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PENTEC INTRODUCTORY REVIEW

A User's Guide and Summary of Pediatric Normal Tissue Effects in the Clinic (PENTEC): Radiation Dose-Volume Response for Adverse Effects After Childhood Cancer Therapy and Future Directions

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Pediatric Normal Tissue Effects in the Clinic (PENTEC) is an international multidisciplinary effort that aims to summarize normal-tissue toxicity risks based on published dose-volume data from studies of children and adolescents treated with radiation therapy (RT) for cancer. With recognition that children are uniquely vulnerable to treatment-related toxic

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effects, our mission and challenge was to assemble our group of physicians (radiation and pediatric oncologists, subspecialists), physicists with clinical and modeling expertise, epidemiologists, and other scientists to develop evidence-based radiation dosimetric guidelines, as affected by developmental status and other factors (eg, other cancer therapies and host factors). These quantitative toxicity risk estimates could serve to inform RT planning and thereby improve outcomes. Tandem goals included the description of relevant medical physics issues specific to pediatric RT and the proposal of dose-volume outcome reporting standards to inform future studies. We created 19 organ-specific task forces and methodology to unravel the wealth of data from heterogeneous published studies. This report provides a high-level summary of PENTEC's genesis, methods, key findings, and associated concepts that affected our work and an explanation of how our findings may be interpreted and applied in the clinic. We acknowledge our predecessors in these efforts, and we pay homage to the children whose lives informed us and to future generations who we hope will benefit from this additional step in our path forward.

Preamble

Our PENTEC consortium strives to quantify radiation dose-response relationships for the long-term consequences of treating children with cancer and to enable risk mitigation through more informed decision-making by their dedicated caretakers. We recall Guilio J. D'Angio's[1] admonition to us all: "Cure is not enough."

Introduction

It is gratifying to provide an overview of the results of the Pediatric Normal Tissue Effects in the Clinic (PENTEC) project presented in this issue of the *Red Journal*. The PENTEC project has been a complicated effort, with the original investigators having aged more than a decade during the process. We all have learned from one another, been humbled by the efforts of clinicians and scientists throughout the world, and become more profoundly aware that the journey before us to improve the knowledge base in this realm is immense. We acknowledge our forebears in the study of adverse events of RT for cancer, including Emami, Rubin, Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC), Hypo-fractionated Treatment Effects in the Clinic (HyTEC), the international multi-institutional cooperative groups devoted to studying the toxicity of cancer therapy in children (particularly the Childhood Cancer Survivor Study), and the specific groups tasked with addressing toxicity management, such as the International Late Effects of Childhood Cancer Guidelines Harmonization Group. We dedicate the PENTEC effort to the children and their families who were, and continue to be, afflicted by this devastating disease and the long-term health effects of cancer therapy, and we hope our efforts help mitigate this burden for future generations.

We herein provide a high-level summary of PENTEC's background, methods, key findings, associated concepts that affected our work, and how our findings may be interpreted and applied in the clinic. At the start of this collaboration in 2012, we were pessimistic that the available data would be sufficient to contribute meaningfully to our understanding of late effects in children and adolescents. In many cases, we were pleasantly surprised by the quality of published data, allowing for normal tissue complication probability (NTCP) modeling. The diverse perspectives of our multidisciplinary expert collaborators (eg, radiation and pediatric oncologists, medical physicists, modelers, epidemiologists, and subspecialists) facilitated the thoughtful syntheses of published outcomes presented in this issue of the *Journal* while also highlighting many still-unanswered questions.

PENTEC's background: Historical perspective

The effects of x-rays on human tissue were reported in some detail by Leopold Freund in 1897, based on what is arguably the first rational therapeutic use of x-rays—conducted for a hairy nevus in a 5-year-old girl. Part of Freund's rationale came from the report of an incidental case of radiation epilation documented in the *Wiener Medizinische Wochenschrift* on October 3l, 1896.[2] In 1903, Georg Perthes reported on the effects of roentgen rays on the epithelial tissues of juvenile chicks.[3] In 1906, Bergonié and Tribondeau described that cells were particularly sensitive to radiation if they were undifferentiated and had a high rate of cellular division and a long cellular lifespan.[4] In the 1940s Charles Hinkel was among the first to study the late effects of radiation in developing animals through investigations of the effects of roentgen rays on the growing bones of albino rats.[5] Recognizing this morbidity in growing children, Neuhauser in 1952 reported on strategies to circumvent scoliosis by use of judicious placement of treatment fields.[6] During the subsequent decades, it has been increasingly recognized that the spectrum and character of radiation-induced late adverse events in children differs from that in adults. This is largely explained by a different pathogenesis in tissues that are still developing and the associated functional consequences.

Genesis of and motivation for PENTEC

The differences in pathology of adverse radiation effects in children and adults led the QUANTEC Steering Committee to omit radiation effects in children from most of their organ-specific overviews; it was thought that this was a topic

best tackled by a subsequent collaborative study group with specific expertise in the treatment of childhood and adolescent and young adult cancers, survivorship, and research and care of late effects. This led to the formation of PENTEC, with the aim to summarize (and model where possible) published data regarding long-term, radiation-associated normal tissue injury in children. A central theme is to better understand whether developing, homeostatic, and senescing tissues are differentially vulnerable and how the mosaic of organs in children, which develop at different rates and in different temporal sequences, are thus affected.

The number of patients potentially affected by PENTEC is incalculable. Although cancer is fortunately uncommon in children, the potential years of life affected or lost among those who are not cured and the chronicity of treatment toxicity among those who are cured make the burden of childhood cancer immense. Between 2013 and 2017, the annual rate of cancer per 100,000 persons was 16.8 in children aged 0 to 14 years and 75.9 in adolescents or young adults aged 15 to 39 years.[7] While more than 80% of these patients will survive ≥5 years,[8] late excess mortality is a disturbing reality that often lasts decades. Armstrong et al[9] evaluated this among 34,033 5-year survivors diagnosed before age 21 in the Childhood Cancer Survivor Study cohort. This retrospective cohort study included >25,000 5-year survivors of childhood cancer diagnosed from 1970 to 1999 from 31 institutions in North America. With a median follow-up of 21 years (range, 5-38 years), 3958 deaths occurred during the 1970 to 1999 study period, with 51% attributable to recurrence or progression of the primary cancer, 41% to health-related causes other than the primary cancer, and 8% to external causes. Of the 1618 deaths related to other health-related causes, 46% were due to subsequent malignant neoplasms, 15% cardiac, and 13% pulmonary causes. The silver lining is that 15-year health-related mortality declined from 3.5% in the early 1970s to 2.1% in the 1990s, primarily owing to decreases in rates of deaths from cardiopulmonary causes and subsequent malignancies.[10] Of note, these numbers represent total mortality rates among cancer survivors, and the distribution of causes changes with increasing attained age of the population assessed.

Several factors contribute to this decline in health-related mortality, which coincides with a decline in the use of RT for childhood cancer during the same period. In a report of children treated from 1973 to 2008 and who were registered to the Surveillance, Epidemiology, and End Results program, the overall rate of radiation use was 27% across all diagnoses, with the lowest for retinoblastoma at 2% and the highest for Hodgkin lymphoma at 72%. The use of RT to treat patients with pediatric cancer declined over time between the 1970s and 2000s. The tumors with the greatest decline in radiation use from 1976 to 2008 were acute lymphoblastic leukemia (from 57% to 10%), non-Hodgkin lymphoma (from 57% to 15%), and retinoblastoma (from 30% to 2%). Additional large decreases have been seen for central nervous system tumors (from 70% to 39%) and neuroblastoma (from 60% to 25%).[11]

Modifications in RT play a role in reducing health-related mortality in childhood cancer survivors. Among these are (1) improved selection of patients (ie, identifying those most likely to benefit from RT); (2) radiation dose de-escalation for some disease sites; (3) improvements in RT techniques (eg, more conformality of target volumes while minimizing normal-tissue exposures); (4) improvements in systemic therapy and supportive care; and (5) improvements in diagnostic tools for cancer detection and toxicities. Finally, it is noteworthy that the decrease in burden of severe, life-threatening, or fatal late effects is heterogeneous across malignancies and time intervals, leaving great opportunities for further improvement. Therefore, by using the information from PENTEC to reduce the incidence of radiation-associated late effects and hence improve the therapeutic ratio, PENTEC's benefits may be broad.

In summary, because many children with cancer are cured, understanding the genesis, natural history, and dose-volume-outcome relationships for late adverse normal-tissue effects is critically important. This can equip physicians to make difficult decisions for the judicious use of RT.

Methodologies Including Identification and Resolution of Encountered Obstacles

Identifying and extracting the data

We used a highly structured, systematic approach to identify published investigations for review and included a bias assessment of these studies. Each organ-specific task force identified clinically meaningful normal-tissue endpoints and search terminology for literature databases. Literature searches were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, with relevant reports identified over a broad range of years specific to the endpoint. The upper age limit for most reports was set at 21 or 25 years, and the majority of patients in each report were not to exceed this age; however, this also varied by the organ and endpoint. For most task forces, thousands of abstracts were identified. Based on a screen of the abstract (and in some cases, full text), the teams identified reports with sufficient detail to allow some level of quantitative analysis. These reports were subsequently reviewed by our clinical physicists for the feasibility of estimating radiation doses to the organ of interest and by our modelers for the possibility of calculating the probability or incidence of specific endpoints and the data sufficiency for meta-analysis. Papers identified from the systematic search were supplemented with published reports of interest known to the expert review team. For some task forces, the list yielded few relevant reports, offering limited or no opportunities for meta-analysis; whereas for others, a detailed dose-response analysis was possible.

Physics considerations for assessment of dosimetric quality

A key limitation in many published reports was the lack of dosimetric detail; the degree of these dosimetric uncertainties was considered in each of the task force reports. When organ doses were not reported in publications, they were estimated from reported prescription doses when feasible, and a percentage of dose uncertainty was estimated. This avoided the potential errors that would be introduced by assuming tumor doses were also organ-at-risk doses. Dose corrections ≥10% in magnitude were made for selected publications, such as for breast, cardiovascular, thyroid, liver, and musculoskeletal organs (see individual reports for details and justifications). To our knowledge, this type of systematic assessment of dosimetric quality for every paper that entailed meta-analysis modeling has not generally been reported in the literature. The approach and methods of our medical physics group are discussed by Olch et al in their introductory report.[12]

Challenges in determining and analyzing relevant endpoints

For each organ, identifying clinically relevant endpoints to study was a challenge due to the heterogeneity in endpoint definition and grading across studies. Several toxicity grading scales have been used over the years, and they are often inconsistent, not uniformly applied, and/or incomplete, thus hampering data pooling and analysis of data from different studies over time. The specific diagnostic tests (ie, laboratory testing and imaging) and the frequency of screening for toxicities was also highly variable (as might be expected), compromising the ability to determine time intervals to injury. Some relevant publications dated back to the 1970s, with patient treatments occurring as early as the 1950s, allowing for reasonable follow-up intervals but with outdated methods for dosimetry, late-effects assessment, and data reporting. Of course, many late toxicities can develop after long latency (eg, cardiac or cerebrovascular effects or second neoplasms), so multiple decades of follow-up may be required for accurate characterization. Moreover, most studies did not report data regarding important comorbidities and lifestyle factors (eg, smoking, diet, exercise), which compromises the ability to isolate the effects of RT. Finally, patient-reported outcomes often varied significantly in frequency and severity from those reported by health care providers. Some examples of how these issues affected the specific reports are shown in the 2 left-hand columns of Table 1.

Key Findings From Site-Specific Reports

A summary of the key quantitative dose-volume-outcome organ-specific findings is provided in Table 2, but physicians, planners, and others are encouraged to read the individual reports to better understand the methods, nuances, and limitations of the data. It is crucial to recognize that these task force findings reflect our in-depth collection of data and its analysis and thereby provide guidelines for estimating risks of toxicities. In some cases, there is considerable uncertainty, which is why the findings are not intended to be inviolate and may be modified as needed for specific patients or use in protocols.

A fundamental challenge is to balance the risk of tumor recurrence with the risk of adverse radiation-associated effects. This is particularly critical in children due to the high curability of many childhood cancers and the long life expectancy among childhood cancer survivors. We recognize that at times, it is necessary to accept increased risks of late effects in order to deliver sufficient dose and target coverage for tumor control. We also recognize that situations exist in which some critical organs (eg, spinal cord, chiasm) will be prioritized for dose limitations compared with others.

When interpreting excess absolute risk estimates, it is also important to recognize that this risk largely comes from 2-dimensional (and infrequently, 3-dimensional [3D]) planned RT, with considerable dosimetric uncertainties (see Olch et al[12]). In addition, most reports used data from photon therapy (mostly megavoltage photons, including linear accelerators and Co-60 units, and even a few that included orthovoltage data). Seven PENTEC organ-specific reports included data from patients treated with protons (summarized in Table E1 in the report by Milano et al[13]), of which 4 also included focused discussions on risks for normal-tissue injury after proton therapy. However, the dose-volume normal-tissue effects of proton therapy were not separately modeled or analyzed in any PENTEC report. Thus, we cannot unequivocally know to what extent the dose-volume-outcome models in the PENTEC reports apply to patients treated with protons. The following issues may affect this applicability:

1. With photon-based plans, there tend to be strong correlations between many of the normal-tissue dose-volume histogram (DVH)-based metrics (eg, Vx (percent volume of the organ receiving ≥x Gy) or mean dose). Thus, for example, even if mean dose is highly correlated with NTCP, this does not mean that it is somehow "the critical dose-volume metric that determines NTCP." Rather, it is possible that mean dose is simply a "carrier" of the dose effect in NTCP models, even when, in reality, there is a biologically complex interaction between the organ-specific anatomy and physiology and the 3D dose distribution. Similarly, there are situations in which there are good correlations between, say, the mean organ dose and the dose to critical organ subregions. Because proton-based plans yield dose distributions that are substantially different from those of photon-based plans (eg, relating to tissue attenuation and dose fall-off), the associations between the various DVH-based metrics and between these DVH-based metrics and the dose to relevant

Table 1 Representative challenges in determining and defining endpoints and possible solutions

Organ or domain	Challenges	Possible solutions
CNS	Variability in neurocognitive testing and definitions of CNS necrosis	Increase homogeneity in neurocognitive testing and scoring for necrosis
Optic system	Cataract incidence depends on whether it is provider-diagnosed or patient-reported (ie, without vs with symptoms)	When physician-diagnosed, report if vision is clinically impaired
Hearing apparatus	Different thresholds for hearing loss used in different studies to define impairment; scales are designed primarily for high-frequency hearing loss (typical of chemotherapy), but RT may also compromise low-frequency hearing	Uniform toxicity scoring systems that include low- and midfrequency hearing loss
Spinal cord	Myelopathy is rare; data providing denominators for relative or absolute risk estimates are almost nonexistent	Always record total patient numbers in series reporting myelopathy; more reporting of cord dose for patients not having myelopathy
Heart	Various cardiac pathologies depend on injury to subregions of the heart (eg, coronary arteries, valves, ventricles); historical data on the relationships are scarce	Data are rapidly emerging linking substructure doses and longitudinal cardiac outcomes
Pulmonary	Toxicity rates variously defined (eg, symptoms vs changes on imaging); for TBI-associated toxicity, unraveling dose vs dose-rate effects is necessary	Increased homogeneity in toxicity reporting
Breast	No consensus on definition of hypoplasia and very little data from patients irradiated for cancer; this necessitates investigation into older radiation techniques (including brachytherapy) used for benign diseases	Consistent system for measuring breast development with hypoplasia toxicity scoring; similarly for lactation
Musculoskeletal	Insufficient data to assess RT effects on limbs or the dose gradient across vertebral bodies; available data for vertebral body growth are limited by varying thresholds for abnormality and follow-up	Longitudinal data on upper and lower limb growth; more vertebral body growth and deformity data in the context of intentionally targeting or sparing vertebral bodies
Gastrointestinal	Insufficient data to analyze bowel toxic effects or hepatic dysfunction from partial (vs whole) liver RT; inconsistent definitions of sinusoidal obstructive syndrome	Better quantification of radiation exposures and toxicity scoring systems
Genitourinary	Insufficient quantitative data to assess bladder fibrosis causing incontinence and compromised QOL	Grade bladder incontinence
Female reproductive tract	Data quantifying RT-associated vaginal and uterine fibrosis are rare; there is variability in follow-up duration	Grade vaginal fibrosis and uterine development
Male reproductive system	Young boys do not have spermatic analyses performed; surrogates for fertility are hormonal and siring children (affected by many issues)	More homogeneity in hormones measured and normal ranges better defined
SNs	Incidence depends on follow-up time and, potentially, age and chemotherapy; dose to the site of SN is often not known	Consistent reporting of presence or absence of SNs in late effects studies; dose to the site of the SN should be reported
Reirradiation	Variables may affect risks (eg, total dose, fraction size, volume, and location for first and second course of RT); intervals between courses are often not reported	Report all relevant variables and the toxicity scoring scale (eg, symptomatic vs imaging)

Abbreviations: CNS = central nervous system; QOL = quality of life; RT = radiation therapy; SN = subsequent neoplasm; TBI = total body irradiation.

critical subregions are different. For example, Hoppe et al[14] and Hahn et al[15] showed that the correlation between mean doses to the whole heart and to cardiac substructures weakens in the case of proton plans and, more generally, with more conformal photon techniques, owing to more heterogeneous dose distributions across

Table 2 Summary of PENTEC data: Associations between dose-volume metrics and age with risks of radiation-related* toxicity

Organ or tissue	Volume segmented	Endpoint	Dose and volume	Risk, %	Effect of age	Comments, including on chemotherapy
Brain	Whole brain, including brain stem	Symptomatic radiation necrosis	59 Gy to any part	5	Not analyzed	Reirradiation analyzed in more depth in a separate report
			67 Gy to any part	10		
			Composite EQD2/2 of 112 Gy with brain reirradiation	5		
			Composite EQD2/2 of 112 Gy with brain stem reirradiation	7		
	Whole brain	For IQ <85	36 Gy to 10% brain	5	Younger age, independently associated with decreased predicted post-RT IQ	Methotrexate administration is estimated to have an effect of ~6-Gy whole brain uniform dose; whole (vs partial) brain is an independent adverse risk factor for post-RT IQ
			51 Gy to 10% brain	20		
			29 Gy to 20% brain	5		
			42 Gy to 20% brain	20		
			22 Gy to 50% brain	5		
			32 Gy to 50% brain	20		
			18 Gy to 100% brain	5		
			26 Gy to 100% brain	20		
Cerebrovascular	Circle of Willis, major cerebral arteries, or surrogate (ie, suprasellar cistern [preferred] or optic chiasm)	Stroke at attained age of 35 y	D100% 30 Gy	~1	Although attained age was analyzed, age at time of RT was not	Risks are low, but increased over general population; data were derived from prescribed dose; this dose covers the circle of Willis and surrogate structures (D100)
			D100% 45 Gy	2-3		
			D100% 54 Gy	3-4		
		Stroke at attained age of 45 y	D100% 30 Gy	2-4		
			D100% 45 Gy	4-9		
			D100% 54 Gy	7-13		
		Cerebral vasculopathy at attained age of 17 y	D100% 30 Gy	~0.2	Not analyzed	
			D100% 45 Gy	~1		
			D100% 54 Gy	~4		
Optic and ocular structures	Retina	Retinopathy	42 Gy D_{max}	5	Not analyzed	Higher fraction size correlates with greater risk of retinopathy and optic neuropathy
			62 Gy D_{max}	50		
	Optic nerve and chiasm	Optic neuropathy	57 Gy D_{max}	5	Not analyzed	
			64 Gy D_{max}	50		

(*Continued*)

Table 2 (*Continued*)

Organ or tissue	Volume segmented	Endpoint	Dose and volume	Risk, %	Effect of age	Comments, including on chemotherapy
	Lens	Cataract, self-reported	Mean 12 Gy	5	Childhood age does not appear to affect risks; children may have greater risks than adults (or are better screened)	Some chemotherapy agents are independently associated with cataract formation
			Mean >40 Gy	50		
	Lens	Cataract, ophthalmologist-diagnosed	No radiation	>5		
			Mean 9 Gy	50		
Neuroendocrine	Hypothalamus and pituitary gland	Growth hormone deficiency	D100% 15 Gy	5	Unable to quantify or model potential effects of age on risks, although cohorts with younger age had greater crude risks	-
		Central hypothyroidism	D100% 22 Gy	20		
		Adrenocorticotropic hormone deficiency	D100% 34 Gy	20		
Spinal cord	Spinal cord	Myelopathy	Without chemotherapy: D0.03 cc <54 Gy D1 cc <50.4 Gy	Rare	Data insufficient to analyze	NTCP modeling was not feasible; chemotherapy use (particularly intrathecal chemotherapy) appears to lower threshold for toxicity
			With chemotherapy: D0.03 cc <50.4 Gy; D1 cc <45 Gy			
Cochlea and middle ear	Cochlea	Hearing loss: if a threshold exceeds 20 dB at any frequency	With no chemotherapy		Greatest risk in children <5 y, although independent effects of dose and age were not elucidated	Higher-frequency hearing loss is more common; platinum-based chemotherapy adds to risks; 300 mg/m^2 shifts the dose-response curve by ~7 Gy
			Mean <35 Gy	<5		
			Mean 50 Gy	30		
Salivary glands	Both parotid glands	Acute grade >2 xerostomia	Mean 35-40 Gy	32	Not analyzed	Mean <26 Gy recommended
		Chronic grade >2 xerostomia	Mean 35-40 Gy	13-32%		
Dentition	Primary and permanent teeth	Dental developmental abnormalities	Data not pooled or modeled; based on 1 study, recommend avoiding >20 Gy, particularly for ages <4 y		Younger age and earlier stage of dental development associated with increased risk	Alkylating agents increase risk
Thyroid gland	Thyroid gland	Compensated (subclinical) hypothyroidism (all patients)	Mean 10 Gy	12	Aged 14-30 y: 1.3-fold greater risk than younger patients; Table 6 in thyroid report breaks down risks of any hypothyroidism (clinical and subclinical) by age and sex	Females: 1.7-fold greater risks vs males
			Mean 20 Gy	25		
			Mean 30 Gy	44		
		Uncompensated (clinical) hypothyroidism (all patients)	Mean 10 Gy	4		
			Mean 20 Gy	7		
			Mean 30 Gy	13		

(*Continued*)

Table 2 (*Continued*)

Organ or tissue	Volume segmented	Endpoint	Dose and volume	Risk, %	Effect of age	Comments, including on chemotherapy
Lung	Whole lung	Symptomatic (grade 2) pneumonitis	V20 <30% Mean <12 Gy	<5 <5	Not analyzed; from published studies, age does not generally affect pneumonitis risks	Late toxicities, including subclinical or asymptomatic impaired pulmonary function, were more common but not modeled
		Symptomatic (grade 2) late pneumonitis	V27 <20%	<5		
Lung	Whole lung exposure with total body RT	Idiopathic pneumonitis syndrome	Prescribed 11 Gy (EQD2/2.3)	3.6	Not analyzed	TBI lung dose metrics (eg, midlung point dose) could not be successfully modeled, possibly due to uncertainty in actual lung dose[†]
			Prescribed 12 Gy (EQD2/2.3)	47.5		
Heart or cardiovascular	Heart	Heart failure	Mean 20 Gy	1.1	Not analyzed and reported to be nonsignificant in earlier studies	Risks at 30 y after radiation; Table 3 in the article describes hazard ratios per 10 Gy
		Coronary artery disease	Mean 20 Gy	2.1		
		Valvular disease	Mean 20 Gy	0.5		
		Any cardiac disease	Mean 20 Gy	3.8		
			Mean 10 Gy + <250 mg/m^2 cumulative anthracycline	3.4		
			Mean 10 Gy + >250 mg/m^2 cumulative anthracycline	4.8		
Liver	Whole liver	Hepatic sinusoidal obstructive syndrome	D100% 10 Gy	6.1	Children (age <20) more susceptible than adults	Nonalkylating chemotherapy after whole-liver RT increased toxicity risks
			D100% 20 Gy	14.5		
Kidney	Kidneys	Hypertension	Whole kidney 9.6 Gy	5	Not analyzed	Whole kidney is either both kidneys in TBI or WAI in Wilms tumor; or 1 kidney for Wilms tumor after nephrectomy. Risk with RT + cisplatin is 1% greater vs cisplatin alone Risk with RT + ifosfamide is 5% greater vs ifosfamide alone; doses in EQD2/3.4
		Grade 2 CKD	Whole kidney 10.2 Gy	5		
		Grades 3-5 CKD	Whole kidney 14.5 Gy	5		
			RT + cisplatin V10 >25%	5		
			RT + ifosfamide V10 >40%	10		
		Grade 2 CKD	WAI Wilms (1.5 Gy × 7)	4		
		Grade 3-5 CKD	WAI Wilms (1.5 Gy × 7)	1		
		Grade 2 CKD	TBI 1.5 × 8, bid	6		
		Grade 3-5 CKD	TBI 1.5 × 8, bid	2		
		Grade 2 CKD	TBI 2 × 6, bid	8		
		grade 3-5 CKD	TBI 2 × 6, bid	3		
Testes	Testicles	Oligospermia at 1 y	Mean >1 Gy	>90		Testicular dose historically was estimated from expected internal scatter or solid-state skin dosimeters; luteinizing hormone production increased with higher doses, but no clear relationship was observed

(*Continued*)

Table 2 (*Continued*)

Organ or tissue	Volume segmented	Endpoint	Dose and volume	Risk, %	Effect of age	Comments, including on chemotherapy
		Low testosterone level	Mean 0.2-12 Gy	25		
			Mean 12-19 Gy	40		
			Mean >20 Gy	68		
		Low follicle stimulating hormone	Mean >0.5 Gy	40-100		
Breast	Breast bud	Perceived breast hypoplasia among those treated at <4 y	0 Gy	15	Not analyzed	-
			0 to <0.34 Gy	38		
			0.34-0.97 Gy	61		
			≥0.97 Gy	97		
			≥6.27 Gy	95		
	Mediastinum	Unsuccessful breast feeding among those treated at 14-40 y	27-46 Gy	39	Not analyzed	-
Ovaries and uterus	Least affected ovary (ie, ovary with least exposure)	AOF	No chemotherapy		Increasing risk of AOF and POI with increasing age	AOF risk increases with greater cyclophosphamide exposure; insufficient data to model uterine growth or fibrosis, or vaginal fibrosis, stenosis, dryness, and mucosal thinning
			2 Gy	1-5		
			Age 1 y 24 Gy			
			Age 2 y 20 Gy			
			Intermediate dose of alkylator			
			2 Gy	4-7		
			Age 1 y 22.5 Gy			
			Age 2 y 17 Gy			
			High dose of alkylator	6-13		
			Age 1 y 17 Gy			
			Age 2 y 13 Gy			
		POI	No chemo or RT	<5		
			No chemo			
			<10 Gy: by age 20 y	12		
			<10 Gy: by age 30 y	17		
			<10 Gy: by age 40 y	50		
			>10 Gy: by age 20 y	71		
			>10 Gy: by age 30 y	83		
			>10 Gy: by age 40 y	100		
			Intermediate dose of alkylator			
			<10 Gy: by age 20 y	41		
			<10 Gy: by age 30 y	53		
			<10 Gy: by age 40 y	94		

(*Continued*)

Table 2 (*Continued*)

Organ or tissue	Volume segmented	Endpoint	Dose and volume	Risk, %	Effect of age	Comments, including on chemotherapy
			>10 Gy	100		
Musculoskeletal	Vertebra	Clinically significant scoliosis and growth stunting	<2 y: >10 Gy	At risk	Younger age at time of radiation was highly predictive of adverse outcomes in scoliosis and spine growth	
			2-6 y: >20 Gy	At risk		
			>6 y: >30 Gy	At risk		
Second neoplasms	Not applicable	Subsequent malignant CNS tumor				
		EAR after 20 Gy exposure	At age 50 At age 75	1.6 4.5	No discernible effect of age on risk	Sex did not affect risk of malignant CNS tumors
		EAR after 50 Gy exposure	At age 50 At age 75	3.9 11		
		Subsequent meningioma				
		ERR/Gy = 0.44‡	Not applicable		Younger age at time of RT increases risks	Females had higher risk of meningioma
		Subsequent sarcoma				
		EAR after 20 Gy exposure	At age 50 At age 75	0.2 0.9	Younger age at time of RT is associated with increased risk of sarcoma	No effect of sex on risk of secondary sarcoma
		EAR after 50 Gy exposure	At age 50 At age 75	0.3 1.2		
		Subsequent lung cancer				
		EAR after 20 Gy exposure	At age 50 At age 75	0.3 6	Data on age were insufficient to assess for lung cancer risk	No effect of sex on risk of secondary lung cancer
		EAR after 50 Gy exposure	At age 50 At age 75	0.7% 0.15		

Abbreviations: AOF = acute ovarian failure; CKD = chronic kidney disease; CNS = central nervous system; D100 = minimum dose to 100% of organ, or minimum organ dose; Dmax = maximum dose to organ at risk; D*x*% = minimum dose received by the hottest *x*% of the organ; EAR = excess absolute risk; ERR = excess relative risk; EQD2/*X*: equivalent dose at 2 Gy per fraction calculated via the linear-quadratic model assuming an alpha/beta ratio of *X* Gy; IQ = intelligence quotient; NTCP = normal tissue complication probability; POI = premature ovarian insufficiency; RT = radiation therapy; TBI = total body irradiation; WAI = whole abdominal irradiation.

* Following conventional fractionation unless otherwise indicated.

† Fractionated low dose rate EQD2/2.3 (T1/2 = 0.5 hour); steep dose response in the range of 11-12 Gy.

‡ Insufficient and inconsistent data precluded calculation of EAR.

the heart. Thus, the PENTEC NTCP estimates and models may not be fully applicable to proton-based plans.
2. Even when these dose-distribution considerations are addressed, uncertainty remains regarding the relative biologic effectiveness (RBE) of protons. Current clinical practice in proton therapy (International Commission on Radiation Units and Measurements report 78[16]) applies a constant, spatially invariant, "consensus" RBE value of 1.1 (for nonspecialists, there is not a single numerical definition of RBE, and use of the multiplicative factor of 1.1 corresponds to the so-called cobalt-Gray equivalent to convert prescribed photon doses to proton doses). This value was historically chosen as reasonable in light of available in vitro experiments at the midpoint of the spread-out Bragg peak[16] and was felt to be conservative in terms of ensuring sufficient dose to the tumor. It is well established in preclinical models that RBE varies with depth along the proton path[17,18]; specifically, RBE increases toward the end of the range of the protons (ie, in the distal region of the Bragg peak), where tumor-adjacent critical normal tissues could reside. The RBE for normal tissues depends on distributions of linear energy transfer, which is known to be affected by beam arrangements and intensity modulation patterns. The same average absorbed dose to different organs could exhibit distinctively different linear energy transfer and RBE distributions. There is also substantial evidence that RBE varies among different normal-tissue endpoints.[17] Finally, a constant RBE that does not depend on dose per fraction is inconsistent with linear-quadratic fractionation biology.

Consequently, dose-volume-outcome estimates for protons will need to be refined as these dosimetric and radiobiologic considerations are better understood. Several evolving or growing registries will help in this regard. For example, the Pediatric Proton/Photon Consortium Registry, currently with more than 4200 patients younger than 22 years of age, combines late effects data with dosimetry, imaging data, and patient-level factors.[19] Such large data sets will help to inform our understanding of the extent to which photon dose-volume-response relationships also apply to proton therapy.

Finally, these summary data have inherent limitations related to the pooling of information from multiple studies (eg, due to interstudy variations in methods, risk assessment, etc), as noted previously. Additional limitations are discussed in the individual organ- or tissue-specific reports and in the State of the Science report by Bentzen et al.[20]

Additional Considerations Relevant to PENTEC

The following sections are intended to highlight some of the issues that affected our analysis and might affect how the PENTEC information is interpreted and applied in the clinic.

Radiobiologic basis for late normal-tissue toxicity in children

Tissue developmental dynamics include the ability for some individual cell types to achieve homeostasis through restorative cellular repair, along with tissue recovery from cellular repopulation driven by the proliferative capacity of stem cells. Radiation therapy can disrupt these processes, resulting in overt injury. In children, a mosaic of different tissues develops at different rates and in different temporal sequences. Broadly speaking, normal tissues with a high level of cellular proliferative activity and that are typically undifferentiated have increased vulnerability to radiation-associated injury. Moreover, as tissues age, they undergo progressive degenerative changes and gradually lose their proliferative homeostasis through various mechanisms, including apoptosis, loss of stem-cell regenerative capacity, and senescence, which can lead to tissue attrition.[21] Thus, aging can uncover subclinical injury related to previous RT. However, the extent to which injury is "remembered" by a tissue and not expressed until growth remains unclear. Thus, the sensitivity to radiation-induced injury and the timing of the clinical manifestation of this injury are complicated and remain uncertain.

The multifactorial nature of late effects is particularly critical in children

As depicted in Figure 1, host factors (especially age at treatment exposure), comorbid conditions that may develop subsequent to therapy (such as diabetes and hypertension), genetic polymorphisms or epigenetic regulation that can predispose patients to toxicities, tumor factors (eg, impaired organ function due to compression), treatment factors (eg, the surgical loss of a kidney in Wilms or toxic effects of therapy), treatment events (eg, severe acute infections), aging (ie, senescing tissues with reduced repair capacity), and health behaviors (eg, tobacco abuse or a sedentary lifestyle) may affect the risk for adverse events in survivors.

Assessing the effect of age on vulnerability to injury

Although we were unable to demonstrate a strong age dependence for many organs studied, this was perhaps because of the underpowered nature of our analysis and the dearth of data (rather than a true absence of effect). It is also possible that the effect of age was obviated by the older age at treatment for some cancers for which the toxicity endpoints were most relevant. A summary of observed age-related effects on late effect risks is provided in Table 3.

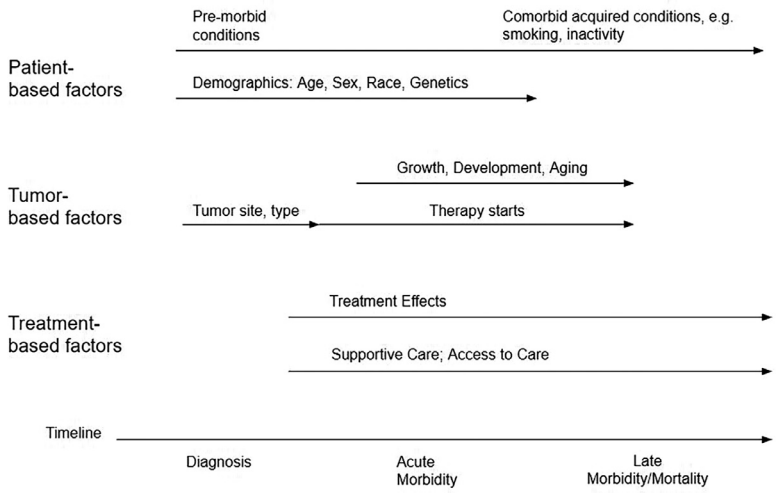

Fig. 1. Factors influencing morbidity and mortality in childhood cancer patients. Arrows indicate different factors exerting effects along the care continuum. The patient- and tumor-based factors are largely nonmodifiable, in contrast to the treatment-based factors. Adapted from Dixon et al.[22]

Assessing the effect of combined chemotherapy and RT on injury

Chemotherapy is a critical component in the treatment of almost all pediatric cancers. For some normal tissues, chemotherapy (either sequentially or concurrently) can dramatically affect the rate and severity of radiation-associated late effects via independent and/or additive (or even synergistic) effects. Indeed, for some of the organs considered in PENTEC, the investigators were able to quantify the added risk from chemotherapy. Furthermore, in some instances, chemotherapy alone (ie, without RT) can cause the same severity of toxicity that is often ascribed to RT. When sufficient information was available to assess the effects of chemotherapy-related factors, these factors were included in the organ-specific reports, and some of these are summarized in Table 4. In addition, other systemic therapies (eg, immunobiologics) may also contribute to adverse effects. However, the length of follow-up for patients treated with these newer agents is limited, so their effects could not be assessed in the PENTEC reports owing to the lack of relevant data. Similarly, surgery, either independently or combined with other therapies, may also cause late adverse effects, but the effects of surgery were not consistently addressed in the PENTEC reports.

Radiation parameters that may be particularly relevant to children

The response to radiation is often affected by the fraction of an organ exposed. In children, the effects of organ and patient motion and other technical uncertainties may be more relevant than in adults[24]; for example, field margins and penumbra may expose a larger portion of involved or adjacent normal tissues and thus have greater clinical effects on children versus adults. Therefore, technologies that aim to mitigate the effects of motion and setup errors might be particularly helpful in children. Similarly, the advantages of highly conformal radiation techniques may be especially important for children (particularly if the motion and setup issues are addressed); for example, intensity modulated RT often reduces the volume of normal tissue exposed to the target dose, and protons usually reduce the volume of normal tissue exposed to a lower dose.

Differential outcomes of different late effects: Life-threatening versus life-altering

We need to be mindful of the spectrum of the outcomes of different late effects. Some adverse effects can be life threatening (eg, subsequent malignancies, cardiopulmonary toxicities), some can be life altering (eg, impaired hearing, infertility, and neurocognitive compromise), and others can span these extremes (eg, obesity, short stature, some endocrinopathies that can lead to severe complications in aging survivors) (Fig. 2). In addition, even within some domains of late effects, such as subsequent malignancies, there is heterogeneity in terms of their cumulative incidence versus their effects on the associated years of life lost. In an elegant modeling study from Brodin et al[25] analyzing treatment planning images and competing craniospinal plans generated for 10 children with medulloblastoma, the projected lifetime cumulative risk of secondary breast and thyroid cancers exceeded that for lung and stomach cancers, but the projected life-years lost was substantially less, because breast and thyroid cancers are more treatable. When the cumulative incidence of specific life-threatening late effects (cardiac disease and various subsequent malignancies) was projected as a function of tissue volume and dose exposures from various radiation technologies (3D, volumetric modulated arc therapy, intensity modulated proton therapy), the potential

Table 3 Effect of age at treatment on the risks of toxicities among children and young adults

Younger age appears to increase vulnerability	Older age appears to increase vulnerability	No or uncertain effect of age
Neurocognition	Thyroid function (primary hypothyroidism)*	Brain radionecrosis
Musculoskeletal growth inhibition	Female reproduction (premature ovarian insufficiency and acute ovarian failure)	Necrosis after reirradiation of CNS tumors
Dentition		Hypothalamic-pituitary function outside of growth hormone
Growth hormone insufficiency (which affects development in younger children)		Optic neuropathy
Hearing		Salivary gland function
Cataract formation (possibly)		Myelopathy
Breast development		Pulmonary (pneumonitis)
Liver function after whole organ exposure		Renal dysfunction
Subsequent CNS meningiomas and sarcomas†		Male reproduction

Abbreviation: CNS = central nervous system.
* Hypothyroid risks appear to increase at ages older than 15 years, but this observation is somewhat confounded by differences in RT doses and chemotherapy use across different age ranges (see Milano et al[23] for details).
† Those assessed included CNS malignant tumors, meningiomas, sarcomas, and lung cancer.

Table 4 Organ-specific long-term effects of chemotherapy agents that affected radiation therapy toxic effects

Location	Observations	Quantification
Central nervous system	Neurocognitive compromise is augmented by methotrexate	Methotrexate is estimated to increase risk similar to 5.9 Gy additional uniform brain dose
Spinal cord myelitis	Intrathecal chemotherapy (primarily vincristine, methotrexate, cytarabine) appears to reduce spinal cord tolerance	Mean RT dose associated with myelopathy was 39.6 Gy in patients also treated with chemotherapy versus 49.7 Gy in those treated without chemotherapy ($P = .04$)
Heart	Anthracycline-associated CHF relatively greater than from RT	For each 100-mg/m^2 increase in cumulative anthracycline dose, hazard ratio for CHF is 1.93 (95% CI, 1.58-2.36), equivalent to 10.5-Gy increase in mean heart dose
Female reproduction	Effect of alkylators on AOF and POI is substantial	AOF risk (after 2 Gy): 1%-5%, CED = 10g/m^2 4%-7%, CED = 20g/m^2 6%-13% CED = 30g/m^2 with risks increasing with attained age POI risk at an attained age of 30 y: With CED = 0 <10 Gy, 17% >10 Gy, 83% After CED ≥ 20 g/m^2 <10 Gy, 53% >10 Gy, ∼100%
Genitourinary (kidney)	Ifosfamide negatively affects renal function	63 g/m^2 of ifosfamide results in an estimated 5% risk of severe toxicity in the absence of RT With ifosfamide, 10% risk of severe toxicity with V10 of 42% (vs 2% risk from RT alone)
Hearing	Exposure to platinum-based chemotherapies adds to the rates of hearing loss at a given cochlear radiation dose level	Cisplatin 300 mg/m^2 lowers "toxic RT dose" by ∼7 Gy
Subsequent malignancies	Anthracyclines and alkylators increase risks for subsequent sarcomas	Odds ratio for a subsequent sarcoma is ≈2 for both anthracyclines and alkylators

Abbreviations: AOF = acute ovarian failure; CED = cyclophosphamide equivalent dose; CHF = congestive heart failure; POI = premature ovarian insufficiency; RT = radiation therapy; V10 = percentage of volume ≥10 Gy.

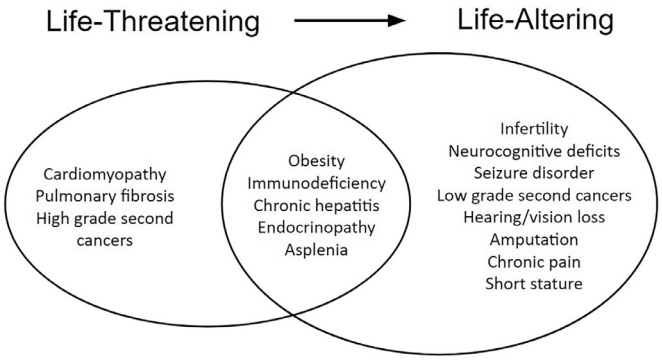

Fig. 2. Spectrum of effects (life threatening versus life altering), recognizing that specific treatment effects range from mild to fatal even within these categories.

for a reduction of projected life-years lost was reduced with more advanced techniques.

Because different toxicities have differential effects on the patient's quality of life, decisions must be made about the importance of 1 toxicity versus another (eg, with regard to severity, time course, etc) when evaluating competing treatment plans for an individual patient. Modern RT techniques are superior to older ones because they reduce the irradiated volume receiving relatively high doses, but in many cases, the tissue exposures are just redistributed rather than eliminated. Studies have been performed that compare the different radiation dose-risk estimations for various tissues, and others have compared the relative importance of these different risks,[26,27] but routine formal quantitative application of these results has not been actualized. Nevertheless, clinicians currently routinely make these semiquantitative tradeoffs during treatment planning. These decisions must often be made in the context of discussion with parents regarding their concerns about or acceptance of specific toxicities.

Interpreting the PENTEC reports and the associated predictive models presented for some organs

Some of our reports offer predictive models to estimate toxicity risks for pediatric patients. Certainly, caution is necessary in interpreting and applying models, because they often describe dose-volume parameters beyond the data used to generate the models. Particular care is needed when models are used to extrapolate to dosimetric regions beyond the available data or extrapolate to clinical settings beyond the available data (eg, based on chemotherapy use, age range at exposure, or duration of follow-up). In the following sections, we discuss the various challenges and considerations in interpreting the PENTEC reports. A comprehensive summary of the normal-tissue dose-response PENTEC modeling report by Hua et al[28] appears in this issue.

Heterogeneity and colinearity of demographic and treatment-related risk factors

Childhood cancer represents an umbrella term for multiple distinct neoplastic disorders affecting children and adolescents. There is wide variety regarding organs and tissues affected, the typical age window of occurrence, and numerous variations of treatment protocol combinations. Although this heterogeneity allows us to differentiate the adverse health outcomes associated with different subgroups, the typical clustering of all the aforementioned factors warrants caution when interpreting results of models presenting estimates of radiation-related risk based on pooled data from different settings, as were sometimes used in PENTEC. For example, the radiation-related risk of ovarian failure will vary substantially depending on the degree of alkylating agent exposure, and pooled estimates of radiation-related risk without adjustment of those with high and low alkylator dose (as was done in the PENTEC report) will mischaracterize the true risk for both groups. In addition, the relevant organs are small and their location is variable, severely hampering the precision and validity of retrospective dose estimation. Also, the evolution of treatment protocols over time, which vary across cancer types, will affect the interpretation of results by, for example, attained age and/or follow-up time. Contemporary treatment concepts, by definition, will not be reflected in risk estimates derived from previously treated patients, although under certain conditions, they can be applied to project potential long-term effects (pending accumulation of sufficient follow-up).

Similarly, it is important to highlight that the pooling of data from different sources can actually mask real dose-response relationships (often termed "Simpson's paradox"). This is discussed in detail in the introductory report from Bentzen et al,[20] and readers are strongly encouraged to be aware of this potential shortcoming.

Challenges in quantifying the risk of late effects

Determining the temporal emergence and risks of late effects in children is particularly difficult, because (1) patients must survive long enough for tissue injury to develop; (2) the number of patients who develop the specific late effect, as well as the number who do not, both affected and unaffected by therapy, must be known; and (3) the long latency period between treatment and the manifestation of damage compromises determination of the key treatment and the host factors most responsible. Thus, the risk estimates in some organ-specific reports and the summary table have large uncertainties. For a more detailed discussion of these issues, see the introductory paper by Bentzen et al.[20]

Unlike large, retrospective observational studies, which often treat RT as a binary yes-or-no exposure variable when calculating the relative risk, the PENTEC risk estimates relate to ranges of doses; moreover, these reports mainly represent observational studies in which radiation dose

estimation strategies were implemented. Ideally, these estimates were based on a dose range with enough samples in each of the component dose bins of interest to reliably fit the dose-response curve. For some organs, however, we lacked such heterogeneity in dose and dose distribution (ie, there were few or no data points in low- or high-dose bins, or the data were clustered around a certain dose), challenging the generation of a reliable dose-response curve. Furthermore, even when heterogeneous dose data are available, not knowing the distribution of doses within the dose bins leads to the potential error of assuming the mean dose for the bin matches the true mean bin dose (see the report by Olch et al[12]). In such cases, there can be significant uncertainty in the shape of the fitted curves. Of note, for some endpoints, older studies of high methodological quality, including adequate organ-dose estimations, allow for comparatively precise quantification of dose effects by taking into account the associations between multiple risk factors (confounders) on an individual level, to an extent not possible in the context of PENTEC's pooling averaged-out risk estimates per included study. If recommendations on study design and reporting as formulated by PENTEC and other organizations are implemented on a wider scale, individual patient data pooling will become possible for PENTEC follow-up efforts. This will effectively combine the strengths of both of these approaches. In addition, the uncertainties in the doses and endpoints were generally large and must be considered in the process of making decisions about the tradeoffs for late effects versus cure or tumor control. To add to the complexity, age, although ideally analyzed as a continuous variable, might by necessity (due to incomplete data) be considered with age groupings based on developmental status at the time of exposure. An example might be biologically based windows relating to female menopause, which affects the baseline risk of certain health conditions (eg, osteoporosis, cardiac disease, and certain hormone-sensitive cancers). See the report on modeling normal-tissue complications in this PENTEC issue.[28]

Importance of determining absolute risk and time-to-event modeling

Constructing treatment plans that balance the risk of complication with those of local or regional failure requires knowledge of the absolute risks for both of them. Given that complications of pediatric treatments can have very long intervals to onset, methods that account for time to event need to be used to model their risk. The most used method has been the Cox proportional hazards model. When results of Cox models were reported, the so-called "baseline hazard function," or $H_0(t)$ (required to convert the commonly reported hazard ratios into measures of absolute risks over time), was often missing in the published literature. Thus, because absolute risk estimates are most helpful in guiding clinical decisions and dosimetric constraints, studies that report only relative risks and not absolute risks are not typically used to generate dose constraints. The reporting and modeling issues involved are further discussed in several of the PENTEC introductory and visionary papers. Remarkably, despite this, some of the PENTEC organ-specific papers[29,30] have managed to derive measures of absolute risk, either by contacting authors to obtain missing $H_0(t)$ values or by estimating them from available information about unirradiated control groups.

Evolving fractionation schedules

In adults, hypofractionation (ie, the use of doses per fraction exceeding 2 Gy) is becoming much more widely applied, and this practice may limit the applicability of prior dose-volume-outcome data that were largely generated from patients receiving approximately 2 Gy/fraction. Hypofractionation has been used less often in children, largely due to concerns regarding the accuracy of total-dose adjustments required to retain the same the risk of late effects and/or tumor control with higher doses per fraction. The majority of information presented in PENTEC was generated from patients treated with "conventionally" fractionated schedules.

Comparison of dose-volume-outcome data in PENTEC compared with QUANTEC and HyTEC

Both QUANTEC and HyTEC advanced our understanding of radiation toxic effects in adults. PENTEC now extends this to younger patients. Milano et al[13] summarize the evolution of PENTEC and compare it to QUANTEC and HyTEC with respect to content, oversight, support, scope, and method of literature review and compare NTCP estimates in children versus adults. The NTCP comparisons in adults versus children are often confounded by marked differences in treatment paradigms that expose normal tissues to radiation (ie, cancer types, prescribed RT dose and fields, and chemotherapy agents used). In addition, because of the years needed to manifest the late effects that are so important in the pediatric population, delivery techniques available for analysis in PENTEC commonly went back to even pre-3D CRT dose constructions, in contrast to HyTEC and QUANTEC, which deal primarily with modern radiation planning and delivery techniques.

Future Directions

There is a clear need for a more robust approach to gather data systematically to better understand the dose-volume-effect relationships for radiation-associated normal-tissue injury in children (see the PENTEC report by Jackson et al[31] in this issue). To promote this, each of our reports includes a future directions section, and we recommend that the interested reader consider them. We herein suggest

a broad spectrum of directions that might move this field (late effects research and survivorship) forward.

1. Refine endpoint definitions and encourage use of standard toxicity scoring scales. The current version of the Common Terminology Criteria for Adverse Events (CTCAE) scoring system used in pediatric late effects is 5.0.[32] We encourage investigators to consistently use the most current CTCAE version. When major changes to the grading system would make it challenging to pool toxicity data from previous eras, it may be prudent to also score toxicities based on the older systems to facilitate pooling of data across studies.
2. Promote the adoption of standardized definitions of organs at risk (and their substructures) that facilitate their delineation for consistent dose-volume determinations. Atlas-based contouring has been shown to improve comparability between observers. It is possible that artificial intelligence-based autosegmentation tools may help to accomplish this in the future.
3. Improve and implement dose-volume metric reporting standards (eg, structure sets, nomenclature, DVH-based metrics [Vx, mean dose], dose calculation grids). Ultimately, the field should move toward sharing of full anonymized 3D dose matrices at the individual patient level.
4. Suggest data analyses and modeling recommendations for specific endpoints and refine and improve pediatric dose-response modeling by incorporating age at treatment, nonradiation treatment variables, and time-to-event analyses in addition to radiation dose and dose distribution for organs at risk.
5. Create systems to enable the pooling of data from multiple centers that can be managed, updated, and analyzed (eg, using standard methods and newer techniques such as artificial intelligence-based approaches). We encourage software companies to incorporate tools that enable the ready extraction of dose-volume data (eg, from RT planning tools) and that help clinicians to easily and accurately record or extract outcomes data (eg, into and from electronic health records).
6. Establish a "living" (ie, perpetually modifiable) resource of normal-tissue protection guidelines as a reference for new cooperative group trials (albeit with the caveat that exceeding a guideline-defined dose is often necessary and recommended to achieve tumor control) and gather trial-specific data to validate and refine PENTEC dose-volume-outcome estimates.
7. Consider the development of systems in which long-term survivors can record their own lifetime outcome data over time, update their personal reports and experiences (patient-reported outcomes), and upload medical reports, thereby providing analyzable data in a new way. Perhaps survivors will be motivated by their own experiences to support such an initiative. An implication of this is to encourage more collaboration between radiation oncology departments and survivorship programs.
8. Encourage international collaboration, including with low- and middle-income countries.
9. Work closely with medical oncology colleagues to capture data on the normal-tissue toxicities of both commonly used and newly emerging systemic agents (eg, chemotherapies and immunobiologics); partner with them to also capture data that address the interactive consequences of these systemic agents and RT.

Postscript

Ultimately, we seek to fulfill our obligation to our childhood patients and their families so that they can celebrate survival without the burden of chronic morbidities. Their lives and our lives are intertwined, and our motivation resides in enabling them to fulfill their dreams.

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