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PENTEC INTRODUCTORY REVIEW

Comparison of Risks of Late Effects From Radiation Therapy in Children Versus Adults: Insights From the QUANTEC, HyTEC, and PENTEC Efforts

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Pediatric Normal Tissue Effects in the Clinic (PENTEC) seeks to refine quantitative radiation dose-volume relationships for normal-tissue complication probabilities (NTCPs) in survivors of pediatric cancer. This article summarizes the evolution of PENTEC and compares it with similar adult-focused efforts (eg, Quantitative Analysis of Normal Tissue Effects in the Clinic [QUANTEC] and Hypofractionated Treatment Effects in the Clinic [HyTEC]) with respect to content, oversight, support, scope, and methodology of literature review. It then summarizes key organ-specific findings from PENTEC in an attempt to compare NTCP estimates in children versus adults. In brief, select normal-tissue risks within developing organs and tissues (eg, maldevelopment of musculoskeletal tissue, teeth, breasts, and reproductive organs) are primarily relevant only in children. For some organs and tissues, children appear to have similar (eg, brain for necrosis, optic apparatus, parotid gland, liver), greater (eg, brain for neurocognition, cerebrovascular, breast for lactation), less (ovary), or perhaps slightly less (eg, lung) risks of toxicity versus adults. Similarly, even within the broad pediatric age range (including adolescence), for some endpoints, younger children have greater (eg, hearing and brain for neurocognition) or lesser (eg, ovary, thyroid) risks of radiation-associated toxicities. 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 radiation therapy dose and fields, and chemotherapy agents used). To add to the complexity, it is unclear if age is best analyzed as a continuous variable versus with age groupings (eg, infants, young children, adolescents, young adults, middle-aged adults, older adults). Further work is needed to better understand the complex manner in which age and developmental status affect risk.

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Introduction: Evolution of Pediatric Normal Tissue Effects in the Clinic

Pediatric Normal Tissue Effects in the Clinic (PENTEC) seeks to explore and advance our understanding of radiation-related toxicity in children. A natural implication of this body of work is to question how adverse events of radiation therapy in children compare with those in adults.[1] In this article, we provide a synopsis of the study of radiation-related toxicity over the past few decades and summarize key findings of dosimetric correlates to normal-tissue complication probability (NTCP) from the individual PENTEC reports, compared with similar measures in adults.

With the advent of 3-dimensional (3D) conformal radiation therapy in the 1980s to 1990s, and later, the development of intensity modulated radiation therapy, there was an emerging need to compare the estimated biologic effects of competing radiation therapy plans. Emami et al,[2] as part of a National Cancer Institute–funded Collaborative Working Group, provided organ-specific tolerance-dose estimates for one-third, two-thirds, and whole organ exposures, relying heavily on expert opinion and experiences from 2-dimensional radiation therapy planning. Despite these limitations, Emami et al[2] provided critical guidance that assisted in the care of countless patients worldwide.

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) special issue was published in this journal (volume 76, issue 3, Supplement) in 2010. The QUANTEC effort provided NTCP estimates based on critical reviews and pooled analyses of data, that updated (by approoximately 20 years) the wotk by Emami et al[2]. QUANTEC's goal was to define quantitative radiation dose-volume-outcome relationships for clinically relevant normal-tissue endpoints. The QUANTEC Steering Committee chose to focus on conventionally fractionated radiation therapy in adults; notable exceptions for which NTCP in children were addressed included cognitive deficits after whole brain radiation therapy[3] and renal dysfunction.[4]

After QUANTEC, 2 separate collaborative networks were formed to extend the overview of quantitative radiation dose-volume risk relationships: (1) HyTEC (Hypofractionated [or "Hy" dose per fraction] Treatment Effects in the Clinic), an initiative led by the American Association of Physicists in Medicine focusing on hypofractionated stereotactic body radiation therapy (SBRT, also known as stereotactic ablative body radiation therapy) and stereotactic radiosurgery (SRS) in adults (volume 110, issue 1), and (2) PENTEC to address radiation therapy risks in children. Table 1 describes key characteristics of the study by Emami et al[2] and the QUANTEC, HyTEC, and PENTEC projects.

The PENTEC effort began in 2012 in an effort to address the unmet need for high-quality pediatric NTCP data. The results of this project are published in this current issue of the Red Journal. Given the similar missions of QUANTEC, HyTEC, and PENTEC, it is worthwhile to highlight the similarities and differences in their methods and findings.

Similarities and Differences Between QUANTEC, HyTEC, and PENTEC

Content

All 3 of the "Tissue Effects in the Clinic" (TEC) efforts reviewed published studies on NTCP risks after radiation therapy, and when feasible, they extracted and pooled data from those studies for quantitative descriptions and dose-response modeling. HyTEC also addressed tumor control probability for several body sites, whereas neither QUANTEC nor PENTEC addressed tumor control probability.

Table 1 Summary of Emami[2] (NCI working group), QUANTEC, HyTEC, and PENTEC initiatives

	Emami et al[2]	QUANTEC	HyTEC	PENTEC
Years work was performed	Approximately 1986-1991	2007-2010	2011-2021	2012-2023
Publication date(s)	1991	2010	2018-2021	2021-2023
Scope	Normal organs and tissues	Normal organs and tissues	Tumors and normal organs and tissues after hypofractionated radiation therapy	Normal organs and tissues; focus on children
Data source	Literature search and working group member's experience	Comprehensive literature review	Comprehensive literature review	Systematic review (PRISMA methodology)
Data type	Primarily 2D data, inferred 3D data	3D data driven	3D data driven	Prescribed dose, 2D or 3D
Support*	NCI contracts	ASTRO/AAPM	AAPM	None

Abbreviations: 2D = 2-dimensional; 3D = 3-dimensional; AAPM = American Association of Physicists in Medicine; ASTRO = American Society for Radiation Oncology; HyTEC = Hypofractionated Treatment Effects in the Clinic; NCI = National Cancer Institute; PENTEC = Pediatric Normal Tissue Effects in the Clinic; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QUANTEC = Quantitative Analysis of Normal Tissue Effects in the Clinic.

* All received publication support from *Int J Radiat Oncol Biol Phys*. For PENTEC, the AAPM provided support for teleconferences before 2020.

Table 2 Manuscript sections used in the organ and tissue-specific QUANTEC, PENTEC, and HyTEC reports

QUANTEC	PENTEC	HyTEC
1. Clinical significance	1. Clinical significance	1. Clinical significance
2. Endpoints	2. Endpoints and toxicity scoring	2. Endpoints
3. Challenges defining volumes	3. Anatomy and developmental dynamics	3. Challenges defining and segmenting anatomic volumes
4. Review of dose-volume data	4. Defining volumes: pediatric imaging issues	4. Review of outcomes data
5. Factors affecting risk	5. Review of dose volume response data and risk factors—search methodology - Review of historical dose-volume data - Dose-volume endpoints -Risk factors - Mathematical/biologic models + epidemiologic issues - Comparison of PENTEC with QUANTEC	5. Factors affecting outcomes
6. Mathematical and biologic models	6. Recommendations for nominal dose volume goals - Special situations - Caveats	6. Mathematical and biologic models
7. Special situations	7. Toxicity scoring recommendations	7. Special situations
8. Recommended dose-volume limits	8. Data reporting standards specific to organ	8. Recommended dose-volume objectives
9. Future toxicity studies	9. Future investigations	9. Future studies
10. Toxicity scoring		10. Reporting standards

Abbreviations: HyTEC = Hypofractionated Treatment Effects in the Clinic; PENTEC = Pediatric Normal Tissue Effects in the Clinic; QUANTEC = Quantitative Analysis of Normal Tissue Effects in the Clinic.

The organ-specific reports from all 3 initiatives followed a similar format (Table 2), with PENTEC adding an additional section titled "Anatomy and Developmental Dynamics," as is uniquely appropriate for pediatric patients. Although each individual organ-specific TEC paper has a section with dosimetric recommendations, the intent of all 3 efforts "was not to suggest *absolute* dosimetric cut-offs, but rather to compile data on the continuum of benefit and risk . . . guiding customized treatment decisions for each patient."[5]

The issues of the Red Journal associated with these 3 initiatives were similarly organized into introductory papers, organ- and site-specific papers, and visionary papers. All 3 TEC efforts emphasized the need for improved data reporting to better facilitate future data pooling and modeling.

Oversight and support

QUANTEC received support from the American Society for Radiation Oncology (ASTRO) Research Council and the American Association of Physicists in Medicine (AAPM) Science Council. For PENTEC, the AAPM facilitated the structuring of a special committee and support for teleconferences. The HyTEC effort was under the umbrella of the AAPM Working Group on Biological Effects of Hypofractionated Radiotherapy/SBRT. Most HyTEC papers were reviewed by the Therapy Physics Committee and Science Council in addition to the HyTEC Steering Committee. QUANTEC and PENTEC remained independent of AAPM or ASTRO committee review, although all papers underwent rigorous review through the QUANTEC or PENTEC Steering Committees, as well as Red Journal peer reviewers and editors. All 3 TEC initiatives received support from ASTRO to publish a special issue in the Red Journal. Five of the 7 members of the QUANTEC Steering Committee are also members of the PENTEC steering committee (Søren M. Bentzen, Louis S. Constine, Andrew Jackson, Lawrence B. Marks, and Ellen Yorke), and several of these investigators also helped lead HyTEC.

Scope and literature review technique

The most obvious difference between QUANTEC and HyTEC versus PENTEC is the patient population analyzed (adults vs children). With children, biodevelopmental considerations are critical in the understanding of risk from radiation therapy, as described in depth in the paper by Bates et al.[40] Children are also more likely to receive cytotoxic chemotherapy, often at high doses. Genetic predispositions to cancer, and possibly genetic predispositions to toxicity from cancer-related therapy, are also of particular importance to children.

For QUANTEC and HyTEC, the authors of each organ-specific paper performed comprehensive literature searches

to identify studies to be included for analyses. PENTEC embraced a more rigorous approach; systematic review was required for all PENTEC reports using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses methodology. The PENTEC organ system task groups included epidemiologists (Leontien Kremer and Cécile Ronckers) who conducted the literature searches in a consistent and rigorous manner across task groups and were also involved in composing and reviewing reports. Whereas QUANTEC and HyTEC were tasked with describing NTCP risks with more modern radiation therapy planning and delivery techniques (eg, 3D radiation therapy, intensity modulated radiation therapy, SBRT, SRS) than those available at the time of the report by Emami et al[2], PENTEC needed to include some data from non−computed tomography−based treatments delivered in the 1980s or earlier to ascertain risks in long-term survivors. As a result, the individual PENTEC reports provide a separate objective assessment of the dosimetric methods used in each of the studies that were included in the PENTEC models, thus providing some judgment as to the quality of these data.[6] These assessments are generally located in the online appendices for each report. Notably, some of the HyTEC, PENTEC, and QUANTEC organ-specific reports included patients treated with proton therapy (summarized in Table E1), some with focused discussions on NTCP risks after proton therapy. However, proton therapy was not separately modeled or analyzed in any HyTEC, PENTEC, or QUANTEC report. In recent years, dosimetry standards for both proton therapy and photon-based therapy have been evolving, albeit more nascently with proton dosimetry. With proton therapy dosimetry, there is a need for more refined integration of biologic effectiveness relative to linear energy transfer, particularly at the end of range, which is most critical when an organ at risk is near the edge of the target volume.

PENTEC did not specifically address SBRT or SRS in children, and thus, comparisons with HyTEC are limited. The organs, tissues, and sites included in PENTEC versus QUANTEC are somewhat different (Table 3), and many of the endpoints within PENTEC are unique to children (footnoted in Table 3), thus limiting direct comparisons of PENTEC with QUANTEC. Because children are developing (and not simply smaller adults), the effects of organ- or tissue-specific radiation-related toxicity (both with regard to endpoints and outcomes) can be very different in children versus adults.

Comparing NTCP in Children Versus Adults

In the following sections and in Table 4, we summarize the NTCP risks for specific organs and tissues that lent themselves to comparisons between adults and children. A few of these comparisons relied on data outside of the QUANTEC and PENTEC reviews. Furthermore, the NTCP risk for some organs and tissues are included where there were reasonable data addressing the effect of age within the pediatric age range at risk, as this might (with some extrapolation) provide some insights as to the sensitivities in adults versus children. We concede that these comparisons are strictly descriptive, because analytical comparisons were not done.

Brain: Necrosis

The QUANTEC reports on necrosis risk in the brain[3] and brain stem[7] specifically considered both pediatric and adult data; although the authors did not perform quantitative comparisons between adults and children, there were no readily apparent differences in risks of toxicity.

Comparing results from the QUANTEC[3] and PENTEC[8] models (Table 5), pediatric patients have a similar or perhaps slightly greater risk of symptomatic radiation-induced brain necrosis (Table 5). QUANTEC also reported that dose fractions >2 Gy and twice-daily fractionated treatment were associated with increased necrosis risk.

The PENTEC model of cranial necrosis included patients with brain stem exposure, whereas QUANTEC separately reported risk of necrosis in the brain stem.[7] Thus, perhaps the slightly lower risks of brain necrosis in adults versus children (from qualitative comparisons of PENTEC and QUANTEC data) may be owed to brain stem necrosis being separately considered in the adults. PENTEC and QUANTEC comparisons are further confounded by the inclusion of patients treated with proton therapy (with dosimetric and biologic effectiveness uncertainties as described previously) in the PENTEC brain report and QUANTEC brain stem report but not in the QUANTEC brain report.

Although published data have described risks of cranial radionecrosis relative to prescribed dose, data specifically correlating dose-volume brain exposure (ie, volume receiving a specific dose) with risks of radionecrosis are lacking and were not included in the QUANTEC or PENTEC models. The QUANTEC brain stem report summarized data on necrosis risks relative to prescribed dose, maximum dose, central dose, and small volume exposures, noting that small volumes (eg, 1-10 cm^3) of brain stem usually tolerate doses <59 Gy, with risks markedly increasing with doses >64 Gy. These data were not modeled. A separate PENTEC report reviewed risks of brain and brain stem necrosis in the reirradiation setting,[9] which was not specifically analyzed in QUANTEC.

HyTEC reported risks of brain necrosis after single-fraction SRS for arteriovenous malformations as well as after single-fraction and multifraction SRS for brain metastases.[10] Although one might anticipate similar risks of toxicity after SRS in children versus adults (given the apparent similar risks after conventional fractionation), the HyTEC authors specified that toxicity in the pediatric population was not addressed due to insufficient data.

Brain: Neurocognition

It is generally accepted that children have markedly greater susceptibility to neurocognitive deficits from brain radiation

Table 3 Comparison of organ- and tissue-specific toxicity endpoints in the various initiatives

Organ or tissue	Endpoints analyzed in QUANTEC	Selected endpoints analyzed in HyTEC	Endpoints analyzed in PENTEC
Central nervous system			
Brain	- Radiation necrosis* - Cognition (in children and adults)	Radiation necrosis	- Radiation necrosis - Neurocognitive impairment - Necrosis after reirradiation†
Cerebrovascular	Not analyzed	Not analyzed	- Stroke - Cerebral vasculopathy
Optic nerves and chiasm (ocular)	Optic neuropathy/vision loss*	Optic neuropathy, vision loss	- Optic neuropathy - Retinopathy - Cataract
Neuroendocrine	Not analyzed	Not analyzed	- Deficiencies of growth hormone† - Central hypothyroidism - Deficiencies of adrenocorticotropic hormone
Brain stem	Brain stem injury or necrosis and cranial neuropathy*	Not analyzed	Necrosis after reirradiation†; otherwise not analyzed separately
Spinal cord	Myelopathy*	Myelopathy*	Myelopathy
Cochlea and vestibular-cochlear nerve	Sensory-neural hearing loss*	Not analyzed	Hearing loss
Head and neck			
Salivary glands (parotid and submandibular glands)	Long-term xerostomia	Not analyzed	Acute and late xerostomia
Dentition	Not analyzed	Not analyzed	Dental developmental abnormalities‡
Thyroid gland	Not analyzed	Not analyzed	Hypothyroidism
Larynx and pharynx	- Laryngeal edema - Vocal function - Aspiration - Dysphagia	Not analyzed	Not analyzed
Thoracic			
Lung	Pneumonitis	Pneumonitis	- Pneumonitis - Any pulmonary toxicity
Heart and cardiovascular	- Acute pericarditis - Late cardiac mortality	Not analyzed	- Any cardiac disease - Coronary artery disease - Heart failure - valvular disease
Esophagus	Acute esophagitis	Not analyzed	Not analyzed
Abdominal			
Liver	Radiation-induced liver disease	- grade ≥3 liver enzyme elevation - grade ≥2 and grade ≥3 "general" gastrointestinal toxicities	- Hepatic sinusoidal obstructive syndrome after whole liver RT - Liver failure
Stomach and small bowel	Acute and late stomach and small bowel toxicity Gastric ulceration	Not analyzed	Not analyzed
Kidney	Radiation-induced kidney injury (from partial- or whole-kidney RT)	Not analyzed	- Renal dysfunction after partial-kidney RT, whole abdominal RT (after nephrectomy), or TBI - Hypertension

(*Continued*)

Table 3 (*Continued*)

Organ or tissue	Endpoints analyzed in QUANTEC	Selected endpoints analyzed in HyTEC	Endpoints analyzed in PENTEC
Pelvic			
Urinary bladder	Bladder toxicity	Late urinary flare after prostate SBRT	Bladder toxicity reviewed but not analyzed
Rectum	- Rectal toxicity - Rectal bleeding	Rectal toxicity after prostate SBRT	Not analyzed
Male genital and reproductive			
Penile bulb	Erectile dysfunction	Not analyzed	Not analyzed
Testes	Not analyzed	Not analyzed	- Spermatogenesis - Androgenic hormone levels
Female reproductive			
Breast	Not analyzed	Not analyzed	- Breast hypoplasia‡ - Impaired lactation
Ovaries and uterus	Not analyzed	Not analyzed	- Acute ovarian failure - Premature ovarian insufficiency - Uterine and vaginal growth‡ reviewed but not modeled
Other			
Musculoskeletal	Not analyzed	Not analyzed	- Impairment in growth‡ - Spine deformities‡
Stem cell transplant	Not analyzed	Not analyzed	Idiopathic pneumonitis syndrome
Subsequent neoplasms	Not analyzed	Not analyzed	Subsequent sarcoma, lung cancer, and benign and malignant neoplasms within the brain

Abbreviations: HyTEC = Hypo-fractionated Treatment Effects in the Clinic; PENTEC = Pediatric Normal Tissue Effects in the Clinic; QUANTEC = Quantitative Analysis of Normal Tissue Effects in the Clinic; RT = radiation therapy; SBRT = stereotactic body radiation therapy, TBI = total body irradiation.

* QUANTEC separately analyzed this endpoint after stereotactic radiation surgery and after conventional fractionation.

† Separate PENTEC report on reirradiation.

‡ Endpoint specifically pertinent to children and young adults (as opposed to older adults).

therapy than adults. In adults, the effect of cranial radiation therapy on cognition has generally only been analyzed by validated neurocognitive assessments and quality-of-life measures, as opposed to IQ (as commonly used in most pediatric reports). Although some studies of pediatric survivors have also focused on cognitive assessments outside of IQ,[11,12] quantitative comparisons of risks in children versus adults are not feasible, particularly in the realm of risks of cognitive effects from radiation exposures to specific brain substructures, which is a growing field of study in children and adults.[11,13,14]

The PENTEC authors estimated that children have a 5% risk of developing an IQ <85 when 10%, 20%, 50%, or 100% of the brain is irradiated to 35.7, 29.1, 22.2, or 18.1 Gy, respectively (with conventional fractionation and without receipt of methotrexate).[8] In addition to higher radiation doses, younger age increases these risks. The QUANTEC authors summarized the findings from several studies demonstrating neurocognitive deficits after brain radiation therapy in adults, and additional, more recent literature substantiates these effects, particularly with memory and recall.[13,15-18] Marked cognitive decline in adults is uncommonly reported when using conventional fractionation and/or palliative doses of radiation,[19] although this is perhaps in part due to the lack of long-term follow-up in most settings in which whole-brain radiation therapy is used in adults. The relationship of age on radiation-related risks on neurocognitive function is unclear within the ranges of age between adolescents and young adults through older adults.

Cerebrovascular

The PENTEC cerebrovascular model predicted risks of cerebrovascular toxicity (including included transient ischemic attack, ischemic or hemorrhagic stroke, Moyamoya, and arteriopathy) increasing with increasing radiation dose and increasing attained age after radiation therapy (with models presented for attained ages of 17, 35, and 45 years).[20] At an

Table 4 Comparison of susceptibility to radiation-induced toxicity in children versus adults

Organ at risk	Toxicity outcome	Dose-volume measure	Children compared with adults	Comments
Brain	Necrosis	Maximum dose	Children have similar or slightly greater susceptibility	Based on comparison of QUANTEC with PENTEC
Brain	Neurocognition	Whole or partial brain dose	Children appreciably greater	Based on published outcomes†
Cerebrovascular	Cerebrovascular events and stroke	Dose to cerebral vessels*	Children have greater susceptibility	Based on published outcomes†
Optic apparatus	Optic neuropathy	Maximum dose	Similar susceptibility	Based on comparison of QUANTEC with PENTEC
Cochlea	Hearing loss	Mean dose	Younger children at greater risk than older children or adults	Reviewed in PENTEC
Spinal cord	Myelopathy	Dose to full thickness of cord or prescribed dose	Insufficient data to draw comparisons	Based on comparison of QUANTEC with PENTEC
Parotid gland	Xerostomia	Mean dose	Similar susceptibility	Based on comparison of QUANTEC with PENTEC
Thyroid gland	Hypothyroidism	Thyroid or neck dose	Older children with greatest susceptibility compared with younger children and adults	Reviewed in PENTEC†
Heart	Any cardiac toxicity	Mean dose	Children thought to have greater susceptibility	Quantitative comparisons of data from PENTEC with data from QUANTEC are not feasible (see text)
Lungs	Pneumonitis	Lung V20-27 and Mean dose	Children have lower susceptibility	Based on comparison of QUANTEC to PENTEC
Liver	Liver disease	Mean dose	Children have greater susceptibility	Based on comparison of QUANTEC to PENTEC
Kidney	Nephropathy	Mean dose or kidney V10-20	Unclear	Based on comparison of QUANTEC with PENTEC
Ovary	Acute ovarian failure	Mean dose to least affected ovary	Children have lower susceptibility	Reviewed in PENTEC, not analyzed in QUANTEC†
Ovary	Premature ovarian insufficiency	Mean dose to least affected ovary	Children have possibly lower susceptibility due to greater reserve (though unknown)	Reviewed in PENTEC; not analyzed in QUANTEC†
Testes	Spermatogenesis	Mean dose	Unclear from data published to date	Not analyzed in QUANTEC†
Testes	Androgenic hormone levels	Mean dose	Unclear from data published to date	Not analyzed in QUANTEC†
Breast	Impaired lactation	Estimated breast dose	Children have greater susceptibility	Not analyzed in QUANTEC†
Breast	Impaired development	Estimated breast dose	Primarily relevant only to children	Not analyzed in QUANTEC†
Musculoskeletal	Impaired spine growth and deformities	Volume (number of vertebral bodies)	Primarily relevant only to children	Not analyzed in QUANTEC†

Abbreviations: PENTEC = Pediatric Normal Tissue Effects in the Clinic; QUANTEC = Quantitative Analysis of Normal Tissue Effects in the Clinic; V_X = volume receiving ≥x Gy.

* Based on dose to vessels within treatment field or (as a surrogate) optic chiasm.

† Outcome was not analyzed in QUANTEC, so susceptibilities in children versus adults are not based on PENTEC versus QUANTEC comparisons.

Table 5 Risk of symptomatic brain necrosis: Comparing PENTEC and QUANTEC summaries

Maximum brain dose		
PENTEC	QUANTEC (adults)	Risk of symptomatic necrosis
*	<60 Gy	<3%
~59 Gy	~72 Gy	5%
~72 Gy	*	8%
*	90 Gy	10%

Abbreviations: PENTEC = Pediatric Normal Tissue Effects in the Clinic; QUANTEC = Quantitative Analysis of Normal Tissue Effects in the Clinic.
* Doses associated with this specific risk level were not reported.

attained age of 45 years, a model for stroke predicted risks of approximately 2% to 4% at 30 Gy and 7% to 13% at 54 Gy. Adults are also at risk of ischemic stroke and other cerebrovascular events after intracranial radiation, although these risks may be relatively low compared with background risks.[21,22] A systematic review of 11 reports that included 4394 mostly adult patients irradiated for pituitary tumors did not identify a consistent increase in stroke risk after radiation therapy.[21]

Although direct comparisons between children and adults are not available, the data suggest that children are plausibly at higher risk than adults for radiation therapy–related cerebrovascular toxicity. For example, some children experience cerebrovascular events during childhood or young adulthood (ie, at a relatively short postradiation therapy interval), which is very uncommon in the general population. Most of the published data on stroke in adults relates to cervical carotid artery exposure from head and neck radiation,[23-25] which the PENTEC groups did not explore. Stroke-like migraine attacks after radiation therapy have also been reported as rare complications for adults or children[26,27] but are not specifically analyzed in the PENTEC models and are arguably too rare to compare risks in adults versus children.

Optic apparatus: Optic neuropathy

PENTEC summarized and modeled published data on risks of optic neuropathy,[28] whereas QUANTEC predicted risks of optic neuropathy from an in-depth summary of data.[30] The PENTEC model for optic neuropathy (including 1 study that included patients treated with proton therapy) predicted a 5% or 50% risk of toxicity after a dose of 57 Gy or 64 Gy, respectively. From the QUANTEC report, maximum optic apparatus doses of <55 Gy, 55 to 60 Gy, and >60 Gy were associated with <3%, 3% to 7%, and >7% to 20% risk of optic neuropathy, respectively. The risks in adults and children seem comparable.

Optic apparatus: Retinopathy and cataract formation

PENTEC also evaluated dosimetric correlates to risks of retinopathy and cataract formation (for which there were relatively more data), which was not analyzed in QUANTEC. The PENTEC authors postulated that children are at greater risk of cataract formation, with the caveat that pediatric survivors are generally followed up more regularly than adults for cataract formation, which could account for apparent differences in reported risk.

Cochlea: Hearing loss

From a PENTEC report (Murphy et al),[22] mean radiation dose to the cochlea (used as a surrogate for any auditory structure, including external, middle, and inner ear as well as central auditory pathways) was evaluated to quantify radiation therapy–related risks of sensorineural hearing loss, defined to be a threshold loss of >20 dB at any frequency. A mean cochlear dose ≤35 Gy was associated with <5% risk of hearing loss versus approximately 30% risk for a mean cochlear dose of 50 Gy. Risks were significantly greater in the high-frequency range. Children younger than 5 years of age are at greater risk than older children, although independent effects of dose and age on radiation therapy–related hearing loss could not be characterized from the compiled data. Platinum-based chemotherapy carries risks of otological toxic effects, with some studies suggesting additive (as opposed to synergistic) effects with radiation therapy on hearing loss; although the PENTEC report summarized data on this, it was not specifically modeled. The QUANTEC authors[31] reported <30% risk of clinically significant hearing loss with mean cochlear doses <45 Gy, although they conceded that definitions of hearing loss vary in the literature and that reported risks depend on the auditory frequency range assessed and exposures to platinum-based chemotherapy. Whether adults are more or less sensitive than children to radiation-related hearing loss is unclear, and even though younger children carry greater risks than older children, the PENTEC authors are unsure if this difference is related to differences in radiation sensitivity versus confounding factors.

Spinal cord: myelopathy

For radiation-induced myelopathy in children, the PENTEC authors[29] suggested that risks of myelopathy are low with the spinal cord dosimetric limits currently used in Children's Oncology Group studies:

- D0.03 cc of ≤54 Gy (or 50.4 Gy with chemotherapy) with ≤56 Gy acceptable as a minor deviation (generally only when absolutely necessary to sufficiently treat the patient)

- D1 cc of ≤50.4 Gy (or 45 Gy with chemotherapy), with ≤54 Gy acceptable as a minor deviation

However, the low risks that are anticipated are with the caveat that there are insufficient data to adequately quantify these risks, because the denominators for relative or absolute risk estimates are almost nonexistent in published reports. Notably, the QUANTEC report[32] found radiation myelopathy to occur in <1% of adults treated to ≤54 Gy with conventional fractionation. For the PENTEC effort, there were not enough reported cases of radiation myelopathy to perform normal-tissue complication probability modeling, and much of the data predated 3-dimensional conformal radiation therapy. The PENTEC authors explicitly state that there is no evidence that the spinal cord in children is more or less radiosensitive than in adults. Children receiving intrathecal chemotherapy appear to be at increased risk of radiation-associated spinal cord toxicity.

Central endocrine complications

The PENTEC report on central endocrine complications from radiation therapy[33] showed dose-response relationships with 50% risks of late toxicity for deficiencies of growth hormone, central hypothyroidism, and adrenocorticotropic hormone with doses of approximately 25 Gy, 40 Gy, and 60 Gy, respectively. PENTEC was not able to model radiation therapy effects on gonadotropin production due to insufficient published data. The PENTEC authors were unable to derive "firm conclusions" about the effect of age on risks of radiation-induced hypothalamic-pituitary toxicity, although they acknowledged that their data suggested younger age was associated with greater risks. A 2018 study of 189 pediatric patients enrolled in 1 of 3 different prospective studies and treated with cranial or cranial-spinal radiation therapy showed that younger (vs older) children were more susceptible to deficiencies in growth hormone, thyroid hormone, adrenocorticotropic hormone, and gonadotropin.[34] QUANTEC did not perform analyses on central endocrine complications in adults. Although it is unknown if children or adults are more at risk of central hormone suppression from radiation therapy, children are markedly more susceptible to effects from growth hormone deficiency, which can cause growth delays, among other adverse effects. In older adults, baseline growth-hormone levels are appreciably lower than in adolescents and young adults, and growth-hormone deficiency may not be readily diagnosed owing to nonspecific symptoms such as fatigue, reduced muscle mass, and decreased libido.

Salivary gland: Xerostomia

The calculated risks of xerostomia from parotid radiation from the PENTEC model[35] appear to be similar to those from the QUANTEC model[36] (Table 6). From the PENTEC model, a mean dose of 35 to 40 Gy to both parotid glands is associated with an approximate 13% to 32% risk of late grade 2 xerostomia, and risks linearly increase at doses above 35 Gy. Notably, the PENTEC model had no data for mean parotid doses <25 Gy, and thus, risk estimates at lower doses are uncertain. Neither PENTEC nor QUANTEC reported on risks associated with radiation exposure to other salivary glands. Much of the data on submandibular gland and minor salivary gland radiation dose-volume effects in adults were published after the QUANTEC report was published (summarized by Milano et al[37]), and the PENTEC authors described only 1 study analyzing submandibular gland exposure in children.

Thyroid gland: Hypothyroidism

Adults and children are susceptible to radiation-induced hypothyroidism. Although there was not a QUANTEC report on hypothyroidism, classic data from Stanford University elegantly address the effect of age (at the time of radiation) on this risk.[38] Considering a wide continuum of ages, the risk of hypothyroidism increases with age among children and young adults, peaks in the 20- to 30-year age range, and continually declines with increasing ages up through >60 years. The Stanford analysis is imperfect because, among children, radiation doses tended to increase with age, and chemotherapy was more frequently used (than in adults); indeed, radiation dose (and not age) was the dominant predictor of outcome in the multivariate models. Among adults, most patients received approximately 44 Gy to the neck, and multivariate models noted that

Table 6 Risk of symptomatic xerostomia: Comparing PENTEC and QUANTEC summaries

Mean parotid dose		
PENTEC	**QUANTEC (adults)**	**Risk of symptomatic xerostomia**
Mean 35 to 40 Gy for both parotids	*	13%-32% Late grade 2 xerostomia
*	At least 1 gland with mean <20 Gy or mean 35 to 40 Gy for both parotids	<20% Risk of long-term reduction

Abbreviations: PENTEC = Pediatric Normal Tissue Effects in the Clinic; QUANTEC = Quantitative Analysis of Normal Tissue Effects in the Clinic.
* Doses associated with this specific for this risk level were not reported.

chemotherapy use and sex (with women at higher risk) were the dominant predictors of outcome, and increasing age was associated with a modest reduction in risk (relative risk decreased by 0.99 per each additional year of age). A PENTEC report[39] similarly demonstrated greater risks of hypothyroidism in female versus male patients and also showed (from 2 other studies that provided more granular data for modeling) increased risk of hypothyroidism among children aged >14-15 years at the time of radiation therapy compared with younger patients (consistent with the Stanford study).

Heart: Cardiotoxicity and cardiac death

The PENTEC investigators separately modeled any cardiac disease, heart failure, coronary artery disease, and valvular disease and reported incremental risks, as hazard ratios, for each 10-Gy increment (as either mean dose or prescription dose).[40] The modeled excess absolute risk (EAR) of developing any cardiac disease by 30 years after receiving a mean heart dose of 20 Gy as a child was 3.8%, with a hazard ratio of 1.88 (95% CI, 1.75-2.03) per 10 Gy. This hazard ratio estimate means that the EAR after, say, a mean heart dose of 30 Gy increases to 7.0% (95% CI, 6.6%-7.6%). Risks of cardiac death relative to cardiac dosimetry were not analyzed. The QUANTEC review in adults described previously published models, though it did not provide an NTCP model from the summarized data.[41] For adults, "conservative model-based estimates" predicted a <1% EAR of cardiac mortality >15 years after radiation therapy with a V25 <10% (ie, volume of lung receiving <25 Gy) with conventional fractionation. Specific dosimetric predictors of any cardiac disease, heart failure, coronary artery disease, and valvular disease were not analyzed or reported. Although the overall 3.8% EAR of cardiac disease suggested for children is numerically greater than the 1% EAR of cardiac death cited in QUANTEC, these endpoints are different, and it is very possible that some incidence of cardiac toxicity in adults goes undiagnosed. Given the different outcomes analyzed and different dosimetric predictors of risks, drawing quantitative comparisons between the risk estimates from QUANTEC and PENTEC is not feasible. Furthermore, comparative data between adults and children are lacking on risks relative to cardiac substructure dosimetry, which may be more predictive than whole-heart mean radiation dose or partial volume exposure. This is a growing area of research for both adults and children.[42]

Lung: Radiation pneumonitis

Comparison of data from PENTEC[43] and QUANTEC[44] suggest that children are generally at less risk of radiation pneumonitis than adults (Table 7), although the PENTEC data were limited by the low number of events in the studies included in the model.

Table 7 Risk of symptomatic pneumonitis: Comparing PENTEC and QUANTEC summaries

Dosimetric lung measure	Risk of symptomatic pneumonitis
PENTEC	
Total lung V20 < 30%	<5%
Mean lung doses of <12 Gy	<5%
QUANTEC (adults)	
Total lung (minus GTV) V20 ≤ 30%	<20%
Mean lung dose < 20 Gy	<20%

Abbreviations: GTV = gross target volume; PENTEC = Pediatric Normal Tissue Effects in the Clinic; QUANTEC = Quantitative Analysis of Normal Tissue Effects in the Clinic; Vx = volume of lung receiving >*x* Gy.

The QUANTEC data are largely derived from patients with local-regionally advanced lung cancer and thus include mostly prior or current smokers with reduced lung reserve. This might be a factor for the apparent lower susceptibility among children. However, some data suggest that smoking history in adults lowers the risk of radiation-induced pneumonitis but not the risk of functional sequelae,[45,46] thus hampering direct comparisons between adults and children. In addition, the range of radiation therapy doses prescribed to children are typically lower than those used in adults, further complicating comparisons. Although HyTEC provided summary data for the risks of symptomatic radiation-induced lung toxicity after 3- to 5-fraction SBRT,[47] comparable data in children are lacking.

A separate PENTEC report reviewed risks of idiopathic pneumonitis syndrome (IPS) from total body irradiation.[48] QUANTEC nicely summarized the rates of pneumonitis after single-fraction or multifraction whole-lung radiation therapy with "large-field" radiation therapy (1 study), total body irradiation (1 study), elective treatment of the whole lung for osteosarcoma (3 studies including mostly pediatric patients), or hemibody radiation therapy for bone metastases (1 study). The report showed low risks of pneumonitis after whole-lung doses of <7 to 8 Gy in 1 fraction and <20 to 25 Gy at 1.5 to 2 Gy per fraction. Currently, total body irradiation is the most common scenario in which the whole lungs are irradiated. The whole lungs are also irradiated in children with lung metastases from Wilms tumor, rhabdomyosarcoma, and Ewing sarcoma. Given the limited data on pneumonitis risks after whole-lung radiation exposure and the multitude of factors that affect risks of IPS after total body irradiation (such as type and dose of administered systemic agents, total and fractional radiation therapy dose, and radiation dose rate), meaningful comparisons of IPS risks in adults versus children are not feasible.

Kidney: Kidney disease and hypertension

Comparisons of the risks of radiation-associated nephropathy between adults and children are challenging, largely owing to different treatment paradigms (including nephrotoxic chemotherapy agents) in patients with radiation exposure to their kidneys. For example, the clinical scenario associated with Wilms tumor (ie, where 1 kidney is removed and the remaining kidney is sometimes irradiated using whole abdominal radiation) has no analogous situation in adults. Whereas risk of kidney injury after total body radiation was discussed in both QUANTEC and PENTEC reports, the QUANTEC report[4] did not separately analyze adults.

QUANTEC summarized NTCP data from both adult and pediatric patients but did not provide separate risk estimates or models for children versus adults.[4] For partial kidney radiation, all of the reviewed data were from studies of adults; the volume of kidneys receiving more than approximately 20-23 Gy and the mean kidney dose both predicted risks of renal toxicity. The QUANTEC authors predicted that bilateral kidney V12 < 55% and V20-23 < 30%-32% were associated with <5% risk of renal dysfunction. The PENTEC authors[48] specifically analyzed partial kidney exposure, relying on a 2021 St. Jude Lifetime Cohort Study that reported odds ratios for kidney V5-V20 for risk of kidney disease.[50] In that cohort study, kidney V5-V10 was significantly associated with risks of advanced-stage chronic kidney disease, whereas V15-V20 was not; V5-V20 was not significantly associated with risks of proteinuria. The PENTEC authors reported risks of severe toxicity relative to V5-V10 being heavily dependent on what chemotherapy agents were used (Table 8). The PENTEC authors also describe kidney dosimetric correlates to hypertension. Although the QUANTEC authors described endpoints of proteinuria and hypertension, neither of these endpoints, nor severe toxicity, were addressed as separate outcomes.

Table 8 Risks of severe renal toxicity relative to kidney radiation exposure and chemotherapy agents as reported in PENTEC

Kidney dose measure*	Chemotherapy agent	Risk of severe kidney toxic effects
V5-10 ≤ 100%	None	<5%
V5-10 ≤ 100%	1500 mg/m^2 carboplatin	<5%
No radiation exposure	480 mg/m^2 of cisplatin	3%
V10 = 26%	480 mg/m^2 of cisplatin	5%
No radiation exposure	63 g/m^2 of ifosfamide	5%
V10 = 42%	63 g/m^2 of ifosfamide	10%

Abbreviation: PENTEC = Pediatric Normal Tissue Effects in the Clinic.
* Bilateral kidneys.

Liver: Radiation-induced liver disease

Comparison of data from PENTEC[51] and QUANTEC[52] suggest that younger children are generally at more risk of toxic effects than adults. The QUANTEC report summarized NTCP data for radiation-induced liver disease (RILD), described as "anicteric hepatomegaly and ascites"), although it did not provide models from pooled data. The authors described, for patients undergoing palliative whole-liver radiation therapy, approximately 10% risk of RILD with 33 Gy in 1.5-Gy fractions. For comparison, the PENTEC report described risks of RILD (described as sinusoidal obstructive syndrome) of 6.1% and 14.5% after whole-liver doses of 10 Gy and 20 Gy (with conventional fractionation), respectively, thus suggesting greater susceptibility to RILD in children.

For conventionally fractionated partial-liver radiation therapy in adults, QUANTEC reported that whole-liver mean doses of ≤28 to 32 Gy are associated with ≤5% risk. For the pediatric population, 2 articles described liver toxicity associated with higher partial-liver radiation doses, although the data were insufficient to generate NTCP models.

Comparisons of susceptibility between adults and children are confounded by the greater longevity in children versus adults and a greater use of hepatotoxic chemotherapies in some common pediatric treatment regimens. These factors would tend to increase the reported risks in children versus adults. However, adults more often have underlying liver disease (particularly in patients with primary liver malignancies) and/or hepatic involvement by cancer, which would tend to greatly increase their risk of RILD. Nevertheless, despite these risk factors in adults, children appear to be more at risk of RILD, suggesting possible greater inherent susceptibilities.

Ovary: Acute ovarian failure

In the PENTEC report,[53] the radiation dose to the least affected ovary associated with a 5% risk of acute ovarian failure progressively decreased (from 7 to 2 Gy) with increasing age from 1 to 20 years, suggesting adolescent and young adults are more at risk than younger children. It is generally understood that declining numbers of oocytes (ie, reducing reserve) tend to increase risks of radiation therapy–induced ovarian failure over time. Relatively high exposure to alkylating chemotherapy increased risks of radiation-induced acute ovarian failure, with a similar trend of greater risks with older age. There were no good comparative data in adults for ovarian function, and this issue was not considered in QUANTEC.

Subsequent neoplasms

Among childhood cancer survivors, the PENTEC report[55] showed that younger age at time of primary diagnosis was

associated with an increased risk of subsequent meningioma and sarcoma. Although no effect of age was observed for subsequent gliomas, the PENTEC authors cautioned that the large variation in risk estimates might have masked this association. Insufficient data precluded assessment of age on subsequent lung cancer. Children are considered more susceptible than adults to radiation-associated subsequent malignancies for several reasons, including greater inherent susceptibility, genetic susceptibility in children with cancer, and more years out from radiation therapy at any given attained age. However, QUANTEC did not model risks of subsequent malignancies, and robust comparative data are limited.[56]

Organs and tissues susceptible to impaired development as children age to adults

Radiation-associated impairment of maturation or development of specific organs and tissues is largely unique to children and can lead to severe chronic toxicities that extend into adulthood (discussed in detail by Bates et al).[40] For example, the risks to developing bone (eg, with unfused growth plates) and associated soft tissues are discussed in the PENTEC report on musculoskeletal effects (Nanda et al).[54] Similarly, the PENTEC head and neck report[35] describes risks of dental developmental abnormalities. Risks of maldevelopment of the breast (eg, with impaired growth and lactation) and gynecologic organs are addressed in other PENTEC reports.[53,57] Reduced urinary bladder capacity after radiation therapy is described (but not explicitly analyzed) in the genitourinary PENTEC report.[49] In general, these effects will be more pronounced with younger age due to the greater degree of still anticipated maturation and development. Thus, for the most part, there are not corresponding issues in adults. Although radiation therapy in adults can cause dental caries (related at least in part to salivary dysfunction), breast fibrosis or shrinkage, bone weakness or fracture, and muscle atrophy, the severity and incidence of these issues is generally far less clinically relevant in adults versus children. In adults, an analogy to maldevelopment perhaps relates to the impaired healing that can be seen after surgery or bone fracture in previously or subsequently irradiated tissues,[58,59] a topic not included in QUANTEC.

Summary and Conclusion

For some organs and tissues, qualitative comparisons suggest that children have similar (eg, brain for necrosis, optic apparatus, parotid gland, liver), greater (eg, brain for neurocognition, cerebrovascular, breast for lactation), less (ovary), or perhaps slightly less (eg, lung) risks of radiation-induced toxicity compared with adults. Similarly, even within the pediatric age range, younger children appear to experience greater (eg, hearing and brain for neurocognition) or lesser (eg, ovary, thyroid) risks of some radiation-associated toxicities. These comparisons are imperfect due to many confounding issues (eg, marked differences in treatment paradigms, normal-tissue exposures, cancer types, chemotherapies, etc). For developing organs and tissues, children are exquisitely more sensitive to the effects from radiation due to risks resulting from impaired development (eg, musculoskeletal tissue, teeth, breasts, gynecologic organs). For these organs and tissues, comparative studies are not needed, because these events are generally not seen in adults (Table 3). To optimally assess the effects of age on toxicity risks, NTCP modeling would include comprehensive patient- and treatment-specific data and potential confounding variables of interest in addition to age. Additional work is needed to better understand these issues.

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