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Pediatric Normal Tissue Effects in the Clinic (PENTEC): An International Collaboration to Analyse Normal Tissue Radiation Dose–Volume Response Relationships for Paediatric Cancer Patients

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Abstract

With advances in multimodality therapy, childhood cancer cure rates approach 80%. However, both radiotherapy and chemotherapy can cause debilitating or even fatal late adverse events that are critical to understand, mitigate or prevent. QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) identified radiation dose constraints for normal tissues in adults and pointed out the uncertainties in those constraints. The range of adverse events seen in children is different from that in adults, in part due to the vulnerability/characteristics of radiation damage to developing tissues, and in part due to the typical body sites affected by childhood cancer that lead to collateral irradiation of somewhat different normal tissues and organs compared with adults. Many childhood cancer survivors have a long life expectancy and may develop treatment-induced secondary cancers and severe organ/tissue injury 10, 20 or more years after treatment. Collaborative long-term observational studies and clinical research programmes for survivors of paediatric and adolescent cancer provide adverse event data for follow-up periods exceeding 40 years. Data analysis is challenging due to the interaction between therapeutic and developmental variables, the lack of radiation dose–volume data and the fact that most childhood malignancies are managed with combined modality therapy. PENTEC (Pediatric Normal Tissue Effects in the Clinic) is a volunteer research collaboration of more than 150 physicians, medical physicists, mathematical modellers and epidemiologists organised into 18 organ-specific working groups conducting a critical review and synthesis of quantitative data from existing studies aiming to: (1) establish quantitative, evidence-based dose/volume/risk guidelines to inform radiation treatment planning and, in turn, improve outcomes after radiation therapy for childhood cancers; (2) explore the most relevant risk factors for toxicity, including developmental status; (3) describe specific physics and dosimetric issues relevant to paediatric radiotherapy; and (4) propose dose–volume outcome reporting standards for publications on childhood cancer therapy outcomes. The impact of other critical modifiers of normal tissue radiation damage, including chemotherapy, surgery, stem cell transplantation and underlying genetic predispositions are also considered. The aims of the PENTEC reports are to provide clinicians with an analysis of the best available data to make informed decisions regarding radiation therapy normal organ dose constraints for planning childhood cancer treatment, and to define future research priorities.
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Key words: Late effects; paediatric cancer; PENTEC; radiation therapy; survivorship; treatment guidelines

Every child begins the world again
(Henry David Thoreau)

Introduction

Although the cellular and subcellular effects of ionising radiation are identical in adults and children, the tissue remodelling and functional consequences of radiation injury differ markedly. The fibrotic–atrophic pathway dominates the radiation pathogenesis of late normal tissue

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effects across the age range [1]; what is unique to children, however, is that this pathway interferes with growth and tissue maturation and may result in hypoplasia and hypofunction [2]. This gives rise to a marked dependence for the risk and severity of these effects as a function of the child's age (a surrogate for development) at the time of irradiation [3]. Additionally, the long latent period for many of these effects also creates a dependency of risk as a function of attained age. In a report from the Childhood Cancer Survivor Study, the 30-year cumulative incidence for severe (grade 3) or disabling/life-threatening (grade 4) conditions or death (grade 5) due to a chronic condition was 42% [4]. In another report from this same cohort study, the 30-year cumulative mortality was 18% among long-term survivors; radiotherapy increased the risk 2.2-fold [5]. Overall, 60–90% of childhood cancer survivors will develop one or more chronic health conditions, and 20–80% will experience severe or life-threatening complications [6–8].

The challenge for clinicians is to devise therapy that can simultaneously optimise health-related quality of life and maximise the child's life expectancy. In fact, it is the late adverse effects of treatment that have driven the evolution of therapies for many childhood curable cancers. Unfortunately, many paediatric malignancies require an aggressive treatment approach that often causes a substantial risk of late adverse effects. Thus, the potential to ameliorate or prevent such normal tissue damage, or to manage and rehabilitate affected patients, requires an understanding of normal tissue tolerances to radiation and systemic therapy across the age spectrum. This is affected by the total and fractional dose of radiation, the dose rate, overall treatment time, radiation modality and radiation dose distribution [9]. Cytotoxic or molecular targeted agents may have a direct effect on normal tissue injury, but in addition may interfere with radiation damage induction and processing. PENTEC (Pediatric Normal Tissue Effects in the Clinic) seeks to unravel this conundrum by exploring and defining normal tissue tolerance in developing children as a function of radiation dose/volume, type and scheduling of chemotherapy, and surgery. This information can ideally be used to inform radiation oncologists, patients and parents on the risk–benefit of multimodality therapy involving radiation therapy, define treatment planning radiation dose constraints and propose new research directions. PENTEC has three main objectives:

- To establish quantitative evidence-based dose/volume guidelines to inform treatment planning and potentially improve outcomes for survivors of radiation therapy for childhood cancers;
- To appreciate clinical, dosimetric and modelling complexities that are important to paediatric radiation therapy;
- To recognise the special considerations for normal tissue radiation response of children/adolescents, e.g. the interplay between development and radiotherapy effects, and the impact of other risk factors such as systemic therapies.

Physics Considerations

Most of the published literature reviewed by the PENTEC work groups reports outcomes in children treated before the computed tomography treatment planning era. In these studies, it is common for reported doses to be those prescribed to the tumour, rather than doses to adjacent critical normal tissues. When normal-tissue doses are reported, uncertainties resulting from a lack of three-dimensional planning need to be considered, such as hand calculation-based planning often to a single reference point. Correction for tissue homogeneity was only carried out in the recent two decades; therefore, previously reported doses might be somewhat under- or over-estimated. Much higher levels of uncertainty should be expected when organs are located out of field or in the penumbral regions, such as the gonads or the lens. Even when the treatment fields were designed to include the entire structure, such as vertebral bodies, this target may not have received a uniform dose simply because of the rapid dose fall-off of electron and orthovoltage beams commonly used before the 1980s. In a minority of cases, the organ dose has been retrospectively reconstructed based on computational phantoms of varying complexity aided by a review of patient treatment records [10,11]. These tend to be the basis for large-scale epidemiology studies that group organ doses into wide bins. Nonetheless, a number of quantitative late effect studies have analysed continuous dose metrics to assess the shape of the dose–response curve, taking advantage of rich treatment and outcome data collection [12]. When organ doses were not reported, and treatment methods were not sufficiently described, then it is necessary to assume common field arrangements for the era in which the patient was treated, and this may lead to dosimetric inconsistencies that are difficult to quantify. The physicist members of each working group were tasked to participate in the review of the papers used in the modelling of the dose–response data to provide guidance on interpretation of the stated doses. PENTEC task forces and future late effect studies are encouraged to clearly state the methodology and assumptions made in estimating the organ doses as well as how this affects derived dose–volume constraints.

With the advent of three-dimensional computed tomography-based treatment planning, prospective archival registration of patient dose–volume histograms and centralised storage of Digital Imaging and Communications in Medicine (DICOM)-based treatment plans is increasingly advocated. The advantages of the latter include the possibility to re-contour organs at risk and/or to add contours of tissues that previously were not considered of prime interest in treatment planning. Widespread use of three-dimensional conformal and other multibeam techniques did not occur until after 1990; therefore, large-scale studies addressing side-effects after 30 or 40 years of follow-up will not be available soon. Extrapolations from risk measures derived from older cohorts treated with other techniques resulting in different dose distributions across an organ will remain important for at least another two decades while the 'modern radiotherapy' survivor cohorts mature [13].

Epidemiological Considerations

Epidemiological studies are a cornerstone to increase our knowledge on the impact of ionising radiation on human health [14,15]. The late G. D'Angio, a paediatric radiation oncologist, introduced such study designs to investigate the side-effects among children treated for cancer [16]. Several existing large-scale cohort studies provide knowledge on radiation-related side-effects among children, adolescents and young adults spanning over four decades of follow-up for those treated in the 1970s and 1980s. Comparatively few clinical trials randomise radiotherapy dose schedules, let alone trials comparing old and newly developed technology for radiotherapy. Nonetheless, opportunities to study side-effects of radiotherapy beyond 90 days after initial treatment based on clinical trials are increasingly available.

Large-scale retrospective cohort studies, including hundreds or even several thousands of 1-, 2- or 5-year childhood cancer survivors typically involve retrospective registration of treatment characteristics to a varying degree of detail (and completeness), whereas smaller-scale efforts typically allow for a more in-depth characterisation of treatment per individual; short-term side-effects cannot be studied here. For the pre-millennium era, in-depth studies rely on retrospective radiation dose reconstruction, using two-dimensional simulation films and radiotherapy treatment charts as a basis to derive mean organ doses, or, in nested case–control studies, to estimate the radiation dose received by the tissue that later developed a second tumour or adverse normal tissue effects [17,18].

Modelling Considerations

Normal tissue complication probability modelling applies a relatively well-defined set of statistical tools. What is typically modeled is the probability (or incidence in a group of patients) of a dichotomous (binary or yes/no) endpoint as a function of dose and volume; adjustments can also be made for patient-level risk factors or other treatment modalities. Central to this is a sigmoidal dose response curve, frequently assumed to follow a logistic or, in case of the Lyman model, a probit dose-response relationship [19]. Analysis of late end points require an analytical method that takes latent time and censored observations into account and this is often accomplished using the Cox proportional hazards model or in some studies a mixture model [20,21]. In general, it is necessary to model both the effect of follow-up time since treatment as well as attained age. In some situations, attained age has been used as the underlying time scale, rather than follow-up time [22]. In terms of reporting the outcome of a Cox model analysis, it is desirable to report the baseline hazard function in addition to the estimated hazard ratios. This will allow assessment of the progression of the dose response of toxicity over time. Note though, that the proportional hazards assumption may or may not be fulfilled for a given end point. This assumption should be tested to evaluate whether this model is an adequate description of risk–time relationships.

This data analytical framework is not always a good fit for the end points of relevance in childhood cancer survivors, largely for two reasons. First, because of continuous growth and development in childhood cancer survivors, modelling the probability of exceeding a threshold effect size (i.e. dichotomising the outcome) represents a loss of information when the end point is naturally represented as a continuous (scale) variable, e.g. retardation of bone growth [23], intelligence quotient decline [24] or endocrine function [25]. In these cases, a more adequate description may be obtained from considering the actual value at a given time point as a function of dose, age or other variables. In the case of serial observations, the measurements at different time points will not be independent and this must be taken into account in the modelling approach. Second, many of the late morbidities associated with childhood cancer therapy are not specific to treatment. Examples could be cardiovascular events evaluated as valvular dysfunction or acute coronary events, or second solid malignancies. These events will also occur with a given probability in external (non-cancer survivor) controls. In this case it is more informative to consider the excess absolute risk or the excess relative risk of developing the morbidity at a given attained age. Again, multivariable models may be used, which allows for the consideration of covariates.

When individual-level dose assessment is available, the linear-quadratic model is often applied to adjust for dose–time fractionation [12,14]. Adjustment for patient characteristics or other treatment modalities in multivariable models and, where relevant, stratified analyses, is key owing to the importance of these variables for risk estimation. This relates to the increasing number of side-effects from chemotherapeutic agents and their additive or synergistic effects with radiation that are being recognised and the fact that demographic and treatment details are far from being uniformly distributed in a childhood cancer survivorship cohort [26].

Reports of paediatric late effects often have a relatively small sample size, may have heavy censoring, i.e. relatively short follow-up in many patients, or may not have accurate individual organ doses. PENTEC researchers face the dilemma of whether to exclude those data that probably underestimated the incidence of morbidity or have a significant uncertainty in estimated doses.

Infants and young children may require specific toxicity evaluations to capture effects on cognitive ability and cooperation. An example is the use of auditory brainstem response and optoacoustic emissions for evaluating hearing of younger children and pure-tone air conduction testing for older children. When test methods and toxicity scales change during long-term follow-up, care should be taken to minimise the influence of such changes in model fitting. Another source of variability arises from variation in the selection of end points and toxicity grading instruments adopted by different institutions. Judgement should be exercised in determining if models built based on synthesised data are reliable given the heterogeneity, and if

they contradict empirical experience. When modelling toxicity for paired organs, such as ovaries, cochlea and kidneys, one should consider if the radiation effect can be assessed per organ, and measures of organ function in the literature reports to be synthesised are consistent with each other. Glomerular filtration rate for kidney function is an example of a test where it is difficult to tease out the effect of differential irradiation to paired organs.

Data Identification and Abstraction Methodology

Like its predecessor QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) [27], the PENTEC collaboration aims to provide a comprehensive overview of the published literature on long-term side-effects of radiation therapy for cancer in children and adolescents and to derive guidance for current and future clinical practice on the dose–volume–risk relationship for several organs at risk. Given the potential impact of these findings on care for individual patients, adequate methodology and critical appraisal of available data is required.

The PENTEC Core Group thus proposed a standardised methodology to identify, select and evaluate eligible evidence. The methods were based on the experience with systematic review development within the Cochrane Childhood Cancer Group [28] and with clinical guideline development [29]. A systematic review summarises the evidence on a specific subject in a transparent and reproducible manner.

PENTEC uses a four-step approach for identification and extraction of data for each organ-specific report. Each working group (task force) prepared a protocol with support from Core Group members with experience in systematic reviews, guideline development and epidemiology (LK, CMR). First, relevant clinical questions were formulated, e.g. 'What is the association between radiation dose/volume and impaired spermatogenesis, defined as azoospermia and oligospermia, in male childhood cancer survivors treated with radiotherapy involving the testes?' (Figure 1). For each clinical question, a so-called PICO was established, unequivocally defining four elements of eligible research findings: P = patient, I = intervention; C = comparison; O = outcome. Second, based on the PICOs, the Cochrane Childhood Cancer Group together with the individual task force leaders developed a literature search in an iterative process. Then each of the four elements of the PICO was translated into standardised terms that could be entered in a PubMed search combined by AND or OR (Figure 2). Most searches were of the form: #Radiotherapy AND #Childhood Cancer (4) AND #<specific outcome>. The exceptions were the clinical questions for total body irradiation as a conditioning for haematopoietic stem cell transplantation where the intervention (I) was defined more specifically compared with the standardised radiotherapy search term developed for other chapters. The expert task force leader was consulted at least once during the building of the final search definition, to allow for further adaptations. Generally, a balance was necessary between overly specific search terms, resulting in a few hundred potentially eligible titles, but missing several relevant reports, versus a rather general search that captures thousands or tens of thousands of reports. Third, a set of initial inclusion and exclusion criteria for eligible research studies were defined, based on study design (e.g. no case reports), patient groups (e.g. maximum proportion of adults in a study), radiation assessment definition (depending on preferences of the respective task force and availability of evidence that greatly varies across health outcomes); and outcomes. Also, some groups chose to limit eligible reports to English only, depending on foreign language proficiency of their respective group members, and most groups limited the eligibility to reports published in recent decades only (Figure 3). Fourth, the data were abstracted and general aspects of the quality of studies, such as selection bias or follow-up bias, were assessed by one or two task force members, using model data extraction and coding forms where needed with organ-specific extensions or modifications to suit the goals of the respective task force. Finally, data analysis, including descriptive synopsis of the most relevant reports and, where possible, meta-analysis, will be undertaken. The analyses are currently in progress. The final compendium of reports will include a series of introductory reviews that discuss relevant methodological issues (Table 1) and 'visionary' reviews that look to the future (Table 2). The organ-specific reports will discuss a spectrum of critical elements inherent to fulfilling the objectives of PENTEC (Table 2). The organ-specific teams and leaders are denoted in Table 3; the PENTEC core committee members are detailed in Table 4.

For example, for the report on male reproductive system, one of the clinically-relevant side effects is related to androgen deficiency and spermatogenesis. The precise research questions of interest can then be defined as:

- "What is the association between radiation dose/volume and the risk of androgen deficiency, defined as low testosterone and/or high FSH, in male childhood cancer survivors treated with radiotherapy involving the testes?
- "What is the association between radiation dose/volume and impaired spermatogenesis, defined as azoospermia and oligospermia, in male childhood cancer survivors treated with radiotherapy involving the testes?

There may be studies that describe the clinical outcome in terms of inhibin B levels; It should be discussed within the author group if these studies should be included. Within the International Guideline Harmonisation Group (IGHG) for surveillance of childhood cancer survivors (www.ighg.org), we decided that these studies will not be included because this measure was shown not to be a suitable surrogate marker of sperm concentration (Green et al, 2013)..These examples are meant to serve as proposals that should be discussed in the organ-specific working groups.

Fig 1. Example research question.

Radiotherapy AND Childhood Cancer AND Hearing Loss

Definitions

1. Childhood cancer
(((leukemia OR leukemi* OR leukaemi* OR ALL OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology)) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia lymphocytic acute) OR (leukemia, lymphocytic, acute[mh])

2. Radiotherapy
radiometry OR radiation dosage OR radiation dose OR radiation doses OR radiation dosis OR radiation dosage* OR radiation dosimetry OR radiation dosimetr* OR dose-response relationship, radiation OR radiometr* OR radiotherapy dosage OR radiotherapy[sh] OR radiotherapy/adverse effects OR irradiation dose OR radiotherapy dose OR dose calculation OR near beam dose OR in beam dose OR outside beam dose OR out of beam dose OR radiation/epidemiology OR Radiation monitoring OR Organs at risk OR radiation effects[sh] OR radiation injury OR radiation injuries OR radiation OR Radiotherapy/complications[Mesh] OR NCTP OR normal tissue complication probability OR DVH OR Dose Volume Histogram OR Radiotherapy Planning OR Conformal/adverse effects OR Dose Response Relationship, radiation OR Organs at Risk/Radiation Effects OR Radiation Injuries/Prevention and Control OR Chemoradiotherapy/Adverse Effects

Example outcome:

3. Hearing Loss
Deafness OR hearing loss OR Loss, Hearing OR hearing disorder OR hearing disorders OR auditory OR hearing impairment OR hearing impairments OR hearing impairment* OR heari* OR audiology OR audiologic OR audiometry OR audiometr* OR audiogram OR audiography OR ototoxicology OR ototoxic* OR hypoacusis OR hypoacuses OR hypoacus* OR ototoxicity OR deaf* OR cochleotoxicity

Result in Pubmed (Sept 23,2013): n=544 reports fulfill these criteria, and are therefore eligible for title/abstract screening

Fig 2. Example PubMed search strategy.

Summary: Challenges, Needs, Hurdles, Knowledge Gaps

PENTEC has revealed a multiplicity of challenges in exploring and defining normal tissue tolerances in developing children as a function of radiation dose/volume, chemotherapy and surgery. This information could inform individual radiation oncologists regarding tolerance doses, inform protocols regarding radiation dose constraints, and envision research directions. However, PENTEC has identified several hurdles to surmount:

- Inadequate data on the organ developmental changes that alter tissue radiation effects, and shortcomings of existing models.
- Inadequate data on the association of radiation dose/volume/fraction size and other parameters that impact radiation sensitivity to injury.
- Inadequate consideration of confounding factors (surgery, chemotherapy, pre-existing conditions) in decision-making on radiation dose–volume fractionation choices.
- Inadequate data analytical methods and insufficient reporting of modelling results.
- Inadequate patient-level dosimetry for relevant organs at risk.

Selected examples of more specific knowledge gaps are:

1. Age dependence of dose tolerances for most organs; for some we have excellent data but for most we have huge data deficiencies.
2. The influence of chemotherapy (agents, doses) on radiotherapy dose tolerance for many organs.
3. For many paediatric organ systems, we lack data on plasticity/compensatory potentials following injury.

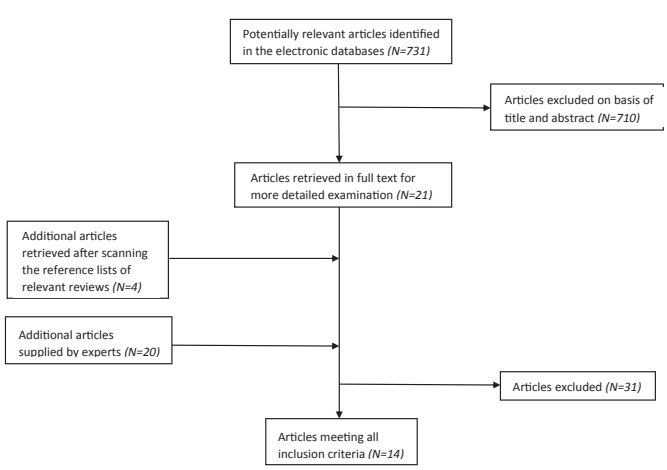

Fig 3. Example flow diagram to show included and excluded studies.

Table 1
Introductory and visionary reports

Introductory reports	Visionary reports
Introduction to scientific issues	Methodology for accurate data acquisition of radiation dose data
Summary of paediatric NTCP data and models	Biomarkers and surrogate end points
Paediatric bio-developmental considerations	Paediatric imaging issues
Paediatric physics aspects	Secondary malignancy as impacted by evolution of technology
Epidemiological considerations	Recommendations for reporting and gathering data—to co-operative groups
Improving NTCP and modelling in paediatrics	Future directions
Contrasting PENTEC versus QUANTEC	

NTCP, normal tissue complication probability; PENTEC, Pediatric Normal Tissue Effects in the Clinic; QUANTEC, Quantitative Analysis of Normal Tissue Effects in the Clinic.

Table 2
Sections within each organ-specific report

Required sections	Content
Anatomy and developmental dynamics	•Define anatomy as it impacts normal tissue damage •Describe anatomic and physiological development according to age as it impacts organ sensitivity to damage and repair
Clinical significance	•Describe the clinical situations where the organ is irradiated •Describe the frequency, characteristics, significance of injury
End points and toxicity scoring	•Address strengths and limitations of existing systems •Recommend how to score organ injury •Describe the different end points often considered when assessing injury •Describe the time course of organ injury
Challenges defining volumes: paediatric imaging issues	•Describe recommended imaging modality and acquisition methods •Discuss the impact of intra-/inter-fractional organ movement or volume change during the course of treatment •Discuss the need for contouring planning organ at risk volumes •Note normal organ contouring atlases or reference existing publicly available atlases
Review of dose–volume response data/risk factors	•Review of dose–volume data: for each organ (tissue), published data on toxicity risks as correlated with dosimetric parameters and other relevant variables (i.e. age, developmental status), are reviewed. From the available data, meaningful dose/volume limits with associated risk rates are presented. Include data on various dose fractionations, adequacy, quality and bias. •Dose–volume end points: –Organ function: laboratory/subclinical end points, imaging end points, physiological/functional issues –Organ development: impact of age –Second malignant neoplasms: volume, dose •Risk factors: genetic predispositions, gender, race, age, co-medical conditions •Chemotherapy/combined modality: relevant chemotherapy data impacting radiation sensitivity •Mathematical/biological models + epidemiological issues: for each organ, models that have been used to relate dose/volume data to normal tissue complications and second malignancies in the organ are summarised, together with associated model parameters, limitations and uncertainties •Recommended dose/volume limits: the available information is condensed into meaningful dose/volume limits, with associated risk rates, for clinical application. Limits are according to end points and age. •Level of evidence: specify for each report •Special situations: situations where the presented data/models may not apply (e.g. hypofractionation)
Toxicity scoring recommendations	•Recommendations on how to score organ injury and toxicities
Interventions and management	
Contrast paediatric and adult NTCP data	
Future investigations	•Describes areas in need of future study

NTCP, normal tissue complication probability.

Table 3
PENTEC working groups

Organ	Principal investigator
Central nervous system	Anita Mahajan, MD
Head and neck	Arnold Paulino, MD
Cerebrovascular	Shannon MacDonald, MD
Endocrine	Gregory Wheeler, MBBS, FRANZCR
Hearing	Torunn Yock, MD
Ocular	Stephanie Terezakis, MD
Thyroid	Michael Milano, MD, PhD
Pulmonary	Mary Frances McAleer, MD, PhD
Breast	Karen Marcus, MD
Cardiovascular	David Hodgson, MD, MPH, FRCPC
Gastrointestinal and hepatic	Julie Bradley, MD
Genitourinary	Matthew Poppe, MD
Male reproductive system	Bradford Hoppe, MD, MPH
Female reproductive system	Christine Hill-Kayser, MD
Musculoskeletal/integument	Natia Esiashvili, MD
Spinal cord	Nadia Laack, MD
Second malignancies	Kenneth Roberts, MD
Stem cell transplantation (total body irradiation)	Kathryn Dusenbery, MD
Re-irradiation	Thankamma Ajithkumar, MD

Table 4
PENTEC core committee

Name	Affiliation
Louis S. Constine, MD, FASTRO, FACR	University of Rochester
Soren Bentzen, DSc, PhD, FASTRO	University of Maryland School of Medicine
David Hodgson, MD, MPH	University of Toronto
Rebecca Howell, PhD	M.D. Anderson
Chia-Ho Hua, PhD	St Jude Children's Research Hospital
Melissa Hudson, MD	St Jude Children's Research Hospital
Andrew Jackson, PhD	Memorial Sloan-Kettering Cancer Center
Leontien Kremer, MD, PhD	Emma Children's Hospital/AMC, Amsterdam
Karen Marcus, MD, FACR	Dana Farber Cancer Institute
Lawrence Marks, MD	University of North Carolina
Michael Milano, MD, PhD	University of Rochester
Arthur Olch, PhD, FAAPM	University of Southern California Keck School of Medicine and Children's Hospital Los Angeles
Cecile Ronckers, PhD	Emma Children's Hospital/AMC, Amsterdam
Jackie Williams, PhD	University of Rochester
Ellen Yorke, PhD	Memorial Sloan-Kettering Cancer Center

4. Role of known behavioural risk factors (e.g. smoking, obesity, nutrition, etc.) on radiation-related adverse events (e.g. cardiac, pulmonary, some Second Malignant Neoplasms (SMN), etc.).
5. Dose–response associations for long-term (>10 years .. >20 years … >30 years) risk of almost all of the PENTEC outcomes.
6. Retreatment dose tolerances.
7. For most organs, substructures exist and for these we lack data on dose tolerance, much less the impact of volume (i.e. the entirety of the substructure versus a portion of that substructure). Examples include:
    a. Normal brain substructure tolerances such as the hippocampus, corpus collosum.
    b. Specific cardiac substructures (chambers, valves) and coronary arteries.
    c. Individual and joint roles of cardiac, carotid artery and cerebral vessel radiation exposure on cerebrovascular accident risk.
8. Role of hormonal exposures (either intrinsic deficiencies or external exposures) on the probability of developing organ-specific SMN (in particular hormone-receptor positive tumours).
9. The timing of exposures during the years of development and puberty on bone hypoplasia.
10. Relevance of low-dose exposures versus peak or mean doses on SMNs.
11. Normal tissue tolerances after particle therapy, acknowledging the immaturity of the follow-up data available to address this.
12. Besides exposure assessment for radiotherapy, there is a great need for clear, clinically relevant definitions of health outcomes, and well-described methods to

ascertain health outcomes in the reality of clinical practice, insurance programmes, funding for research and data protection laws [13].

Although PENTEC will address some of these (and multiple other) knowledge gaps, many of these clinically and scientifically important issues will await future investigations.

Conclusions

Advances in radiation therapy and chemotherapy have markedly increased the survival rate for almost all paediatric malignancies. Unfortunately, these treatment modalities on their own or in combination may result in long-term adverse outcomes that may affect the individual's quality of life. Therefore, it is essential to balance the benefits against risks. Both length of survival and the impact of late normal-tissue effects on the quality of that survival must be considered in therapy decision-making. Although the range of adverse effects is well described, the quantitative dose–volume–effect estimates for their generation must be better defined, as well as the impact of risk/patient factors such as developmental status and genetic susceptibility. Other therapeutic factors are also critical to explore; chemotherapy may enhance radiation effects, and very little is known about the evolving use of immunotherapy and how these agents interact with other treatments, including radiation. Thus, the optimal use of radiation therapy in multimodality therapy that can cure children with cancer requires a better understanding of the adverse consequences of all treatment modalities. Finally, new patterns of late morbidity and mortality may emerge as survivors continue to age, and it is only through continued study that such patterns will be identified and interventions for treatment and prevention of adverse effects can be designed. These are the gaps that PENTEC seeks to elucidate and potentially fill.

The PENTEC investigators are gratified to play a role in refining and enhancing the role of radiation therapy in safely and effectively treating paediatric malignancy, and we dedicate our efforts to all future children who will be affected by this malady.

Conflict of interest

The authors declare no conflict of interest.

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References

[1] Bentzen SM. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. *Nat Rev Cancer* 2006;6:702–713.
[2] Krasin MJ, Constine LS, Friedman DL, Marks LB. Radiation-related treatment effects across the age spectrum: differences and similarities or what the old and young can learn from each other. *Semin Radiat Oncol* 2010;20:21–29.
[3] Paulino AC, Constine LS, Rubin P, Williams JP. Normal tissue development, homeostasis, senescence, and the sensitivity to radiation injury across the age spectrum. *Semin Radiat Oncol* 2010;20:12–20.
[4] Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, *et al*. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006;355:1572–1582.
[5] Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL, *et al*. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol* 2009;27:2328–2338.
[6] Geenen MM, Cardous-Ubbink MC, Kremer LC, van den Bos C, van der Pal HJ, Heinen RC, *et al*. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 2007;297:2705–2715.
[7] Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, *et al*. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA* 2013;309:2371–2381.
[8] Bhakta N, Liu Q, Ness KK, Baassiri M, Eissa H, Yeo F, *et al*. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). *Lancet* 2017;390:2569–2582.
[9] Cohen L, Creditor M. Iso-effect tables for tolerance of irradiated normal human tissues. *Int J Radiat Oncol Biol Phys* 1983;9:233–241.
[10] Stovall M, Weathers R, Kasper C, Smith SA, Travis L, Ron E, *et al*. Dose reconstruction for therapeutic and diagnostic radiation exposures: use in epidemiological studies. *Radiat Res* 2006;166:141–157.
[11] Lee C, Jung JW, Pelletier C, Pyakuryal A, Lamart S, Kim JO, *et al*. Reconstruction of organ dose for external radiotherapy patients in retrospective epidemiologic studies. *Phys Med Biol* 2015;60:2309–2324.
[12] Sigurdson AJ, Ronckers CM, Mertens AC, Stovall M, Smith SA, Liu Y, *et al*. Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case–control study. *Lancet* 2005;365:2014–2023.
[13] Newhauser WD, Berrington de Gonzalez A, Schulte R, Lee C. A review of radiotherapy-induced late effects research after advanced technology treatments. *Front Oncol* 2016;6:13.
[14] Hawkins MM, Wilson LM, Burton HS, Potok MH, Winter DL, Marsden HB, *et al*. Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. *J Natl Cancer Inst* 1996;88:270–278.
[15] Boice Jr JD, Blettner M, Kleinerman RA, Stovall M, Moloney WC, Engholm G, *et al*. Radiation dose and leukemia risk in patients treated for cancer of the cervix. *J Natl Cancer Inst* 1987;79:1295–1311.
[16] Breslow NE, Norkool PA, Olshan A, Evans A, D'Angio GJ. Second malignant neoplasms in survivors of Wilms' tumor: a report from the National Wilms' Tumor Study. *J Natl Cancer Inst* 1988;80:592–595.

[17] Stovall M, Donaldson SS, Weathers RE, Robison LL, Mertens AC, Winther JF, *et al*. Genetic effects of radiotherapy for childhood cancer: gonadal dose reconstruction. *Int J Radiat Oncol Biol Phys* 2004;60:542–552.

[18] Alziar I, Bonniaud G, Couanet D, Ruaud JB, Vicente C, Giordana G, *et al*. Individual radiation therapy patient whole-body phantoms for peripheral dose evaluations: method and specific software. *Phys Med Biol* 2009;54:N375–N383.

[19] Bentzen SM, Tucker SL. Quantifying the position and steepness of radiation dose-response curves. *Int J Radiat Biol* 1997; 71:531–542.

[20] Bentzen SM, Thames HD, Travis EL, Ang KK, Van der Schueren E, Dewit L, *et al*. Direct estimation of latent time for radiation injury in late-responding normal tissues: gut, lung, and spinal cord. *Int J Radiat Biol* 1989;55:27–43.

[21] Tucker SL, Dong L, Bosch WR, Michalski J, Winter K, Mohan R, *et al*. Late rectal toxicity on RTOG 94-06: analysis using a mixture Lyman model. *Int J Radiat Oncol Biol Phys* 2010;78: 1253–1260.

[22] Yasui Y, Liu Y, Neglia JP, Friedman DL, Bhatia S, Meadows AT, *et al*. A methodological issue in the analysis of second-primary cancer incidence in long-term survivors of childhood cancers. *Am J Epidemiol* 2003;158:1108–1113.

[23] Silber JH, Littman PS, Meadows AT. Stature loss following skeletal irradiation for childhood cancer. *J Clin Oncol* 1990;8: 304–312.

[24] Merchant TE, Kiehna EN, Li C, Shukla H, Sengupta S, Xiong X, *et al*. Modeling radiation dosimetry to predict cognitive outcomes in pediatric patients with CNS embryonal tumors including medulloblastoma. *Int J Radiat Oncol Biol Phys* 2006; 65:210–221.

[25] Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int J Radiat Oncol Biol Phys* 2005;62:738–744.

[26] Teepen JC, van Leeuwen FE, Tissing WJ, van Dulmen-den Broeder E, van den Heuvel-Eibrink MM, van der Pal HJ, *et al*. Long-term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER study cohort: role of chemotherapy. *J Clin Oncol* 2017;35: 2288–2298.

[27] Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, *et al*. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* 2010;76:S3–S9.

[28] Cochrane childhood cancer. Available at: https://childhoodcancer.cochrane.org/.

[29] Kremer LC, Mulder RL, Oeffinger KC, Bhatia S, Landier W, Levitt G, *et al*. A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Pediatr Blood Cancer* 2013;60:543–549.