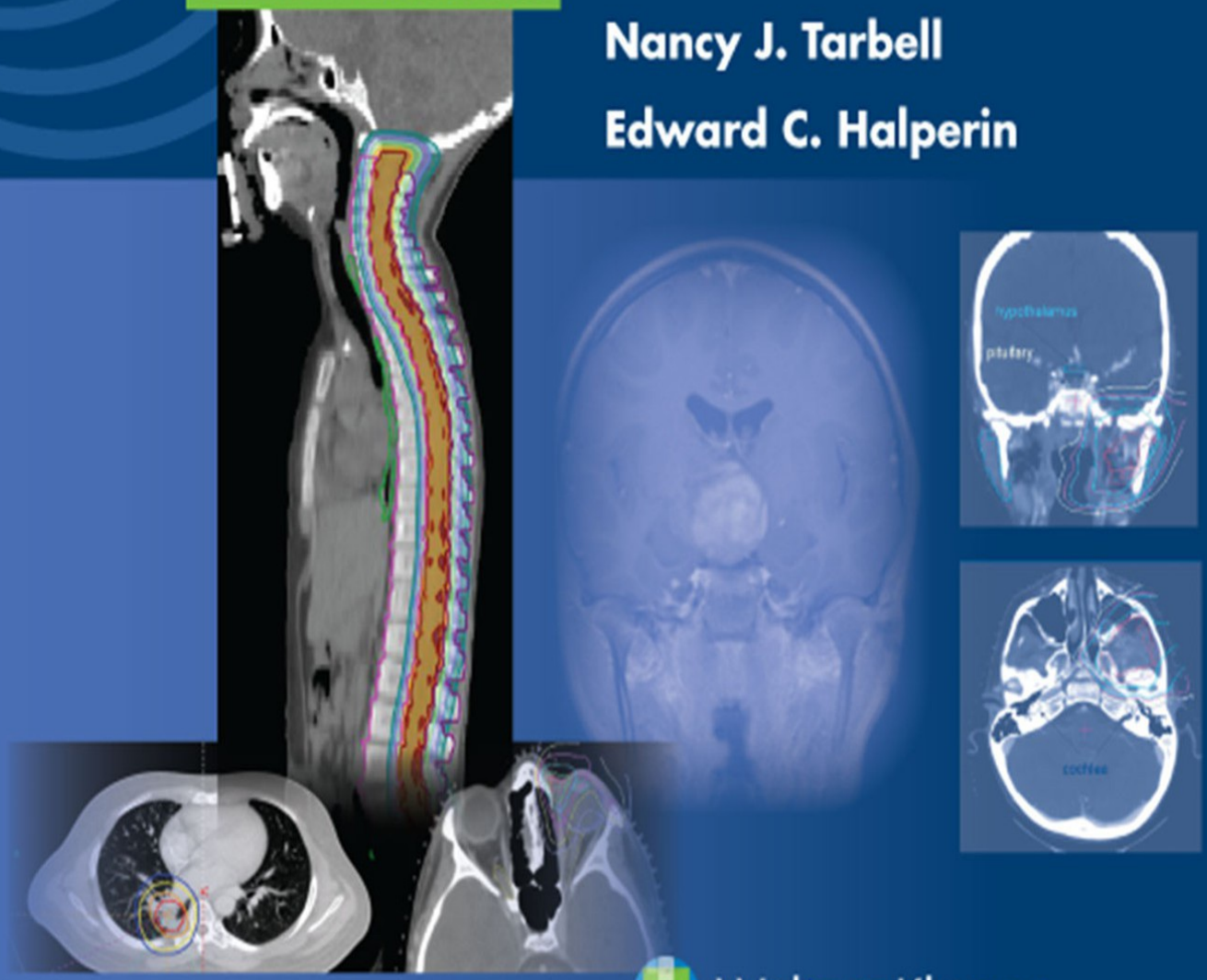
PEDIATRIC RADIATION ONCOLOGY

Sixth Edition

Louis S. Constine
Nancy J. Tarbell
Edward C. Halperin



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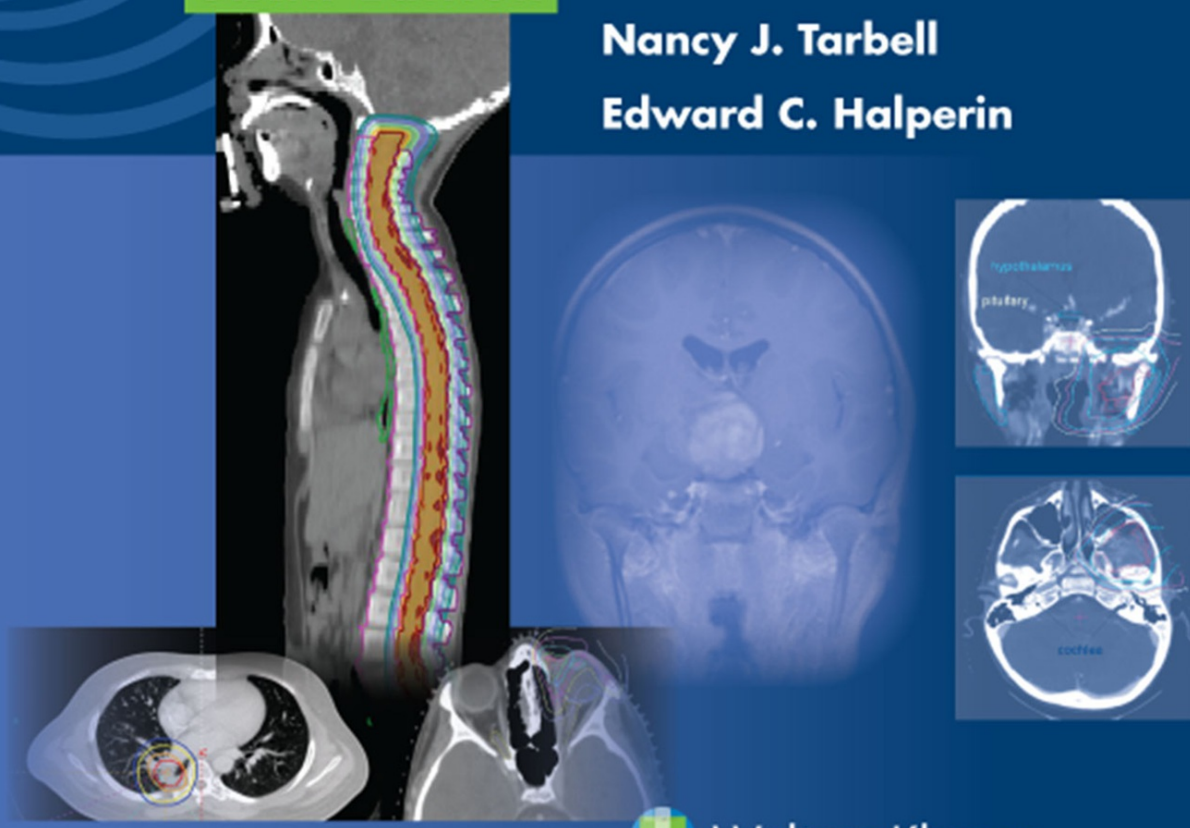

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Pediatric Radiation Oncology

SIXTH EDITION

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Dedication

This book is dedicated both to our own children and to all those children diagnosed with cancer. These children have taught us about life, bravery, pain, openness, innocence, resilience, as well as clinical pediatric radiation oncology. To them we are forever grateful. Through our patients we have learned to more profoundly appreciate our own families. We pause to recognize those children who succumbed to cancer, and to feel gratitude for those fortunate to have survived while retaining a childlike enthusiasm for living despite the burden of malignancy. We hope that the sixth edition of *Pediatric Radiation Oncology* will serve as some small reciprocation for what our patients have given to us.

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Preface

"Every child begins the world again."

Henry David Thoreau

Evil spirits, the disharmony of celestial bodies, and the wrath of the gods were all invoked as etiologies for what we today recognize as *cancinos* or *carcinoma* (coined by Hippocrates). Ultimately, cancer was understood to be a myriad of diseases, but those afflicted were shut away to die if surgical approaches (and those for children were pioneered in the 19th century) failed. In the art of antiquity, children were often depicted as small versions of adults; similarly our treatment approaches were adapted from those suitable for adults. The vulnerability of children to the effects of our therapies required visibility before substantial progress could be made in curing without unacceptable harm. As radiation oncologists, we are fortunate to spend our lives striving to help patients with cancer, curing them when possible, and improving their quality of life when cure is beyond reach.

Marie Curie said: *"Nothing in life is to be feared. It is only to be understood."* She could well have been alluding to the historic fears engendered by the mysterious force that was radiation, but this axiom surely embodies the progress we have made with these diseases. It was the compassion and passionate determination to cure children with cancer that permitted the metamorphosis from hopelessness to optimism in its treatment, and this required the unrelenting efforts of our professional predecessors.

In 1986, one of us (Edward C. Halperin) conceived the idea of a new textbook of pediatric radiation oncology. While several general textbooks in radiation oncology existed, none were specifically devoted to the use of radiation therapy in the treatment of childhood cancer. When Dr. Halperin first proposed such a book, most publishing companies rejected it 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 had the foresight to agree. Dr. Halperin, at that time a 32-year-old assistant professor, invited and persuaded his colleague Larry E. Kun, at St. Jude Children's Research Hospital in Memphis, Tennessee, to join him in the project. Drs. Kun and Halperin then drew up the outline for the proposed book and completed the team with Drs. Nancy J. Tarbell of Boston and Louis S. Constine of Rochester.

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. Our goal for *Pediatric Radiation Oncology* was considerably different because we wanted it to be manageable and engaging for young physicians who had little time for exhaustive investigation in order to understand and propose treatment for a new patient. We sought to write chapters that could be read in one sitting. We envisioned a resident-in-training, the night before morning teaching conference, needing a reliable book to turn to and read a chapter that would render him or her able to reasonably defend a rational treatment approach for their patient. Furthermore, when we first envisioned this book, it was well before the age of computer-augmented searches for journal articles or expert (and trusted) summary information. We intended to synthesize data on pathogenesis, pathology, diagnostic workup, staging, treatment approaches (particularly radiation therapy—indications, doses, volumes, treatment planning), and toxic outcomes. We also intended to provide rational judgment for decision making when data was lacking.

It is hard to believe that three decades have passed since Dr. Halperin's concept both germinated and blossomed into what will now be the sixth edition. Our founding principles remain steadfast. We have tried to compose 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 (including second malignant neoplasms) was also in its infancy.

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 (gracefully and wisely, we hope) through these 30 years together, and through these editions. The reader will see evidence of the original authors having passed the torch to the new generation of pediatric radiation oncologists in the writing of these chapters. Passing the torch is an energy-requiring process since many radiation oncologists do not become experts in pediatrics since the patient numbers are small, obtaining expertise requires

a huge investment of time, and there is little personal financial reward in return for the investment.

The response to this book has been gratifying. We never imagined in 1986 that there would be six 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 six editions of this book have contributed to an improved understanding of the benefits and risks of radiotherapy for children. We remain resolute 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. We hope that this book helps to demystify pediatric cancer and its treatment.

Louis S. Constine
Nancy J. Tarbell
Edward C. Halperin
January 2, 2016

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The preparation and collation of the sixth edition of this book is grounded in the multiple previous editions that resulted from the dedication of the late Ruth Aultman in North Carolina and Kentucky, Rebecca Bunker in Memphis, Laura Finger in Rochester, Erin Cromack and Heidi Fliegauf in Boston, and Vera Rosario and Vilma Bordonaro in Valhalla. Emilie Moyer and the staff of Lippincott Williams & Wilkins were, at all times, courteous and beyond helpful. The conscientiousness and skill of this staff has again given life to our book.

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.

CHAPTER 1

The Cancer Problem in Children

Edward C. Halperin

Page 1In 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 21st 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 causes of death in infants are congenital anomalies, disorders related to short gestation and low birth weight, and sudden infant death syndrome (3). The leading cause of death in children older than 1 year is murder by a close relative. Cancer in children, however, has become a significant problem compared with other causes of childhood mortality (4) (Table 1.1). In the United States, 1 in 285 children will be diagnosed with cancer before age 20 (5). In 2014, there were 10,450 new cases of cancer among children of age 0–14 years and 5330 new cases among children of age 15–19 years in the United States (5,6,7). Cancer is

TABLE 1.1

The Five Leading Causes of Death in the United States in 2011 for 1- to 19-Year-Olds

Cause of Death	Number of Deaths
Accidents	7310
Homicide	2375
Suicide	2089
Cancer	1852
Congenital anomalies	1058

Data from Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015;65:5–29.

Table 1.1 The Five Leading Causes of Death in the United States in 2011 for 1- to 19-Year-Olds

now the leading natural cause of death among children between the ages of 1 and 14 years in the United States (3). In late adolescence, homicide surpasses cancer as a cause of death.

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 (6,8). 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 20th 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.

Figure: The Five Leading Causes of Death in the United States in 2011 for 1- to 19-Year-Olds

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RELATIVE FREQUENCY OF THE VARIOUS TYPES OF CHILDHOOD CANCER

Adults generally get cancer of places where their bodies interact with the environment; for the most part, children do not. Whereas adults often get cancer as a result of tobacco consumption, dietary habits, and sun exposure of the epithelial surfaces of the body, children get cancer as a result of intrinsically occurring mutations provoking oncogene and tumor suppressor gene activity or inactivity (Table 1.2).

TABLE 1.2

The Five Most Common Forms of Cancer in Adults in the United States Compared with the Five Most Common Forms of Cancer in Children

Adults	Children
1. Breast	1. Leukemia
2. Lung	2. Central nervous system
3. Prostate	3. Lymphoma
4. Colon	4. Malignant epithelial neoplasms such as adrenocortical carcinoma, thyroid carcinoma, nasopharyngeal carcinoma, and melanoma
5. Bladder	5. Soft tissue and other extraosseous sarcoma

Note: The childhood cancers are organized by the International Classification of Childhood Cancer Group (excluding basal and squamous cell skin cancer and in situ carcinoma except in urinary bladder).
Data from SEER Cancer Statistics Review 1975–2010, Table 29.1, National Cancer Institute.

Table 1.2 The Five Most Common Forms of Cancer in Adults in the United States Compared with the Five Most Common Forms of Cancer in Children

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 nationality. 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 (7,9) (Table 1.3). 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, whereas the common epithelial tumors of adults are rare in children. Cancers that arise from embryonic cells or in developing tissues and organ systems are characteristic of children and are rarely seen in adults. Examples of embryonal cancers are neuroblastoma, Wilms tumor or

nephroblastoma, medulloblastoma (brain), hepatoblastoma (liver), retinoblastoma (eye), and rhabdomyosarcoma (muscle) (5,10).

Page 2Of 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) are teratomas, retinoblastoma, rhabdomyosarcoma, and neuroblastoma (11,12). In 15-to-19-year-olds, the most common forms of cancer are malignancies of the brain and central nervous system (20%), followed by leukemia (13%), Hodgkin lymphoma (13%), thyroid carcinoma (10%), gonadal germ cell tumors (9%), and melanoma (5%) (6).

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 (5,6,10,13,14) (Table 1.4). In 0-to-14-year-olds, U.S. cancer incidence and mortality rates are lower in girls, whereas in 15-to-19-year-olds, boys and girls have similar cancer incidence rates, with girls having lower mortality rates. This may be related to differences in the frequency of types of cancer in boys versus girls. Non-Hispanic white and Hispanic children have the highest cancer incidence rates. African American children have lower cancer survival rates (5).

About 175,000 cases of cancer are diagnosed annually in children <15 years of age worldwide. Less than 40% of these children are adequately diagnosed and treated (5). 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.

TABLE 1.3

The Incidence Rates of Cancer in the United States for 0- to 19-Year-Olds Expressed as a Percentage of the Total Number of Cancer Cases in This Age Group, 2006–2010

Diagnosis	Percentage of the Total
Leukemia	26
Central nervous system	24
Lymphoma	13
Other malignant epithelial neoplasms such as adrenocortical carcinoma, thyroid carcinoma, nasopharyngeal carcinoma, and melanoma	9
Soft tissue and other extraosseous sarcomas	6
Germ cell and other trophoblastic tumors and neoplasms of the gonads	6
Malignant bone tumors	5
Neuroblastoma and other peripheral nervous cell tumors	4
Renal tumors	3
Retinoblastoma	2
Hepatic tumors	1
Other and unspecified	<1

Data from Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015, *CA Cancer J Clin.* 2015;65:5–29 and SEER Cancer Statistics Review 1975–2010, Table 29.1, National Cancer Institute.

Table 1.3 The Incidence Rates of Cancer in the United States for 0- to 19-Year-Olds Expressed as a Percentage of the Total Number of Cancer Cases in This Age Group, 2006–2010

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 (15). 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 (16). In Cuba, the most common childhood tumor is leukemia (31%), followed by lymphoma (18%), central nervous system (CNS) tumors (15%), sympathetic nervous system tumors (7%), soft tissue sarcomas (6%), and renal tumors (5%) (17). In Thailand, leukemias are most common (40%), followed by CNS tumors (14%), lymphoma (12%), bone tumors (4%), and soft tissue sarcomas (4%) (18). In Eastern Nigeria, lymphoma leads the list (19). 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 (20,21).

TABLE 1.4

The Most Common Causes of Pediatric Cancer Death in the United States, 2007–2011, by Primary Cancer Site for Ages 0–19

Cause of Death	Percentage of All Pediatric Cancer Deaths
Leukemia	29
Brain and other nervous system	25
Bone and joint	8
Soft tissue	8
Non-Hodgkin lymphoma	4
Kidney and renal pelvis	4

Data from SEER Cancer Statistics Review 1975–2011, Section 28, National Cancer Institute.

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TABLE 1.4

The Most Common Causes of Pediatric Cancer Death in the United States, 2007–2011, by Primary Cancer Site for Ages 0–19

Cause of Death	Percentage of All Pediatric Cancer Deaths
Leukemia	29
Brain and other nervous system	25
Bone and joint	8
Soft tissue	8
Non-Hodgkin lymphoma	4
Kidney and renal pelvis	4

Data from SEER Cancer Statistics Review 1975–2011, Section 28, National Cancer Institute.

TRENDS IN CHILDHOOD CANCER MORTALITY RATES

Page 3The 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 (AML), neuroblastoma, and brain tumors, the improvements have been less dramatic or confined to certain subgroups or stages (Table 1.5). In general, however, the diagnosis and treatment of childhood cancer has been one of the success stories of modern medicine.

TABLE 1.5

Trends in 5-Year Relative Survival Rates for Children with Cancer (0–14 Years of Age) in the United States at the Approximate Midpoint of the Last Four Decades

Diagnosis	1975–1977 (%)	1984–1986 (%)	1993–1995 (%)	2004–2010 (%)
All sites	58	68	77	83
Acute lymphocytic leukemia	57	72	84	92
Acute myeloid leukemia	19	31	41	66
Bone and joints	50	57	74	79
Brain and other nervous system	57	62	71	74
Hodgkin lymphoma	81	90	95	98
Neuroblastoma	53	52	67	77
Non-Hodgkin lymphoma	43	70	81	86
Wilms tumor	73	91	92	92

Data from Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65:5–29.

Table 1.5 Trends in 5-Year Relative Survival Rates for Children with Cancer (0–14 Years of Age) in the United States at the Approximate Midpoint of the Last Four Decades

An estimated 1350 cancer deaths in children 0–14 years of age and 610 cancer deaths in 15-to-19-year-olds occurred in the United States in 2014. It is clear that when compared with adult cancer, childhood cancer is a vanishingly rare event. For example, in 2015 there were

158,000 estimated deaths from lung cancer alone in the United States (6). 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 is insufficient. 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 lost or lifetime earnings saved. A lifetime is saved for every child cured of cancer.

Figure: Trends in 5-Year Relative Survival Rates for Children with Cancer (0–14 Years of Age) in the United States at the Approximate Midpoint of the Last Four Decades

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FUNDING OF PEDIATRIC CANCER RESEARCH

In the United States, there is a significant federally funded pediatric cancer research program. Research focuses on treatment in cancer biology and the management of long-term cancer survivors (Table 1.6). We know very little about pediatric cancer prevention in contrast to the extensive efforts in tobacco and alcohol consumption control, reduction in sun exposure, and dietary interventions promoted to reduce adult cancer. Unfortunately, the amount of U.S. federal inflation-adjusted dollars spent on pediatric cancer research has fallen in recent years (Table 1.7).

TABLE 1.6

Percentage of Total Dollars Spent by Scientific Area in Pediatric Cancer Research by the United States National Cancer Institute for Fiscal Year 2013

Scientific Area	Percentage of Total Expenditures
Treatment	44
Biology	17
Cancer control, survivorship, and outcomes research	15
Etiology	10
Early detection, diagnosis, and prognosis	7
Scientific model systems	5
Prevention	2

From National Cancer Institute. A snapshot of pediatric cancers. http://www.cancer.gov/research/progress/snapshots/pediatric.

Table 1.6 Percentage of Total Dollars Spent by Scientific Area in Pediatric Cancer Research by the United States National Cancer Institute for Fiscal Year 2013

TABLE 1.7

The Yearly Investment of the United States National Cancer Institute in Pediatric Cancer Research

Year	Funding in Millions of US Dollars Not Adjusted for Inflation
2009	192.8
2010	197.1
2011	195.5
2012	208.1
2013	185.1

Data from National Cancer Institute. A snapshot of pediatric cancers. http://www.cancer.gov/research/progress/snapshots/pediatric.

Table 1.7 The Yearly Investment of the United States National Cancer Institute in Pediatric Cancer Research