS solid tumors were included for comparison (13)	Patients treated with CRT had lowered short-form IQ. Poorest performance was in those treated with CRT and who had postsurgical complications
53 children treated according to the AML-BFM-87 protocol (median age at diagnosis: 8.5 years, range 0.3–17.5; median time since diagnosis: 5.7 years, 3.8–10.7 years), who got CNS prophylaxis that consisted of ARA-C intrathecal, high-dose ARA-C intravenous and either no CRT ($n = 15$) or CRT ($n = 38$) at a dose of 12–18 Gy depending on age. Patients with relapse or initial CNS involvement and transplanted patients were excluded (14)	In the total group, no significant differences in IQ (assessed by Raven's Matrices) were observed between irradiated and nonirradiated patients
The study investigated if the IQ (assessed by the Hamburg Wechsler Intelligence Test for Adults) in 27 children treated for leukemia decreases in the years after whole brain RT. Mean time between RT and IQ measurement was 9 years (15)	IQ results did not differ significantly from the IQs of the general population. Age and dose were not predictors of a decrease in IQ. The only predictor was time lapse between RT and IQ measurement, which was indicative of an IQ decrease even after 9 years
16 children with brain tumor, treated with CRT or local RT, were compared with 15 nonirradiated children with ALL (16)	On the Wechsler Intelligence Scale for Children—Revised Full Scale, the mean standard scores were significantly decreased in the brain tumor group
A review of studies of children treated with CRT (17)	CRT-treated children manifest significant drops in IQ scores especially when they are in the younger age groups
31 patients (with medulloblastoma or ependymoma) treated with standard dose or reduced dose of RT (18)	There was a 2- to 4-point decline per year in IQ. In the younger patients IQ declined quickly in the first few years after treatment, and then more gradually
138 survivors (73 with ALL and 65 with solid tumors), diagnosed before the age of 15 years, with therapy	IQ scores of solid tumor survivors were higher than in leukemia survivors who had CRT at dosages ≥ 24 Gy

Table 26.1**(Continued)**

Descriptive Characteristics of Study	Findings Concerning IQ
duration over 2 years, had been evaluated at least 10 years after diagnosis (19)	(108 vs. 98; $p = 0.03$), and resembled those of leukemia survivors with CRT at lower dosages (102) or who got no CRT (109). Normal IQ correlated positively with age at diagnosis and negatively with CRT. Survivors of ALL who relapsed scored 14 points less than those who had not relapsed. Decline in IQ following RT persists over time
Comparing the IQ of children with pediatric cancer diagnoses who got different doses of CRT (20,21)	There was less decline in those who got reduced-dose CRT (23.4 Gy vs. 36 Gy) and were older (above 8.8 years) at the time of treatment
Study of the effects of low doses of CRT in 22 children with varied diagnoses undergoing BMT. Fifteen got CRT (range 350–1200 cGy), and seven did not. IQ was tested before BMT and 1 year later in children 2.5 to 6 years with Stanford-Binet IV and those 6 years or older the Wechsler Intelligence Scale for Children–Revised (22)	There were no decrements in IQ in the children who got CRT, regardless of the dose and the child's age. There were also no significant differences compared to baseline in a subgroup who were followed up to 3 years. But there was great variability. There were decrements of 10 points or more in 7 children after 1 year

healthy controls. Further, differences in working memory mediated the observed differences in IQ between the CRT group and controls. However, processing speed did not fully account for the working memory deficit in the CRT group. The data suggest that deficits in processing speed and working memory following CRT may underlie the frequently reported declines in IQ.

A review by Bhatia and Landler (17) showed that affected children are particularly prone to problems with receptive and expressive language, attention span, and visual and perceptual motor skills. They most often experience academic difficulties in the areas of reading, language, and mathematics. In another study a follow-up of 59.6 months after termination of therapy showed a modest but significant decline in reading scores, while mathematics and spelling performance remained stable (26). Mulhern et al. (27) showed that the decline in the reading, decoding, and spelling skills is independent of the risk level of the disease. The deficits in the cognitive skills required in academic setups account for the frequently reported school problems and poor academic performance of children who have undergone CRT (28).

Accordingly, many long-term survivors of medulloblastoma treated with RT had significant school problems (72%), impairments of attention and processing speed (79%), learning and memory difficulties (88%), language disabilities (56%), and deficits in visual perception (50%), or executive functions (64%) (29). Similarly, in 31 patients (with medulloblastoma or ependymoma) treated with standard dose or reduced dose of RT, there were significant declines in visual-motor integration, visual memory, verbal fluency, and executive functioning. But there was no evidence for decline in verbal memory and receptive vocabulary (18,30).

An earlier study with pediatric cancer survivors from a large variety of diagnostic groups showed that CRT was associated with deficits in several, primarily nondominant hemispheric neuropsychological functions, most likely to be reflected in nonverbal intelligence, perceptual abilities, and distractibility (31). Further evidence about the effects

of CRT on cognition comes from a study which showed that academic achievement, verbal knowledge and reasoning, and perceptual-motor abilities were significantly lower among CRT-treated groups of patients and that there were significant negative associations between CRT dose estimates for cortical regions and perceptual-motor abilities (7). Again, in a group of 138 survivors (73 with acute leukemia and 65 with solid tumors), who had been diagnosed before the age of 15 years, had been treated over 2 years, and were evaluated at least 10 years after diagnosis, assessment of cognitive functioning showed that the most affected cognitive areas were comprehension, arithmetic ability, attention, visual and verbal memory, causative reasoning, and visual-motor coordination. No relationship was found between sensory sequelae (that were mostly mild) and cognitive capacities (19).

In a group of pediatric patients with malignant posterior fossa tumors, some of whom were treated with reduced-dose CRT and some with standard dose, tested 1 year after treatment and at several points later, no significant differences in cognitive performance were found between the groups. Their performance declined for spelling, mathematics, and reading according to achievement tests and ratings by parents and teachers. However, data analyses revealed that there was no loss of skills but a reduced rate of skill acquisition (28). Further, comparing 16 children with brain tumor, who had been treated with CRT or local RT, with a group of children diagnosed with ALL who did not get RT, showed that the former group was assessed by mothers and teachers as functioning with a significantly decreased tempo on a visual analog scale. Low speed and hypoactivity seemed to limit the majority of these children in school and daily life activities (16).

A special emphasis has been placed on two distinct cognitive functions: memory and attention, both because deficits in these functions showed up in a great number of studies and because they may be responsible for further cognitive difficulties and hence also for lower academic achievements in

general. Memory deficits following CRT are a recurrent finding. Thus, Massimo et al. (32) reported a study with 60 children diagnosed with ALL, treated between 1974 and 1978 with or without CRT, who were in complete remission. A psychological investigation performed at least 2 years after terminating therapy showed one clear finding: All those who underwent CRT had memory impairment. Another study showed that children treated with CRT for medulloblastoma had verbal memory deficits in retrieval and recognition verbal memory following RT (33,34).

Concerning attention, deficits following RT were reported by Mulhern et al. (20).

Kiehna et al. (35) evaluated 120 patients with primary brain tumors, aged 2–24.4 years (median, 9.2 years), before CRT, weekly during CRT, and serially up to 60 months after the start of CRT. Evaluations of attention were done by means of the computerized Conners' Continuous Performance Test, which provides scores for errors of omission (inattentiveness), errors of commission (impulsivity), reaction time, and an overall index of performance. Before CRT, patients had a mild inattentiveness. During CRT, impulsivity decreased significantly. After CRT, inattentiveness increased significantly, and global attention disorders were associated with different types of brain tumors. A decline in impulsivity and relative stability of the other evaluated scores over the course of CRT show the absence of early radiation-related cognitive sequelae.

A further study on attention was performed on 22 children (mean age at diagnosis 7.62 years) about 2.5 years after treatment termination, in order to examine the relationship between auditory attention span, time elapsed since the initiation of RT ($M = 2.43$ years) and adaptive functioning, assessed by the Vineland Adaptive Behavior Scales. Attention span was found to mediate the relationship between time since the initiation of RT and daily living skills. These findings were specific to attention and reflected neither a generalized neuropsychological decline nor the effect of increasing time since RT. Thus, they suggest that time since RT may directly decrease attention and that poor attention in turn may be associated with lower adaptive functioning on daily life tasks (36).

In sum, CRT brings about decline in a whole range of specific cognitive functions, both verbal and nonverbal, especially memory, attention, and processing speed, as well as global intellectual functioning as revealed in IQ scores, school performance, and academic achievements. The impairment shows up within 1–2 years after treatment termination and is progressive. It is likely that impairment in some functions affects further functions. Factors responsible for increased severity of impairments are younger age when RT is applied (especially lower than 5 years) and high-dose RT (at least standard dose).

Further Factors Involved in Cognitive Functioning

Several studies found further variables affecting the cognitive impairment. Possible predictors of lower cognitive functioning were investigated in a study of children with ALL, 5–14 years old, in continuous complete remission and without evidence of current or past CNS disease, evaluated 9–11 months after diagnosis. IQ was found to be unrelated to history of somnolence syndrome. IQ and achievement were unrelated to age at irradiation, irradiation-examination interval, and radiation dosages. The strongest predictor of IQ and achievement was parental social class (37). Again, in ALL survivors with

complete remission for 3.5 years, parental education levels accounted for more of the neuropsychologic variability than other factors, such as age at diagnosis, type of therapy, or sex of child (38). In a further group, in addition to statistically significant evidence for cognitive impairment, absence from school during treatment and age at diagnosis were more predictive of reading and spelling academic achievement than having received CRT (31).

A recommendation voiced by many researchers and practitioners in this field is that patients at risk for cognitive deficits should undergo a neuropsychological evaluation at baseline, at transition points in academic education, and/or annually in order to assess their difficulties and their vocational or educational progress (17). In addition, it is recommended to develop and apply targeted cognitive rehabilitation and training programs in order to remedy the specific cognitive deficits or even forestall them before the damage spreads. Some initial attempts have already been reported (39,40).

Several kinds of factors seem to be involved in regard to the cognitive impairment noted often in children who underwent RT. The major ones seem to be the initial diagnosis, the dosage and extent of RT, the age of the child when RT was applied, and the kind of environment in which the child functions. It appears that up to now not enough research efforts have been invested in clarifying the relative contribution of each of these factors to the overall effect and to the possibility of compensating for a negative impact of one factor by enhancing the positive impact of another factor. The child's environment is the main factor whose positive impact can be enhanced more readily than that of the other factors. Surprisingly, this is the factor that has been studied to a lesser extent than the others. It includes components, such as psychosocial support by parents and the health professionals, belief in the child's ability to overcome difficulties, enhancement of achievement motivation, and a host of other positive contributions to the child's sense of well-being on all levels. The chances for success of well-designed interventions are high because cognitive abilities or deficits are only one of the factors that determine the overall level of functioning at school or at work.

Social and Behavioral Effects of RT

In view of the difficulties and crises that children undergo in the course of the disease, the treatments, and their sequelae, it can be expected that they may suffer from difficulties in behavioral adjustment. A body of studies shows that children who had undergone RT tend to have problems in social adjustment and in mood, especially depression (Table 26.2). The problems persist beyond the termination of treatment. It has also been noted that the child's behavioral adjustment depends in addition on stress in the family and coping of the parents (48).

It seems that many of the pediatric cancer survivors are at risk for having problems in social adjustment and interpersonal relations in general. Given the stability of poor peer relationships and known linkages between peer problems and subsequent academic and psychiatric difficulties, it is evident that more attention should be devoted to the social adjustment of the pediatric cancer patients so as to diagnose as early as possible likely problems and launch intervention projects for their minimization.

Table 26.2**Behavioral and Social Effects of RT**

Descriptive Characteristics of Study	Findings Concerning Social and Behavioral Effects
Early studies with heterogeneous samples of pediatric cancer patients who underwent RT (41–45)	Tendencies for problems concerning mood and withdrawal from others were observed
Effects of scores on the index of CNS treatment intensity on social behavior in children with varied diagnoses who underwent RT (46)	Higher treatment intensity was associated with poorer peer acceptance, fewer friendships, greater social sensitivity— isolation, and diminished leadership—popularity based on peer report. Effects were stronger for boys and younger children (<10 years old) at diagnosis. Treatment intensity was related only to teacher perceptions of aggressive– disruptive behavior but was unrelated to social self-perceptions
Comparison of survivors of brain tumors with those who have been treated with RT, in the age range of 18 to 30 years (47)	The group who got RT reported the achievement of significantly fewer milestones in the psychosexual and social domains and scored lower on quality of life than the other survivors
Long-term survivors of medulloblastoma treated with RT were compared with healthy controls (29)	The patients rated social functioning as the most affected dimension of quality of life. Parents' ratings of the patients' social behavior were lower than those by the patients. Survivors over 18 years of age ($n = 12$) reported difficulties in maintaining relationships with a boyfriend or girlfriend
138 survivors (73 diagnosed with acute leukemia, 65 with solid tumors—nephroblastoma or sympathetic nervous system tumor), all diagnosed before the age of 15 years, with duration of therapy over 2 years, and the time elapsed since diagnosis at least 10 years (19)	Mood disorders were evaluated. In the survivors group there were higher scores of depression but not of anxiety
16 children diagnosed with brain tumor, who had been treated with CRT or local RT, were compared in adjustment with a group of 15 nonirradiated children diagnosed with ALL (16)	On the Achenbach checklists filled by mothers (CBCL) and teachers (Teacher's Report Form), the children who got RT were rated lower on overall adjustment. Many of the difficulties of these children in daily life activities were related to their tendencies for slowness (low speed) and overall hypoactivity
Social functioning of children with medulloblastoma treated with low-dose RT or standard dose (21)	Children treated with low-dose RT functioned socially better after RT than those who got standard dose RT
Children with malignant posterior fossa tumors, some of whom were treated with reduced-dose CRT and some with standard dose. The performance of children was assessed 1 year after treatment and at several time points later (28)	According to the parents' ratings, the children had medium problems in social withdrawal, depression, and anxiety, and fewer problems in aggressiveness and oppositional behavior. With increasing time since end of treatment, there was an increase in social problems. According to the teachers' ratings, social withdrawal and social problems increased with time, reaching after 12 years the clinically significant range
A sample of 49 survivors (out of 60 children) with ALL, some of whom have been treated 20 years earlier (in 1974–1978) with CRT whereas others have not. Only the parents were interviewed (32)	All adults achieved good physical, cognitive, emotional, and behavioral development and adjustment. The survivors with RT and those without did not differ significantly in education, occupational level, marriage, and fertility from the corresponding age–class national figures

RT, radiotherapy; CNS, central nervous system; CRT, cranial radiotherapy; ALL, acute lymphoblastic leukemia; CBCL, Child Behavior Checklist.

Children's Distress in the Course of RT

There are several obvious reasons why it may be expected that children undergoing RT are likely to be distressed and anxious. First, the treatment is given under special unfamiliar conditions to the child, which differ from those of chemotherapy; second, the child stays alone during the treatment; and third, the child is required not to move during the treatment. Anesthesia that is often used for the alleviation of RT-related

anxiety may have various shortcomings, such as increased risks for medical complications, and difficulties in eating and sleeping (49) (Fig. 26.1).

One study focused on the distress that the children experience prior to their first RT experience which was to be a simulation session in which no RT was administered but the procedural demands and overall experience were identical to actual RT (50). The participants were 80 pediatric cancer children



Figure 26.1 Positioning and immobilization device for a patient with brain tumor.

with various diagnoses, 2–7 years old, with no or mild degrees of functional impairment, about to receive RT in an outpatient clinic. After explaining to them the study, and before the simulation was introduced, information about distress in the children was obtained directly from the children through a behavioral observational checklist and by checking their heart rate, and indirectly from the parents by means of questionnaires that they were asked to fill (State-Trait Anxiety Inventory and a questionnaire about RT). The findings showed that 65% of children manifested at least some degree of anticipatory behavioral distress, while 16% manifested high distress both in their behavior and heart rate. The major factors that contributed to the child's high level of distress were younger age of the child and higher expectations of the parents that the child would experience distress, which in turn was at least partly a function of the child's young age. Notably, the parents' anxiety levels were unrelated to their expectations of the child's distress reactions.

A further study (51) with a similar sample of 79 children applied as a measure of distress prior to the simulation session also anesthesia, in addition to the above-described measures of Observation Scale of Behavioral Distress and heart rate. At simulation, 62% of patients required pharmacological intervention for completing the procedure. Further, younger age and higher behavioral distress predicted the use of anesthesia for the simulation. Higher baseline heart rate predicted lower behavioral distress. Notably, a prone position (as opposed to a sitting position) during simulation was related to increases in behavioral distress and higher heart rate.

In sum, the reported studies provide clear evidence that pediatric cancer patients are prone to experience distress prior to the simulation session, in the simulation session, and in the course of administration of RT proper. These findings confirm a host of informal observations of health professionals that children experience distress in the course of RT.

Intervention Procedures for Reducing Distress during RT

Various psychosocial procedures have been utilized in the hope of minimizing the use of anesthesia or sedation for the administration of RT in children.

Bucholtz (52) emphasized the need for developing skills in nurses designed to provide comfort to the children and their parents in the RT setup. An interesting behavioral procedure designed to teach cooperation and motion control to preschoolers and older children with special needs was described by Slifer, Bucholtz, and Cataldo (53). Out of 10 children (3–7 years old), 8 benefited from the behavioral program and were not in need for sedation or anesthesia for completing RT (Fig. 26.2).

Another study (54) focused on children 2–5 years old that are commonly assumed to be in need of sedation for RT. They presented outcome data on 63 children in this age range indicating that sedation can be minimized in this age group by means of an effective play preparation program. Over a 5-year period (1994–1999) in a pediatric oncology center, of 1030 treatment days, only 111 days required sedation (10.8%), for the whole age range. No general anesthetics were given. Only 6 patients were sedated for the whole of their treatment (9.5%), with 52 patients requiring no sedation at all (82.5%).

There have also been attempts to develop full-fledged programs for alleviating the children's stress and anxiety. Thus, one program was designed to provide the children and their families with coping strategies that would minimize the necessity for anesthesia (55). The program is based on preparing the children and the parents for the procedure, while attending flexibly to the needs of each particular child. After applying the program with 55 children, the reports showed increases in satisfaction with care among the child, family, and staff involved.

Klosky et al. (56) developed an interactive intervention program for reducing RT distress among pediatric cancer patients in a simulation session. The effects were measured in the children by occurrence of sedation, observed behavioral distress, and heart rate, and in the parents by anxiety questionnaires. Seventy-nine children receiving RT simulation were assigned randomly to an interactive intervention group or a modified control group. The intervention included a 7-minute filmed modeling of the procedure, exposure to an interactive Barney character, and passive auditory distraction by use of a noninteractive Barney character (so as to emphasize the need for immobility in the simulation room). In the control group, the children were exposed to a cartoon video, a noninteracting children's control character and stories on a cassette in the simulation room. The results showed that children in the intervention group had lower heart rate than the control participants, but there were no differences between the groups in sedation or distress manifested in behavior.

Another intervention that has potential for reducing RT-related distress in pediatric cancer patients is based on a psychoeducational approach (57). The study focused on 223 consecutive pediatric cancer patients receiving 4141 RT fractions during 244 RT courses between February 1989 and January 2006. The experimental group included 90 RT courses corresponding with 1561 RT fractions; the control group included 154 RT courses corresponding with 2580 RT

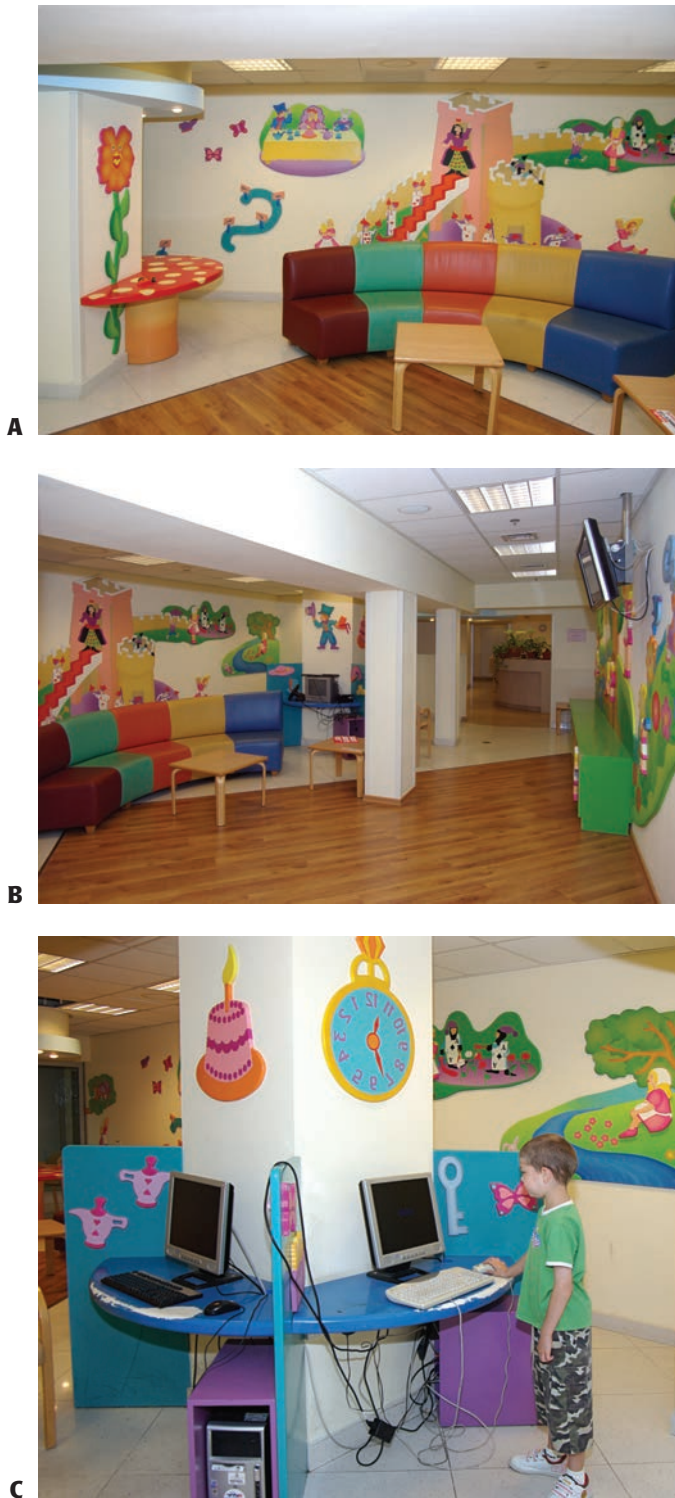


Figure 26.2 A–C: Pediatric radiation oncology waiting room, Sheba Medical Center, Tel Aviv, Israel.

fractions. The intervention included talks with the patient and the parents about practical aspects of the upcoming RT and an age-appropriate explanation of the RT treatment and procedure, implemented by picture books, playful inclusion of toys, and a reward system using beads as tokens for every completed RT session. Attendance by one of two specially trained nurses at least for preparing the CT, RT simulation,

and the first RT session and as weekly visits during the RT itself was accomplished, so that each patient was met on the average five times for the duration of 5 to 7.5 hours. The groups did not differ in age at RT, gender, diagnosis, localization of RT, and positioning during RT. The major result was that following the intervention there was a reduction in the need for using anesthesia: in the experimental group, 9% of the children needed anesthesia as compared to 21% in the control group. Further, the median age of cooperating patients without anesthesia decreased from 3.2 to 2.7 years.

In sum, the psychosocial intervention programs show the utility of preparations of this kind for reducing the distress and anxiety of the children, increasing their cooperation with the procedure and minimizing the need for applying anesthesia. LeBaron and Zeltzer (58,59) have pioneered the use of guided imagery and hypnotherapy for reducing pain and anxiety in children with cancer. Other means for overcoming the anxiety of children evoked by RT may be based on art therapy, play therapy, music therapy, role playing, drama, and production of stories. These and other psychological procedures that could be applied for reducing the distress of undergoing RT are described by Kreitler, Oppenheim, and Segev-Shoham (60). Developing, applying, and evaluating such programs would render it possible to select in each case the best program inline with the needs of the child, the utility of the intervention, and the resources of the clinic or hospital.

The Views of the Children and the Parents about RT

In order to get a more comprehensive view of the problems and difficulties involved in undergoing RT from the perspective of the patients, we conducted a preliminary survey with 20 children and 20 parents (not of the interviewed children) in two major medical centers in Israel. The participants were selected randomly as a convenience sample. The children were 7–17 years old, of varied diagnoses, all of whom were either in the last phase of RT or terminated the treatment 0–10 days previously. It was expected that the survey conducted with the actual participants in the RT procedures would provide information about problem areas that have not been discerned in the research focused on psychosocial aspects of RT up to now. The survey was based on conducting individual guided interviews in line with an ordered set of questions. The questions were the same for parents and children, except for necessary but minor differences in wording. The major questions were whether the child has undergone RT, for how long and to which part of the body; awareness of immediate or short-term side effects of RT; awareness of long-term effects of RT; any difficulties concerning RT that the children had; any particular behaviors of the children in regard to parents and friends or at school noted during RT; the difficulties the children had experienced during RT; comparing the difficulty of RT to chemotherapy and to what has been expected prior to RT; and suggestions for rendering RT easier.

Results Based on Interviewing Parents

The interviews of the parents indicated that 55% of the children got RT to the head, 15% to neck, 5% to the chest, 15% to the abdomen, and 10% to the limbs. The child got RT 7–35 times. Eighty percent claimed that RT had immediate or short-term effects, which were mainly the following: nausea, diarrhea, reddening of the skin in the treatment area, loss of hair in the treatment area, tiredness, somnolence, headaches, and

impaired gustatory and olfactory sensations. A higher number (85%) claimed they knew of possible long-term effects, which were mainly cognitive impairment (40%), fertility difficulties (30%), problems in regard to growing and overall development (40%), and the risk of a secondary cancer (20%).

Concerning difficulties of the treatment, the parents mentioned the emotional difficulty (50%) and the technical difficulty they had to get to the hospital every day for RT (60%). Concerning the difficulties of the children, the parents mentioned in particular the difficulty of waiting for the treatment in a waiting room shared by children and adults, the unpleasantness of getting the treatment in the radiation unit that is not the regular ward with which the children are familiar, the fear evoked by the noise of the machine, staying alone in the treatment room, coming to the hospital every day, and tiredness. As compared to chemotherapy, all parents (100%) noted that RT was easier, but as compared to the expectations beforehand, 20% claimed that RT was more difficult than they had expected, 45% claimed it was easier, and 35% claimed it was as they had expected beforehand.

The major suggestions of the parents for rendering RT easier referred to the following three issues: information, site of RT, and support treatment. Concerning information, most of the parents (85%) emphasized the desirability of improving the provision of information about the treatment and its effects beforehand as well as in the course of the RT itself to the parents and to the children, using verbal materials implemented by films, videos, and modeling, especially for the children, in order to make it easier to understand the material and recall it. Concerning the site of RT, the parents emphasized the desirability of using waiting rooms and treatment rooms designed specifically for the use of children alone rather than for the use of both adults and children, and prepare waiting rooms with toys, pictures, music, and other objects for distracting and relaxing the children prior to the treatment. Concerning support, most of the parents emphasized the necessity of providing continuous psychosocial support to the parents (85%) and to the child (75%) prior to the treatment and in the course of it, at least to the termination of RT.

Results Based on Interviewing the Children

The interviewed children got RT to varied organs or body parts, according to their self-reports: the head (35%), face (10%), neck (10%), abdomen (15%), chest (10%), back (5%), and limbs (15%). All children said that they got RT at least several times. Almost all children (95%) distinguished between chemotherapy and RT, although some claimed that RT was a phase of chemotherapy. Concerning side effects, the majority (70%) listed several short-term side effects, mainly feeling sick, losing hair, feeling tired, difficulty to concentrate, pain, nausea, no appetite, feeling sad, and feeling lonely. A higher percentage (90%) said that they knew about long-term effects. The effects they mentioned were fertility problems (90%); body image deformities (90%; e.g., irregularities in the skin, brown dirty-looking skin, too short neck, remaining small and not growing up tall as other children, shorter limb, baldness for ever); various physical disorders (75%; malignancies, heart problems, endocrine disorders, remaining in general "weak" or vulnerable in regard to diseases); and various social and interpersonal issues (35%; e.g., being rejected by other kids, not finding friends or partners because of physical deformities or aesthetic appearance).

Concerning difficulties of the treatment, children mentioned the difficulty of having to come everyday to the hospital for getting RT (80%) and the unpleasantness (i.e., anxiety, fear, tension, sense of being abandoned) associated with being alone in the RT room (85%). Especially frequent were descriptions of the experiences the children had in the RT room. For example, one 8-year-old child said, "I feel as if all the world recedes far away and gets smaller and smaller, and I am the last dot in that increasing emptiness." Another 12-year-old said, "When I get into the room I am afraid that when I get out there will be no one to meet me and I will be alone outside too." Only a few children (30%) referred to the difficulty of the technical setup but mentioned in this context only the unpleasantness of getting the treatment in an unfamiliar ward, rather in the ward in which they had undergone chemotherapy and other treatments. No one mentioned anything concerning the fact that in the radiation unit children were treated in the same location as adults. When asked to compare RT with chemotherapy, 60% said RT was easier, whereas 40% said they are equally difficult although for different reasons. As compared to the expectations they had beforehand, 60% claimed that RT was more difficult than they had expected, 20% claimed it was easier, and 20% claimed it was as they had expected beforehand. Notably, those who said that RT was more difficult than they had expected complained about the misleading information they had received concerning RT. As one child said, "I did not think about radiation and I even waited for it because everyone in the ward said that it is easy, that I go into a room and one hardly feels it; but then I saw that I had to be alone in the room with the noisy machine and I had to stay paralyzed ... it is horrible" (Fig. 26.3).

The children were also asked about their suggestions for rendering the RT easier for children. Most of the children provided suggestions. The major suggestions referred to decreasing the feeling of loneliness in the RT room, for example, by enabling the child to hear the voice of the parents or nurse outside, by listening to music, or by seeing projected pictures. Other suggestions referred to being able to discuss the experience with someone from the staff or the family everyday and getting the treatment in some place close to home so as to be able to avoid the traveling to the hospital everyday.



Figure 26.3 A 7-year-old with leukemia receiving cranial irradiation; immobilization thermoplastic mask and wrapped to avoid falling.

Some Comments Concerning the Interviews

Both sets of interviews indicate that the parents and the children identify RT as a distinct phase of the treatment the child gets and are, on the whole, aware of the common short-term and long-term effects of RT. The emphasis of the parents on the need for more information coincides with the results of a recent study that shows that although the parents feel knowledgeable about neurocognitive late effects of RT, they continue to have a need for further information, and those who reported high emotional distress wanted the information earlier than the others (61).

The interviews with the children highlighted both the emotional distress of the children in the RT room and their suffering through the procedure. Notably, many children do not share the commonly expressed attitude toward RT as easier than chemotherapy. In addition, children brought to the fore a specific domain of long-term side effects that has not received sufficient attention in the psychosocial studies up to now. These are the effects of RT on the body image. Children noted specifically changes in limbs, skin, stature, body symmetry, scalp, and hair, that may affect the functioning of their body and change their physical appearance. The functional and aesthetic problems associated with the damaged body image may affect the children's functioning also in other domains. The children themselves mentioned that an impaired physical appearance may affect the attitude of peers to them in the present and perhaps also in the future and thus alienate them at school and affect negatively their academic achievements. The distress of the children that may be caused by the difficulties of coping with physical handicaps and impaired physical appearance deserve the awareness and attention of health professionals no less than the distress of children in the course of the RT itself.

SUMMARY

The chapter deals with psychosocial effects of radiotherapy in pediatric cancer patients. The presented materials are based on empirical published studies referring specifically to RT, amplified by a survey conducted by the authors with parents and children undergoing RT. The major reviewed domains include cognitive effects, behavioral and social effects, and distress in the course of RT. The major cognitive effects of CRT and RT are declines in general intelligence and specific

deficits in nonverbal and verbal cognitive functions, mainly memory and attention, that increase with time since RT and are especially notable in children who have received RT at a younger age. Yet, there are indications that overall academic performance may be a function of factors additional to the cognitive deficits and sometimes overriding the deficits. The major social and behavioral effects concern interpersonal relations and possible difficulties in social adjustment. Children are conscious of short-term and long-term effects of RT, and emphasize in particular body image changes. Various programs for alleviating the distress of children during the administration of RT are underway. Yet, it appears that children still suffer unduly in the course of RT, mainly because of the need to be alone and without moving in the treatment room. Psychosocial interventions designed to alleviate distress in the course of RT and also after termination of treatment are highly recommended for improving the children's quality of life during the course of treatment and in later years.

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