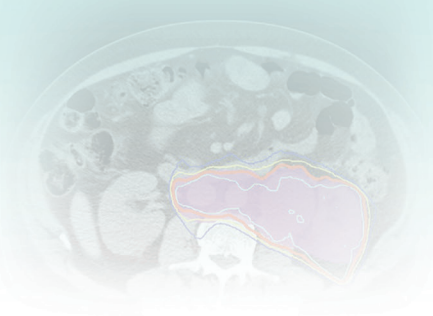
Overview



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CANCER IN CHILDREN

An estimated 15,780 newly diagnosed children (10,450 in birth to 14 year olds) and adolescents (5330 in 15- to 19-year olds) were diagnosed with cancer in the United States in 2014.[1] Cancer remains the most-common disease causing death in children; it is second to accidents in all causes of death between birth and 14 years of age. Approximately 1900 cancer deaths occur annually in children and adolescents.[1,2] After a plateau in pediatric cancer survival, the rate of decline in cancer mortality in this age group over the past decade has resumed the progress noted previously in the evolution of combined-modality therapy.[2]

For children ages 1 to 14 years old, the most-common cancers are leukemias and central nervous system (CNS) tumors, together accounting for more 50% of cancers in children. Acute lymphoblastic leukemia (ALL) alone accounts for 26% of cases in children; acute myeloid leukemia (AML), 5%. The other most frequent types are neuroblastoma, non-Hodgkin's lymphomas, and Wilms' tumor. For adolescents 15- to 19-years old, the most-common cancers include Hodgkin's lymphoma, thyroid cancer, CNS tumors, germ cell tumors (especially testicular); other relatively common types include non-Hodgkin's lymphomas, bone tumors, and melanoma (Table I-1).[1] Between 2001 and 2009 epidemiology studies showed a stable overall incidence of cancer in children and adolescents with a noteworthy increase in thyroid and renal carcinomas; a significant increase in overall cancer rates in African American children and adolescents; and a decrease in the incidence of melanoma and extracranial-, extragonadal-germ cell tumors.[3]

With contemporary therapies, long-term disease control—*in most tumor systems tantamount to cure*—is achieved in approximately 80% of children and adolescents; 5-year relative survival increased from 58% for children 1- to 14-years old diagnosed between 1975 and 1977 to 83% for those diagnosed from 2003 to 2009.[1] Survivors of childhood cancer often have physical and functional limitations that prevent them from achieving their full potential and compromise quality of life. Late mortality (30% among those surviving at least 5 years post-diagnosis) is increasingly related to secondary neoplasms and cardiac or pulmonary deaths as a result of treatment, rather than to recurrent cancer.[4,5] The cumulative incidence of second cancers at 30 years following initial diagnosis in childhood was 20.5% in the Childhood Cancer Survivors Study analysis.[6,7] Current strategies and clinical investigations seek to maintain or improve disease control, while reducing therapeutic interventions associated with long-term morbidity and mortality; identifying local-regional and overall disease control achievable with radiation therapy is often weighed against specific radiation-related late morbidities and secondary malignant neoplasms (SMN), in particular.[6-8]

Genetically defined cancer susceptibility or predisposition syndromes are known to account for approximately 10% of pediatric cancers; a recent study suggests that more than 25% of patient with pediatric cancer may have an inherited genetic cause based on a strong family history of cancer, cancer types strongly associated with hereditary cancer, history suggestive of a genetic diagnosis, or family history of another medical condition associated with genetic cancer.[9,10] Many cancer predisposition syndromes have implications not only for primary tumorigenesis but also for enhanced radiation sensitivity related to secondary carcinogenesis and, less frequently, somatic effects.[8,11] Retinoblastoma is the "classic" autosomal dominant hereditary cancer associated with the *RB1* tumor suppressor gene and a high rate of SMNs: a cumulative risk of 36% SMN by 50 years post-diagnosis, data showing a three-fold higher risk following orbital radiation therapy compared to those treated without irradiation.[12-14] Li-Fraumeni syndrome is caused by heterozygous germline mutations in the *TP53* tumor suppressor gene.[15] The syndrome is associated with an increased risk of cancer in children and young adults, especially bone and soft-tissue sarcomas, adrenocortical carcinomas, choroid plexus carcinomas, and frequent multiple primary tumors in a given patient.[16] Aside from the classic neurofibromas and optic nerve/optic tract gliomas associated with neurofibromatosis type 1 (NF1), malignant peripheral nerve sheath tumors, low-grade gliomas outside the visual pathways, and pheochromocytomas occur rather commonly in children and adolescents with NF1.[17] The number of inherited cancer predisposition syndromes related to pediatric oncology is impressive, as is the increasing recognition of late radiation effects in such cohorts.[8,11,17,18]

Approximately two thirds of children with cancer in North America are treated on clinical protocols, primarily studies coordinated by the Children's Oncology Group (COG), one of the pediatric disease-specific consortia (New Approaches to Neuroblastoma Therapy, NANTS; Pediatric Brain Tumor Consortium, PBTC; Therapeutic Advances in Childhood Leukemia and Lymphoma, TACL), and independent trials at the few major institutions able to mount clinical trials. Challenges remain in ensuring appropriate multimodality therapy for adolescents and young adults with pediatric types of cancer, as well as the enormous lack of resources for treating children with cancer in the developing world.[2,3,19,20]

Radiation therapy is a major component of coordinated, multimodality therapy for children. In the most common childhood cancer, ALL, the prior use of preventive cranial irradiation was initially associated with then remarkable cure of ALL, but more recently recognized primarily in

TABLE I-1 Common Neoplasms Occurring in Children and Adolescents

Disease Type	Childhood Cancers (%)	Role for Radiation Therapy
Acute Leukemias	**24**	
• Acute lymphoblastic (ALL)	*18*	1. Limited number may benefit from preventive cranial irradiation (high-risk T-cell, <5% ALL cases) 2. Therapeutic CNS-RT for CNS relapse 3. Total-body irradiation (TBI) or total lymphoid irradiation (TLI) in bone marrow transplantation (BMT) for recurrent/high-risk ALL
• Acute myeloblastic (AML)	*5*	1. TBI in BMT
Central Nervous System	**18**	
• Glial tumors	*12*	1. Local RT for many low-grade presentations, often at progression 2. Local RT for all high-grade presentations
• Ependymomas	*1*	1. Local RT for virtually all presentations
• Craniopharyngiomas	*1*	1. Local RT for incompletely resected or progressive/recurrent tumors
• Medulloblastomas and other embryonal CNS tumors	*3*	1. Systematic craniospinal irradiation + local boost for children ≥ 3 years 2. Local RT in children < 3 years (investigational)
• CNS germ cell tumors	*1*	1. Ventricular RT with local boost and chemotherapy vs. ventricular or craniospinal RT for germinomas 2. Ventricular or craniospinal RT plus chemotherapy for "malignant" germ cell tumor
Malignant Lymphomas	**15**	
• Hodgkin's lymphoma	*9*	1. Local (involved field) in combined modality therapy 2. TLI or TBI in transplantation settings for recurrent disease
• Malignant lymphoid tumors	*6*	1. Local RT for symptom control or recurrent disease
Neuroblastoma	**5**	1. Local regional RT for regionally advanced disease 2. Palliative RT (bone; soft tissue) 3. TBI in high-dose therapy/stem-cell rescue regimens (investigational)
Wilms' Tumor	**4**	1. Local/regional RT in advanced disease or unfavorable histology 2. Visceral RT in metastatic disease
Retinoblastoma	**3**	1. Ocular RT in consolidative or progressive/recurrent settings
Soft-Tissue Sarcomas	**6**	
• Rhabdomyosarcomas	*3*	1. Local/regional RT for most (intermediate/advanced or alveolar histology) presentation
• Other soft tissue	*3*	1. Local/regional RT based on histology, site, size, and age
Bone Sarcomas	**6**	
• Osteosarcoma	*3*	1. Limited postoperative use in central sites
• Ewing's sarcoma	*2*	1. local RT for "nondispensable" primary site 2. Local postoperative RT following marginal resection 3. Visceral and bone RT in metastatic disease
Hepatic Tumors	**1**	1. Limited postoperative or palliative RT
Germ Cell Tumors	**5**	1. Limited local/regional RT

Modified from SEER Cancer Statistics: http://seer.cancer.gov; Ward E, et al: Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 64(2):83–103, 2014, and Smith MA, et al: Declining childhood and adolescent cancer mortality. Cancer 120(16):2497–2506, 2014.
CNS, *Central nervous system;* RT, *radiation therapy.*

unique association with late morbidities. Current therapeutic approaches largely obviate irradiation except for instances of CNS relapse or in the context of bone marrow transplantation for relapsed, refractory, or genetically virulent forms of ALL, where total body or total lymphoid irradiation is a part of the conditioning regimen.[21-25]

Data from St. Jude Children's Research Hospital show the proportion of newly diagnosed children who receive irradiation for all forms of cancer has increased over the past 18 years from approximately 40% to nearly 60%, even with the elimination of preventive cranial irradiation in institutional ALL protocols.[22] A retrospective study of NCI's SEER database reports significant reduction in radiation therapy, though, between 1973 and 2008 for children with ALL, non-Hodgkin's lymphoma, and retinoblastoma, with modest declines in brain cancer, bone cancer, Wilms' tumor, and neuroblastoma; whether SEER reporting is accurate reradiation utilization is questioned.[26] In major referral centers for pediatric cancer, pediatric cases have increased, particularly in CNS tumors (reported at 25% to 65% of cases undergoing radiation therapy) and for tumors requiring abdominal and pelvic and head and neck irradiation.[27]

Increased utilization of radiation therapy in regional and national referral centers reflects improvements in diagnostic imaging for tumor mapping and in dose conformality with intensity-modulated radiation therapy (IMRT) photon irradiation and the availability of proton beam radiation therapy (PBRT; evolving from standard double scatter technology toward intensity modulated proton therapy with spot beam technology)—all enabling significant reduction in radiation exposure to critical normal structures. Interest in PBRT has been particularly noted in CNS tumors and sarcomas where

dose reduction in neuroanatomic regions related to neurocognitive development and in anatomic sites related to somatic and visceral growth and function has driven centralized referral patterns based on technology.[28-33] Such technologies have favored judicious radiation intervention even in the more vulnerable younger children where rebalancing efficacy and tolerance are critically important, as in CNS atypical teratoid/rhabdoid tumors (AT/RT) and genitourinary rhabdomyosarcomas in girls.[30,34,35] The defensive posture of the radiation oncologist has been replaced by the knowledge base required in clinical and biologic understanding of pediatric cancers, common and evolving drug therapies, and the application of sophisticated radiation technology.

Key radiation parameters are critically important in pediatric therapy, where the relative radiation sensitivities of pediatric cancers compete with the added vulnerabilities of the growing, developing child or adolescent. There are increasing studies in most pediatric CNS tumors, sarcomas, and other common solid tumors showing disease control with diminishing target volumes, essentially shrinking the clinical target volume (CTV) expansion of the tumor volume to take further advantage of three-dimensional treatment planning and more conformal radiation delivery.[35-39] As target volumes are progressively tighter, quality control becomes more critical both at institutional and cooperative group levels. Target volumes in unique tumor settings may actually need to be larger, as with alveolar rhabdomyosarcoma and the potential value of nodal irradiation.[40,41] As well, there have been progressively lower radiation doses shown to be effective in rhabdomyosarcoma, Ewing sarcoma, medulloblastoma, CNS germ cell tumors, and other settings where either (1) combinations of pre- or postirradiation chemotherapy provide an additive effect or (2) postchemotherapy surgery provides microscopic disease only.[35,38,42,43]

Molecularly targeted agents have increasingly been investigated in combination with radiation therapy. Several classes of drugs have shown radiosensitizing potential in preclinical studies and have completed Phase I and Phase II studies in pediatrics (e.g., platelet derived growth factor [PDGF] inhibitors, farnesyl transferase inhibitors [FTI], histone deacetylase inhibitors [HDAC], and Poly[ADP-ribose] polymerase [PARP] inhibitors). The ultimate utility of molecularly targeted agents and the interactions with irradiation will be apparent in tumor systems where specific molecular targets and available pharmacotherapeutics allow prospective clinical trials.

Radiation-related late effects are often more pronounced in children than in adults, especially in somatic changes (growth and development of musculoskeletal tissues) and functional effects (neurocognitive, auditory, endocrine).[6,21,28,32,39,44] Infants and young children are particularly vulnerable to the effects of both irradiation and chemotherapy agents (e.g., alkylating agents, cis-platinum, Adriamycin).[44-46] Alterations in bone growth, muscle development, and intermediate-size arterial caliber tend to be more prevalent in younger patients than in adolescents or adults.[47,48] Threshold radiation levels are recognized for epiphyseal growth, but even low dose exposures can be correlated with changes in height and bone development (both contour and integrity).[48] It is not clear whether visceral tolerances are significantly lower in the younger age group, although the frequent use of combined chemoradiation therapy introduces added concerns regarding radiation tolerance for the heart and lungs, the liver and the kidneys.[49,50] Intermediate-size vessels, particularly at the circle of Willis, show reduced caliber and flow after irradiation in a high proportion of children younger than 1 to 3 years of age, whereas major extracranial vascular effects are otherwise most noteworthy in coronary vessels.[47,51] A high proportion of children evidence hypothyroidism after even low-dose irradiation to the neck; manifestations of reduced testosterone and estrogen levels following low-dose pelvic irradiation are noted after irradiation in childhood or adolescence.[52-54]

Neurocognitive effects of brain irradiation have been well described and correlated with radiation dose, volume, and patient age. Concerns regarding limited life potential attendant to diminished learning and IQ have driven protocol-based attempts to limit radiation use as well as introducing volume and dose constraints in treating children with CNS tumors over the past three decades.[5,21,28,32,39,46,55] Experience with narrow targets to rather high subtotal posterior fossa doses have shown preservation of intellectual function in children as young as 12 months of age in ependymomas.[39,55] Prospective measurements of learning disabilities are key to further assessing the impact of contemporary radiation therapy in localized brain tumors. Clinical trials suggest specific interventions (i.e., pharmacologic and cognitive rehabilitation) may ameliorate some of the learning problems associated with cerebral irradiation.[56]

In pediatric radiation therapy, one must always consider the risk of secondary carcinogenesis, an overall risk that is at least 5% to 10% over three decades of follow-up. The long survival intervals of successfully treated children and the added risks of SMN in the growing or developing tissues (e.g., the pubescent and adolescent breast) and in several of the cancer predisposition syndromes require exquisite balance in indications for radiation therapy and in selecting techniques that might limit carcinogenesis.[4-7,12-14]

The following chapters outline the biology, clinical features, and outcome of the more common pediatric cancers, summarizing the current and evolving roles of radiation therapy in the current approach to childhood cancer and consider the available data and ongoing trials related to radiation modalities and parameters of volume, dose, and fractionation.

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