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PENTEC ORGAN SYSTEM REVIEW

Risks of Spinal Abnormalities and Growth Impairment After Radiation to the Spine in Childhood Cancer Survivors: A PENTEC Comprehensive Review

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Purpose: A PENTEC (Pediatric Normal Tissue Effects in the Clinic) review was performed to estimate the dose-volume effects of radiation therapy on spine deformities and growth impairment for patients who underwent radiation therapy as children.
Methods and Materials: A systematic literature search was performed to identify published data for spine deformities and growth stunting. Data were extracted from 12 reports of children irradiated to the spine (N = 603 patients). The extracted data were analyzed to find associations between complication risks and the radiation dose (conventional fractionation throughout) as impacted by exposed volumes and age using the mixed-effects logistic regression model. When appropriate, corrections were made for radiation modality, namely orthovoltage beams.
Results: In the regression analysis, the association between vertebral dose and scoliosis rate was highly significant ($P < .001$). Additionally, young age at time of radiation was highly predictive of adverse outcomes. Clinically significant scoliosis can occur with doses ≥15 Gy to vertebrae during infancy (<2 years of age). For children irradiated at 2 to 6 years of age, overall scoliosis rates of any grade were >30% with doses >20 Gy; grade 2 or higher scoliosis was correlated with doses ≥30 Gy. Children >6 years of age remain at risk for scoliosis with doses >30 Gy; however, most cases will be mild. There are limited data regarding the effect of dose gradients across the spine on degree of scoliosis. The risk of clinically meaningful height loss was minimal when irradiating small volumes of the spine up to 20 Gy (eg, flank irradiation), except in infants who are more vulnerable to lower doses. Growth stunting was more frequent when larger segments of the spine (eg, the entire spine or craniospinal

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irradiation) were irradiated before puberty to doses >20 Gy. The effect was modest when patients were irradiated after puberty to doses >20 Gy.

Conclusions: To reduce the risk of kyphoscoliosis and growth impairment, the dose to the spine should be kept to <20 Gy for children <6 years of age and to <10 to 15 Gy in infants. The number of vertebral bodies irradiated and dose gradients across the spine should also be limited when possible.

Clinical Significance

Musculoskeletal toxicities are common in survivors of pediatric and adolescent malignancies who undergo radiation therapy at a young age. The impact of radiation therapy varies with the radiation modality used (eg, orthovoltage and Cobalt megavoltage), the chronological and bone age of the patient at the time of exposure and assessment, the site of the musculoskeletal system irradiated, dose and volume of exposure,[1-3] and dose per fraction.[4] The most commonly reported skeletal side effects on growing bone are growth stunting and various types of deformities.[5]

Spinal abnormalities from radiation, which was the focus of this Pediatric Normal Tissue Effects in the Clinic (PENTEC) initiative, usually manifest as decreased stature and/or scoliosis, although kyphosis or lordosis can also occur.[1,2,6,7] Spinal abnormalities are primarily reported in children treated for thoracic and abdominopelvic tumors as well as in those receiving craniospinal irradiation for intracranial malignancies. Scoliosis and/or kyphosis affects up to 20% to 60% of irradiated survivors of childhood Wilms tumor and neuroblastomas.[8,9] This may also result from compounding effects of surgery[9] (such as laminectomies of involved spinal segments or hemi-abdominal disruption of the musculature), resulting in weakness or instability of the hemithorax or hemiabdomen. Kyphoscoliosis is commonly observed during adolescence when there is rapid bone growth. The Childhood Cancer Survivor Studies have demonstrated that survivors with disfigurement and physical impairment of the spine after radiation are at increased risk for emotional distress, including anxiety and depression, compared with healthy siblings.[10,11] Growth stunting is prevalent after childhood radiation and can manifest as reduced sitting height, standing height, or leg length.[12,13]

This PENTEC review aims to review dose-volume outcome data for the spine in children treated with radiation for tumors near or involving the spine. Other effects, such as reduced bone density, fractures, and secondary malignancies involving the axial or appendicular skeleton, have been documented in the literature and should be the subject of future studies.

Endpoints and Toxicity Scoring

The degree of scoliosis and kyphosis is measured using the Cobb method,[14] which is considered the universal standard. Scoliosis is defined as an abnormal lateral curvature of the spine based on a standing radiograph of the spine. Most cases of scoliosis are idiopathic and diagnosed during puberty. A Cobb angle of greater than 25 to 30° is considered significant scoliosis, and greater than 45 to 50° is considered severe by the major orthopedic societies.[15] Kyphosis is excessive convex curvature of the upper spine defined by a Cobb angle of at least 50°.[16] Screening and diagnosis of kyphoscoliosis can be conducted based on physical examinations (patient in standing and bending position, tilt/asymmetry of the shoulders, and lower leg length measurement) and standing radiographs.

There is no standard system for grading radiation-induced toxicity from height reduction and spinal curvature. However, the Common Terminology Criteria for Adverse Effects (CTCAE) system[17] is the most frequently used scale for assessing toxicities from cancer treatments and is used by the majority of the PENTEC groups; therefore, the CTCAE system was selected by this group for the present analysis for scoring of scoliosis. The CTCAE defines scoliosis as "a disorder characterized by a malformed, lateral curvature of the spine." Grade 1 is clinical undetectable and <20°, and grade 2 and higher are symptomatic and at least 20°. Although severe cases of thoracic scoliosis can impair the function of the respiratory system,[18] CTCAE does not specifically account for effects on the cardiopulmonary system. CTCAE version 5.0[17] also scores growth suppression and kyphosis. These are summarized in the Table E1.

Growth stunting is identified by assessing a child's length or height. In children 2 years of age or younger, the sitting height is measured with the child lying down. After 2 years of age, the child should be placed sitting on a stool or table at a convenient height and measured from the top of the vertex to the bottom of the coccyx. Although we recommend using CTCAE for growth suppression assessments for consistency of data collection, for this analysis, we were unable to do so as the data available were in terms of absolute height reduction rather than growth velocity changes.

Anatomy and Developmental Dynamics

Skeletal development and volume over time are a function of interacting genetic, racial, anthropometric, nutritional, and lifestyle factors. These together contribute to the acquisition of peak bone mass, usually by the time normal adolescence and puberty are complete. Hormonal influences play a leading role both in the development and preservation of skeletal health.[19,20]

Vertebral ossification is an ongoing process from fetal development until early adulthood. At birth, these primary ossification centers can be seen as 3 bony centers within each vertebra from C3 to L5. Each of these vertebrae has one ossification center in the centrum (the vertebral body) and one in each half of the neural arch. Cartilaginous attachments, called neurocentral synchondroses, are on each side of the neural arch to the vertebral body and overlap with the ossification center in the arch. Ossification proceeds in an orderly fashion from cephalad to caudal, with ossification occurring first in the cervical vertebrae at age 2 to 3 and progressing inferiorly toward the lumbar region by age 6 to 7. The primary ossification centers of C1 and C2 and the sacrum and coccyx appear at slightly different times compared with the rest of the vertebrae (C3 to L5). Secondary ossification centers appear at the tips of the transverse processes, superior and inferior articulating processes, spinous processes, and ring apophyses of the vertebrae from C3 to L5 around pubertal age (age 10-13) and completely ossify by age 18 to 25.[21] Spine maturity is indirectly measured using the Risser sign (ossification of the iliac apophysis). Assessment of skeletal maturity at time of irradiation can help determine relative risks of growth deficits from radiation in children,[5] as children are likely most vulnerable to the effects of irradiation before ossification is completed, especially before primary ossification centers are closed.

The National Center for Health Statistics of the US Department of Health and Human Services published anthropometric reference data for children and adults in 2015 to 2018, including standing height by sex and age, obtained from the National Health and Nutrition Examination Survey (Table 7 of Fryar et al[22]). From these data, the median percentage of the final height attained by age can be calculated, as plotted in Figure 1. The percentage growth remaining for total stature and various bone segments in males and females was reported by Silber et al[2] based on 3 publications,[23-25] also illustrated in Figure 1.

In addition to absolute attained height, growth velocity in children provides meaningful information. Although growth patterns are subject to numerous influences in the short term, in the long term, they tend to follow a predictable pattern.[7,26] Figure E2 demonstrates typical growth rates (cm/y) in boys and girls from birth to age 18 years.

Defining Volumes: Pediatric Imaging Issues

The contouring of organs at risk should include bones and growth centers in the vicinity of the planning target volume, especially in skeletally immature children (Fig. E3). Many treatment planning systems are equipped with autosegmentation options, in which bones are contoured based on higher Hounsfield units. Manual modification of contours may be needed as noncalcified bones may not be adequately detected by autosegmentation tools.

Although dose constraints for specific ossification centers are not well defined, delineating them during the contouring process can guide the treatment planning system to limit dose as much as reasonably possible. Although both primary and secondary ossification centers play important roles in growth and symmetry, they appear at various time points of skeletal growth, and it may not be feasible to identify and contour each of them. It is recommended, however, to delineate the vertebrae using bone windowing on a CT scan that includes the vertebral body and the vertebral arch, which capture the primary and secondary ossification centers.[5,27] However, in practice, identifying the growth centers can be challenging because the vertebrae in children are often small. Therefore, it is common to delineate the entire vertebrae with or without posterior elements as an avoidance structure during treatment planning.

Review of Dose-Volume Response Data and Risk Factors

Search methodology for identification of studies

Search criteria for studies evaluating the effect of radiation on the musculoskeletal system were developed and agreed on by the task force. An initial search was performed using the PubMed and Cochrane libraries for relevant peer-reviewed articles written in English and published from January 1, 1975, to July 14, 2014. A search for additional data published through May 2022 was later performed, and applicable data were included. Six investigators independently reviewed abstracts and then full texts of articles that any reviewer considered potentially pertinent. Information on study design, source of data, population characteristics, and outcomes of interest were extracted and entered in an electronic data form. Eligibility assessment of the included studies, risk of bias assessment, and data extraction were performed independently and in duplicate. The literature search and selection methodologies used for this analysis are illustrated in Figure E1. Tables E2 to E4 summarize key publications reporting spinal deformities after focal irradiation, growth impairment after irradiation to the axial skeleton, and abnormalities after craniospinal irradiation, respectively.

Scoliosis

Mathematical models

To estimate the risk of scoliosis for a given radiation dose to vertebrae in children, data were extracted from 12 literature reports[8,9,26-35] of primarily young patients with neuroblastoma or Wilms tumor (N = 603; median age at diagnosis or radiation therapy, 0.5-4 years) with follow-up at least through puberty (Table E5). The majority of studies used a Cobb angle threshold of 5° or 10° for scoliosis diagnosis. Three studies[9,32,34] reported a scoliosis rate of 3% to 9% in survivors who did not receive radiation therapy, which were also included in the data fitting. Seven of 12 publications[9,26-30,35] reported individual patient outcome data,

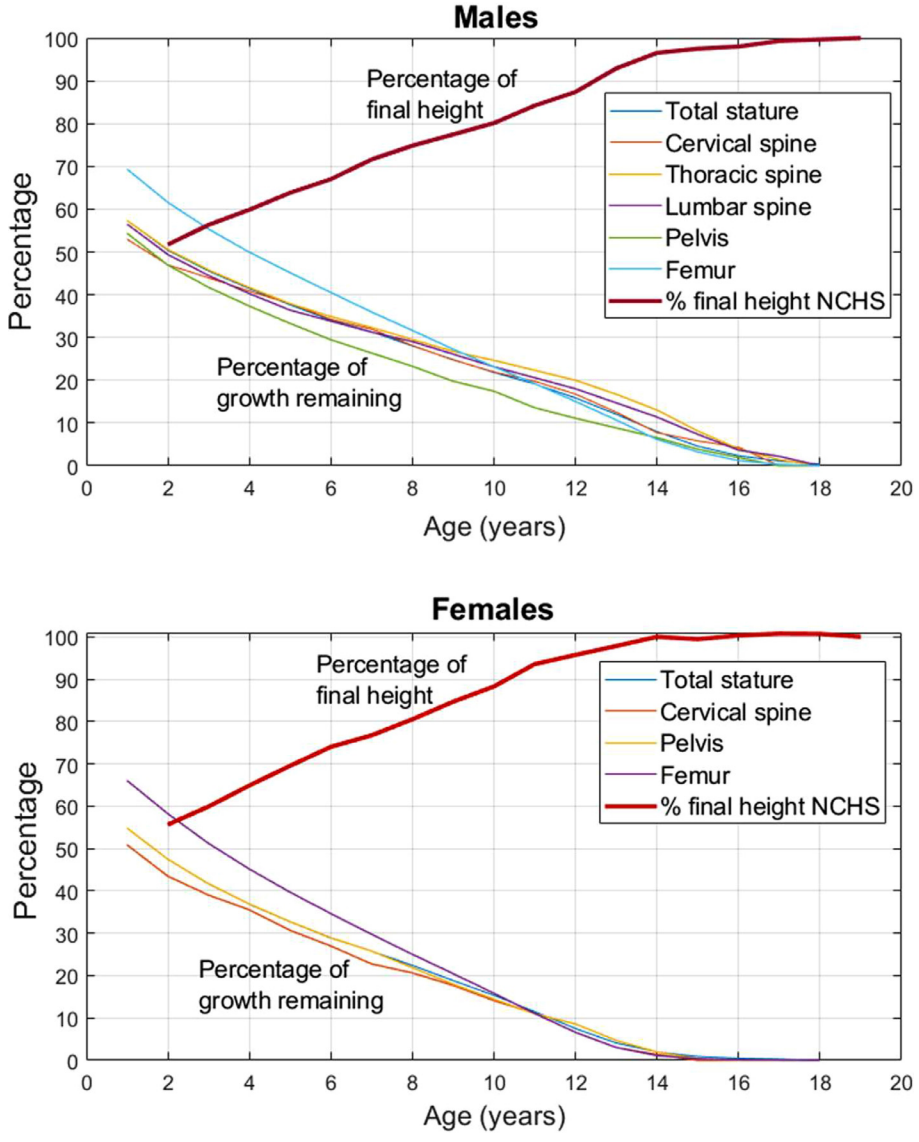

Fig. 1. Age-dependent mean percentage growth remaining and median percentage of final height for males and females. Data of percentage growth remaining were taken from Tables 2 and 3 of Silber et al.[2] Thoracic and lumbar data were not provided for females. The percentage of final height data were calculated from Table 7 of Fryar et al.[22]

which allowed this PENTEC team to calculate the risk of ≥20° scoliosis (CTCAE grade 2 or above; N = 275; median age at radiation therapy, 0.5-3.8 years; Table E6). We were not able to test the effect of sex on scoliosis due to limitations of the synthesized data. Of note, the terms gender and sex are used interchangeably based on the terminology used in the original research papers but refer to biologic sex unless otherwise indicated. When vertebral doses were not reported, prescribed doses were used as surrogates for megavoltage therapy because all selected papers stated that the entire width of the vertebral body was encompassed in the treatment fields. Given the proximity of the vertebral body to the tumor/tumor bed for young patients with neuroblastoma and Wilms tumor and need to treat para-aortic lymph nodes, the typical anterior-posterior-posterior-anterior (AP-PA) field arrangements in historical treatments would include an entire vertebral body circumference. This assumption was made for megavoltage therapy without retrospective dosimetry. For orthovoltage therapy, we estimated the spinal dose based on the beam energy, body size, and beam arrangement. The doses received by the vertebra when treated with orthovoltage beams (1940s-1990s) were calculated to be systematically higher than the reported prescribed doses. The main reason is that dose to bone is significantly higher than dose to water at orthovoltage energies. A method to convert from dose to water to dose to bone was described by Johns and Cunningham.[36] A modification of this method was used to correct reported orthovoltage doses used for toxicity prediction modeling. Historically, Wilms and neuroblastoma radiation treatments were delivered by 2 parallel opposed anterior-posterior fields, with the prescription dose representing the midplane dose. Since the 1950s,

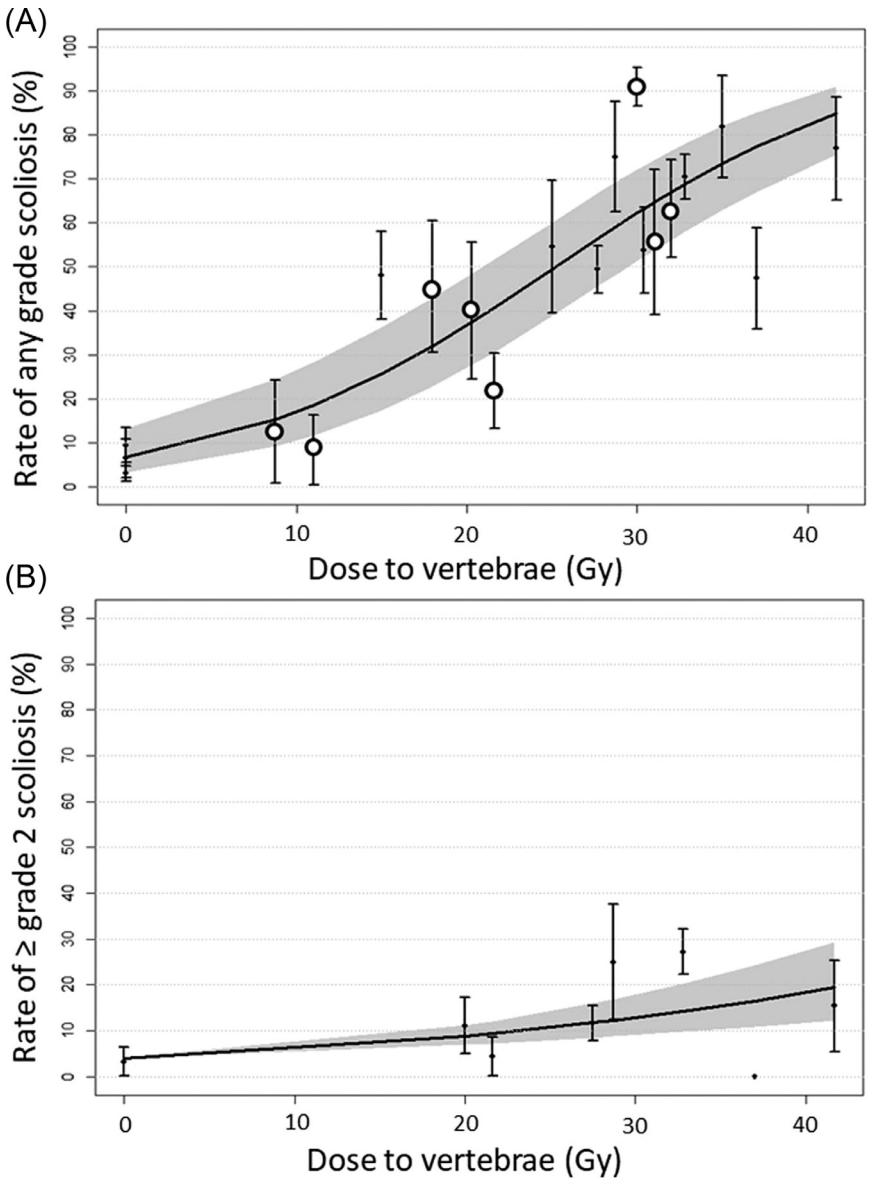

Fig. 2. Dose-effect relationship for scoliosis based on outcome data extracted from 12 (N = 603; for CTCAE any grade; A) and 7 (N = 275; for CTACE grade 2 or above; B) literature reports of young patients primarily with neuroblastoma or Wilms tumor. Solid curves were fit to all data points using the mixed-effects logistic regression model. In (A), open circles represent the studies that defined scoliosis as a Cobb angle of >10°, whereas solid points are >5° or threshold unreported. In (B), all data points are a Cobb angle of ≥20° (clinically significant or CTCAE grade 2 or higher). The shaded area is the 95% confidence interval band. Details for data points and publications are provided in Tables E5 and E6. All studies included in the figure reported that the entire width of the vertebral body was encompassed in the treatment fields. Conventional fractionation was used. *Abbreviation:* CTCAE = Common Terminology Criteria for Adverse Effects.

efforts have been made to include the whole width of the vertebra in the radiation fields. Based on this information, a correction was applied for the position of the vertebra in the fields. For all corrections, the following assumptions were adopted: average patient age of 3 years (reflecting primarily Wilms and neuroblastoma tumor types with average age of 3 years) (anterior-posterior (AP) separation of 13 cm and mid-vertebra depth of 8.7 cm), beam quality of 250 kV/HVL 2.8 mm Cu, 2 parallel opposed fields of 10 × 15 cm, and vertebra position 1 cm from the field edge. These assumptions resulted in a correction of 1.0764. When more information was given in the paper, that was used instead of the stated assumptions. Papers that provided dose to the vertebra were not corrected.[29,30] There was no correction for 1 paper with orthovoltage treatments[9] because it did not provide adequate information. For the publications where corrections were made, the corrections were applied only to orthovoltage doses. It is important to note that because

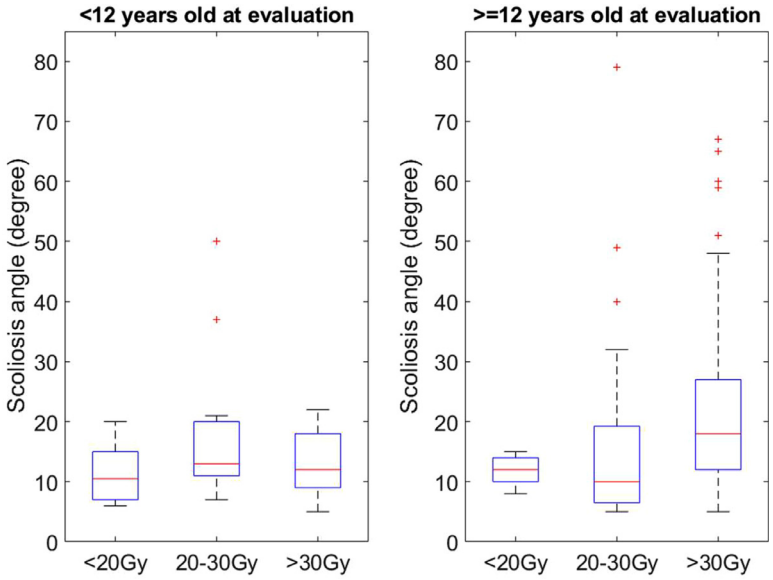

Fig. 3. Box plots (red line = median, box = interquartile range, red plus = outliers) of scoliosis angle demonstrating the effect of dose on severity of scoliosis in 129 childhood cancer survivors before and after puberty who developed scoliosis after radiation therapy, aggregated from 6 publications[9,24-28] that provided individual patient outcomes. The median age at radiation therapy for the entire cohort was 2 years (range, 1 month to 15 years). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

overcorrecting would lead to underestimation of the risks, the lowest possible corrections were applied. For a detailed description of all assumptions and corrections, see Appendix E1.

The crude rate of scoliosis was calculated for each study and plotted against the median dose of the group (or midpoint of the reported dose bin) in Figure 2. The uncertainty in scoliosis rate of each data point was represented by the vertical error bar based on the assumption of binomial distribution. Combined data points were fitted using the mixed-effects logistic regression model to account for potential correlation between data points in different dose bins from the same study and to render a sigmoidal association between the complication risk and the radiation dose. A 95% confidence interval was calculated for the fitted values of the model accounting for the model uncertainty. To investigate the effect of vertebral dose and age at radiation therapy on the severity of scoliosis, individual outcomes of 129 patients who developed scoliosis after treatments were pooled from 6 studies[9,26-30] with treatment fields encompassing the entire width of vertebrae. The median age at treatment was 2 years (range, 1 month to 15 years). The median age at last evaluation was 14 years.

To assess the importance of following survivors through puberty on determining the ultimate rates of scoliosis and its severity, the aggregated data of 129 patients with scoliosis in Figure 3 were divided into 2 groups based on the age at the time of the last evaluation conducted: before 12 years of age (n = 44; median age at radiation therapy and last evaluation was 1.2 years and 9 years, respectively) and after 12 years of age (n = 85; median age at radiation therapy and last evaluation was 2.5 years and 17 years, respectively). Each group was further separated into 3 subgroups based on dose to vertebral bodies.

Outcomes

As shown in Figure 2A and B, for young patients primarily with neuroblastoma or Wilms tumor, the fitted curves estimate a 35% (any grade) and 8% (grade 2 or higher) overall scoliosis rate from 18 to 20 Gy to vertebrae and 50% (any grade) and 10% (grade ≥2), respectively, from 25 Gy without a clear dose threshold. The association between vertebral dose and scoliosis rate is highly significant in our regression analysis ($P < .001$) for data in Figure 2.

The scatter plot in Figure 4 indicates that clinically significant scoliosis (grade 2 and above; Cobb angle ≥20°) can occur in infants (under 2 years of age) with doses as low as 15 Gy to vertebrae, but most cases reported in the literature received ≥20 Gy. For children 2 to 6 years of age, many clinically significant cases of scoliosis occurred after ≥20 Gy. For children >6 years of age, reported scoliosis cases occurred mainly with doses >30 Gy, and most were mild (<20°).

Similarly, Dörr et al[37] reported only minor bone and soft tissue pathology in adolescents older than 12 years, with substantial defects only above 35 Gy for children of 6 to 12 years, but possibly as low as 20 Gy in younger children (<6 years of age). Dörr et al also reported a 5% incidence of substantial osseous hypoplasia in the range of 20 Gy of equivalent dose delivered in 2 Gy fractions, with a/b ratio of 3 Gy ($EQD2_{3Gy}$) and recommended it as the "tolerance dose" for growing bones, particularly in children under 6 years of age at radiation therapy.

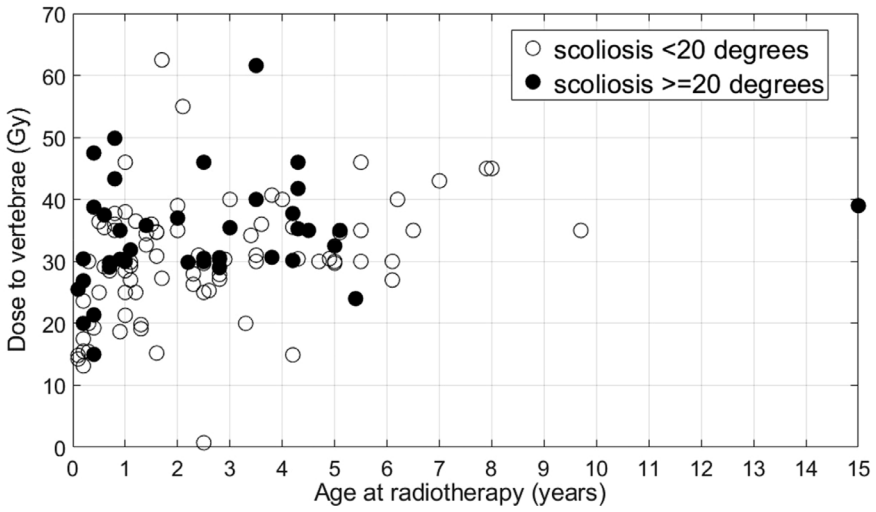

Fig. 4. Scatter plot of scoliosis severity in 129 childhood cancer survivors who developed scoliosis after radiation therapy, aggregated from 6 publications that provided individual patient outcomes.[9,24-28] Median age at last evaluation was 14 years for the entire cohort (13.1 years and 16.8 years for those with <20° scoliosis and those with ≥20° scoliosis, respectively).

As indicated in Figure E2, a sharp increase in growth velocity is seen around the onset of puberty in most children. For vertebral bodies receiving high doses (>30 Gy), significant scoliosis manifested predominantly after the growth spurt, as shown in Figure 3. Although any grade scoliosis can occur in approximately 10% to 40% of patients after vertebral body doses of ≈8 to 20 Gy (Fig. 2A), the severity of scoliosis in this dose range appeared to be mild (<20°) even after puberty (Fig. 3, right).

Height reduction from flank irradiation

Published models

Growth impairment in the spine was commonly reported as standing or sitting height loss (absolute/standard deviation score) or growth rate change for a variety of diseases and irradiated spinal sites. The mean sitting height is 88 cm for girls in the general US population after the pubertal growth spurt (assuming a standing height of 165 cm) and 92 cm for boys (for a standing height of 175 cm).[38]

Two published mathematical models quantitatively predict the absolute loss of standing height from local spinal irradiation. Hogeboom et al[39] developed a best-fit regression model that accounts for the dependence of height on gender and advancing age and predicts the stature loss at the age of 18 years due to flank irradiation based on height measurements of 2278 patients (median age of 35 months at diagnosis) treated in National Wilms Tumor Study Group Trials from 1969 to 1994. The study reported no difference in the radiation effect on stature between males and females. We implemented the Hogeboom mathematical model (Equation 2 in the appendix of their paper) by plugging in the regression coefficients (beta0 = −0.3172 and beta1 = 0.0227 in Table IV of their paper) and a wide range of doses to the spine (5-40 Gy) and age at radiation therapy (0-16 years), assuming no radiation therapy to the lungs and whole abdomen as well as no administration of doxorubicin and cyclophosphamide. Predictions of stature loss from our implemented Hogeboom model were plotted in Figure 5A as a function of age at radiation therapy and radiation dose to the T11-L4 spine (as was used in the Silber model in the following). This model predicts trunk shortening of 2.8 cm for infants receiving 10 Gy to the flank. Even 20 Gy to the flank of a 4-year-old would result in a loss of only 3.5 cm.

A more general model developed by Silber et al[2] predicts the adult stature loss following skeletal irradiation using data from 49 male patients (median age of 7.3 years at diagnosis) treated for a variety of non−central nervous system (CNS) pediatric cancers. It incorporates age at radiation therapy, tumor dose, region and proportion of the spine irradiated, and the ideal stature based on parental heights. For the purposes of this analysis, we assumed that the mean attained male stature at 18 years of age is 176 cm (based on Centers for Disease Control and Prevention data[22]). Stature loss for flank irradiation was calculated based on the Silber equations of MPAS (models predicted adult stature) and GALA (Gray adjusted for location and attained stature) and is plotted in Figure 5B for comparison with the Hogeboom model predictions. We noted that although the Silber equation is published correctly, there appears, in our analysis, to be miscalculation in the example case in the Silber report, which results in an overestimation of stature loss in figure 4 of *their* publication. (Please note that we have not been able to confirm this with the authors of the Silber publication.) As a result, our implemented version of the Silber model predicts less height loss (3.5 cm vs 6.5 cm from 20 Gy to a 2-year-old child). Despite the differences in predicted height reduction between our implemented Hogeboom's and Silber's models, both models predict a loss in stature of less

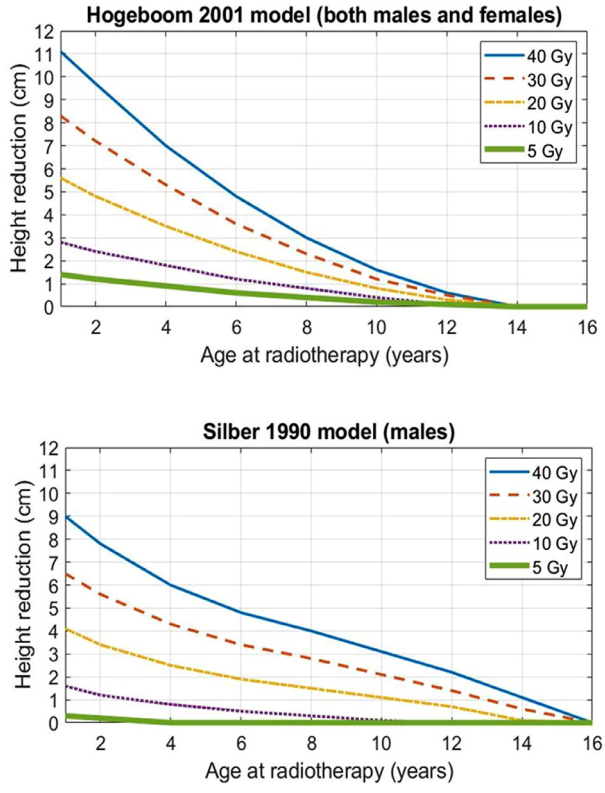

Fig. 5. Predicted age- and dose-dependent standing height reduction after flank irradiation (conventional fractionation), calculated from the Hogeboom 2001 model (top = not gender specific) and the Silber 1990 model (bottom = males only). The treatment fields were extended fully across vertebral bodies from the top of T11 to the bottom of L4. Note that our implemented Silber model predicts a smaller height loss than indicated in their paper. For the Silber model plot, the ideal attained stature for males was assumed to be 176 cm based on the anthropometric reference data from the US Department of Health and Human Services. The stature loss was only estimated for males with the Silber model due to incomplete data of percentage growth remaining for female lumbar and thoracic spines.

than 3 to 3.5 cm from ≤20 Gy flank irradiation to young children who are past infancy (>2 years). It is possible that higher doses at earlier ages result in not only closure of the primary ossification centers but also arrest in development of secondary ossification centers, which can lead to profound height reduction by the time adolescence is achieved. Older children and adolescents may have already developed the secondary ossification center and therefore see insignificant effects on height even when high doses of radiation are delivered at a later age.

One additional paper examined the effect of vertebral body sparing on future growth velocity, although the majority of patients were not yet followed through puberty.[40] Our calculations using their data and their modeling suggest a height loss of approximately 4.1 cm from 22 Gy to the flank fields (T11 to L4) in a young child, assuming 10 years of follow-up, and approximately 3.1 cm from 13 Gy to equivalent fields in a young child. These data also help predict the effect of dose modulation around the spine in an effort to reduce the impact on future spine growth.

Height reduction from irradiating the entire spine

The Silber model can be used to estimate the height reduction after irradiating the entire spine, excluding the skull, from the top of C1 to the bottom of S3. As shown in Figure 6, the reduction is appreciable for 20 Gy or higher at very young ages. The length of the entire spine in males increases by approximately 32 cm from 2 to 18 years of age. As predicted by the Silber model, the reduction in height by 28 cm when delivering 40 Gy to a 2-year-old suggests that 40 Gy approaches the dose that completely stunts spinal growth. Additionally, Willman et al[3] observed an average of 7.7% (13 cm or 2 standard deviations from the mean of the US population) standing height reduction measured beyond puberty when prepubertal children (age of ≤11 years in boys and ≤9 in girls) with Hodgkin disease received >33 Gy to the entire spine. For postpubertal children receiving the same doses, the reduction was only 2.7 cm (0.4% standard deviation).

Height reduction from craniospinal irradiation

Linear mixed-effects models were recently developed by Mizumoto et al[41] to fit the standing heights of 212 survivors of CNS embryonal tumors who received photon craniospinal irradiation and primary site boost to 55.8 Gy at the median age of 8.5 years and were followed for a median of 10.2 years. Figure 7 plots the estimated height reduction, adapted from their Table 2, for males and females receiving ≥36 Gy and 23.4 Gy craniospinal irradiation. Just over half of the cohort received growth hormone replacement. Assuming an expected attained height of 176 cm for healthy males, the models predict a significant reduction of 26 cm from ≥36 Gy craniospinal irradiation to a 4-year-old boy, slightly higher than the 24-cm reduction from 40 Gy irradiation to the entire spine (excluding cranium), as predicted by the Silber model. The reduction in height was estimated by the Mizumoto model to be 15% and 13% for boys receiving ≥36 Gy and 23.4 Gy, respectively, and 12% and 9% for girls receiving ≥36 Gy and 23.4 Gy, respectively, at 4 years of age.

Proton therapy

Proton therapy creates an opportunity to spare the growing vertebral body from radiation therapy given the sharp dose fall-off. Proton craniospinal irradiation has been shown to improve "out-of-target" volume organ sparing.[42] Proton therapy could be designed to treat only the thecal sac, as in

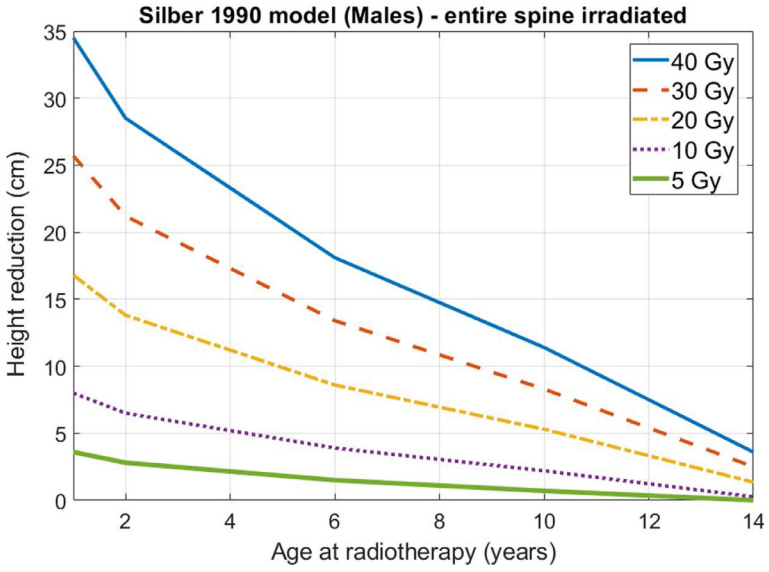

Fig. 6. Predicted age- and dose-dependent (conventional fractionation) height reduction after irradiating the entire spine (top of C1 to bottom of S3) of a male patient, calculated from the Silber 1990 model. The treatment fields were assumed to be extended fully across vertebral bodies from the cervical spine to sacrum excluding the skull. The ideal attained stature for males was assumed to be 176 cm based on the anthropometric reference data from the US Department of Health and Human Services.

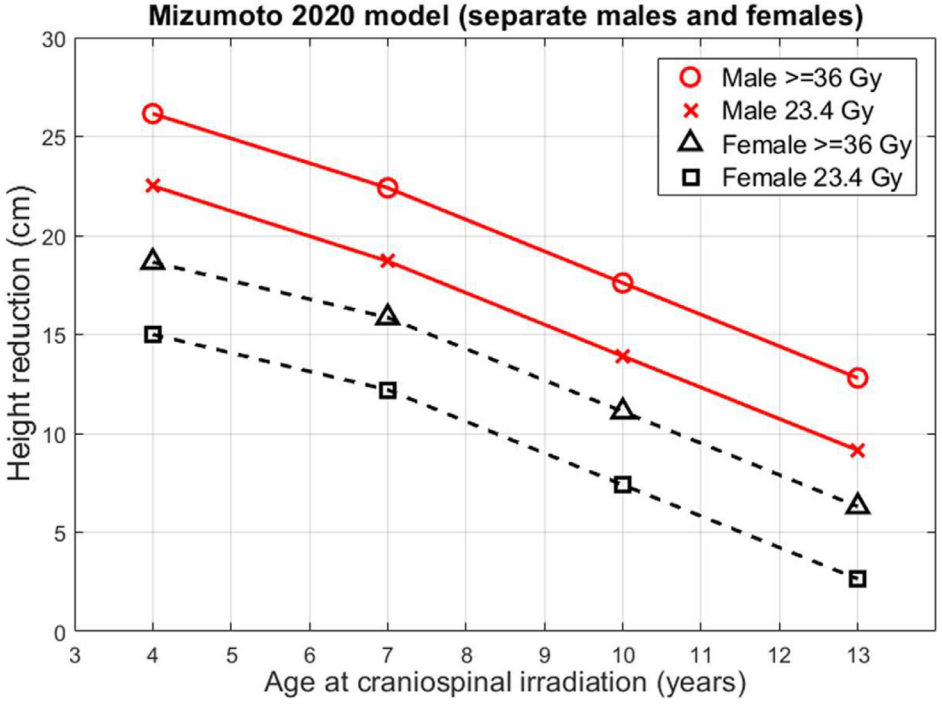

Fig. 7. Predicted reduction in standing height after photon craniospinal irradiation (conventionally fractionated), adapted from Table 2 of Mizumoto et al.[41] Growth hormone replacement therapy was prescribed for 57% of the cohort. No vertebral body sparing was performed. The final attained statures of 161 cm for healthy females and 176 cm for healthy males were taken from the anthropometric reference data published by the US Department of Health and Human Services. For this plot, model 4 in Mizumoto et al,[41] which includes the interaction between time and clinical variables of craniospinal irradiation dose, gender, and race, was selected, and height estimates for different races were averaged.

craniospinal irradiation, or just the retroperitoneal tumor bed, as with abdominal radiation, both scenarios with vertebral body sparing. However, it is rarely possible to completely avoid the vertebral body in these cases, and data describing the long-term impact of partially irradiating a margin of the vertebral body while sparing the remainder of the bone are limited. In a study of 6 children (3 to 5 years of age) with medulloblastoma, vertebral body–sparing proton craniospinal irradiation of 23.4 Gy or 36 Gy was delivered using a posterior-anterior beam stopped at the anterior thecal sac.[43] After a median follow-up of approximately 13 years, there was a small degree of posterior vertebral body height loss in all patients, but compensatory hypertrophy of the posterior aspect of the intervertebral discs was also observed, and no patient experienced thoracic lordosis or chronic back pain or required corrective surgery. There were no apparent negative effects on tumor control with this approach. There are likely additional short-term benefits (eg, reduced acute gastrointestinal toxicities and myelosuppression) to proton therapy beyond the effects on the spine.[44]

Intensity modulated proton therapy appears to achieve vertebral body sparing even more effectively than the passive scattering technique.[45] These data are promising in that proton vertebral body–sparing techniques may further reduce treatment-associated toxicities in growing children, although additional long-term growth outcome data are awaited. Based on this limited experience with proton-based vertebral body sparing, there appear to be fewer adverse effects from irradiation of the posterior elements than irradiation of the vertebral bodies on the development of scoliosis. This may help guide treatment planning algorithms to prioritize the more at-risk anterior elements. A recent analysis of the Pediatric Proton Consortium Registry reported that 18.6% of skeletally immature patients who received proton craniospinal irradiation were treated with the vertebral body–sparing technique.[46] Prospective trials of vertebral body–sparing proton craniospinal irradiation in children are underway.[47,48]

Dose/Volume/Outcome Associations

Dose/volume recommendations

Spine deformities

As demonstrated in the analysis described previously, absolute radiation therapy dose delivered to vertebral bodies appears to be the most significant contributor to spinal deformity, with a strong dose-effect association. Doses <10 Gy cause minimal to no clinically detectable vertebral abnormality regardless of the age at treatment. Clinically significant scoliosis can occur with 15 to 20 Gy to the spine in infancy (<2 years). Children between 2 and 6 years old will have >30% risk of scoliosis with doses >20 Gy, but the degree of scoliosis is usually mild (<20°). Doses approaching 30 Gy or higher to the spine are associated with higher rates of clinically significant scoliosis for children under age 6, but this risk may extend to older children (possibly underreported) before reaching full growth. Whenever possible, efforts should be made to keep doses below 20 Gy, and in infants under age 2, doses should be kept as low as possible (<10 Gy), as this age group is the most vulnerable to radiation affecting their bone growth beyond height loss, such as osteopenia[49] and fracture.[50]

Table E2 details studies that examine rates of scoliosis from radiation therapy. Kyphosis and lordosis appear to be less common than scoliosis and are rarely reported in isolation without scoliosis. This may suggest that dose symmetry over the vertebral bodies in the anterior-posterior direction is less critical than in the lateral direction. Several studies also suggested that asymmetrical growth, or instrumentation, of the neurocentral synchondrosis, which is positioned in the posterior aspect of the immature vertebral body (Fig. E3), did not appear to contribute to scoliosis risk[51,52]; hence, irradiation to the posterior components of the vertebral bodies should have less of an impact on scoliosis risk.

It is also important to limit the number of vertebral bodies irradiated.[40] Field size may be an important contributor toward higher kyphoscoliosis rates, but data are sparse. Most data come from patients treated primarily at low thoracic and lumbar spine segments (Wilms tumor and neuroblastoma). There are also insufficient data to draw conclusions about the differential impacts of radiation therapy on the cervical versus thoracic versus lumbar spine. Full spinal axis irradiation, outside of craniospinal irradiation, is less common now with the elimination of extended fields historically used to treat lymphomas in children and adolescents. Further, older children who were previously treated with high doses and extended fields for lymphomas do not appear to have high rates of clinically significant kyphoscoliosis, likely due to treatment delivered after attainment of puberty, which partly explains the paucity of data in this domain. Although uncommon, some young children will be subjected to irradiation of nearly the entire spine as part of whole lung plus flank or whole abdominal irradiation. The models mentioned previously can help estimate the risk of scoliosis in this cohort based on the dose delivered to the spine.

Table E4 includes relevant studies reporting bone changes after craniospinal irradiation. These patients typically have not had surgery involving the spinal column or surrounding tissues as craniospinal irradiation is used for high-risk CNS malignancies. One series reported a 15-year incidence of scoliosis after photon craniospinal irradiation of approximately 35%, with most cases categorized as mild and none classified as severe.[51] Huynh et al[52] reported a rate of 27% (scoliosis and kyphosis were defined as a Cobb angle of ≥10°), with young age being the most important risk factor. Severity was not further detailed. The true incidence may be underreported. The exact mechanism of scoliosis in this subset of patients is unclear and could not be further elucidated by the task force. It was hypothesized that there

may be contributions from growth stunting and uneven gait from neurologic deficits.

Lateral dose gradient may have a significant effect on risk of scoliosis. However, most studies reported covering the entire vertebral body with a symmetrical dose; yet, as demonstrated, patients still developed kyphoscoliosis. Only 1 study[37] analyzed the relationship between dose gradient across the vertebral body and the incidence of kyphoscoliosis. For children younger than 6 years of age, lateral dose gradients within the vertebral body of 10, 20, and 30 Gy resulted in 50%, 85%, and 100% incidences of substantial kyphoscoliosis, respectively. However, it is unclear whether this is truly due to the gradient or is instead a pure dose effect, as other studies have shown higher incidence of scoliosis with higher doses to the spine, as previously discussed. It is possible that most factors are of importance. There may also be directional and anatomic impacts of gradients that need further elucidation, especially in the conformal radiation therapy era. For instance, if the gradient is in the posterior-anterior direction without reaching a primary ossification center in the vertebral body and only involving very limited secondary ossification centers, it may cause less risk of abnormal spinal curvature. In comparison, the dose gradient in the lateral direction or reaching the entire width of the vertebral body may result in more significant scoliosis/kyphosis/lordosis. The current European consensus guidelines (SIOPE) do suggest minimizing the gradient for both partial spine radiation therapy and craniospinal irradiation for prepubertal children in the lateral and posterior-anterior dimensions when possible but do allow for higher spinal doses depending on the prescription dose to minimize gradient.[53]

The age at time of radiation is one of the strongest risk factors, with younger patients most susceptible to deformities. In our meta-analysis of scoliosis severity, the median age at radiation therapy in the cohort was 2 years, with most patients ≤5 years of age. Due to a limited number of older children in reported studies, the data are limited for modeling the risk for children >5 years of age. The rates of kyphoscoliosis, especially significant cases, should be much less in children treated at older ages. Very young patients (<2 year of age) are susceptible to more frequent and more significant scoliosis, even with lower doses (10-15 Gy). Importantly, long-term follow-up is critical to ascertain true rates of radiation-induced spinal deformities. The reported rates of scoliosis from high-dose radiation to the spine nearly doubled when survivors were followed past age 12, which roughly correlates with the average onset of puberty.

Spine growth stunting

Attainment of ultimate growth of the vertebral bodies was proportional to dose delivered, with changes evident after 10 Gy, but more significant impacts on height were observed with doses >20 Gy. Clinically significant loss of standing height (2 standard deviations below average or >10 cm) may be detectable after high doses (>30 Gy) are delivered to the spine of prepubertal children. Age at time of irradiation is one of the strongest determinants of loss of growth, with the youngest children harboring the greatest risk of height impairment from radiation. Additionally, the number of vertebral bodies and the segment of the spine (cervical vs thoracic vs lumbar) may influence the degree of growth stunting. More profound height loss is observed with irradiation of the entire spine or craniospinal irradiation.

Limitations

Most of the published retrospective clinical studies are from the 2-dimensional era, using AP-PA fields. These studies reported the dose prescribed to the tumor and noted intent to deliver symmetrical doses across the spine. Therefore, the present analysis assumes that the prescription dose was uniformly applied to the adjacent vertebral bodies for megavoltage radiation therapy. However, none of these studies provided detailed dosimetry analyses of spinal dose, which limited our ability to evaluate dose distributions across the vertebral body as well as in the superior-inferior direction and make definitive associations between scoliosis and height loss and the number of vertebral bodies irradiated, location of the spine irradiation, and dose gradients for 2-dimensional and even 3-dimensional era patients.

Furthermore, approximately one-fourth of these patients were treated with orthovoltage beams (roughly 194 of 765 patients), which is associated with increased dose heterogeneity and may exacerbate the effect of dose gradients on kyphoscoliosis outcomes. We made extensive efforts to estimate the received dose to bone in patients treated with orthovoltage beams based on limited information reported in individual papers. Retroactively correcting the dose to bone in older studies with 2-dimensional techniques for modeling of toxicities is fraught with uncertainties, including, but not limited to, various patient and field sizes, beam energies, depth dose distributions, beam arrangements, and potentially inaccurate linear attenuation coefficient data. Additionally, we made conservative bone dose corrections where it was reasonable to do so, but, given that the dose to bone is higher with orthovoltage than with megavoltage (MV), our scoliosis models likely overestimate the risk of deformity and growth impairment for a given prescription dose in patients treated with orthovoltage beams. Furthermore, as noted previously, the models have been built with the assumption that dose across the vertebral bodies was uniform; however, this may not have been the case depending on how close the edge of the field was to the vertebral bodies or if a single field was used, which is information that cannot be gleaned from the available published reports.

Although long-term follow-up data from the modern, conformal radiation therapy era are lacking, a few recent studies[35,37] do provide evidence for the impact of asymmetrical dose delivery and varying dose gradients to a limited segment of the spine on spinal deformities. There may be additional factors that contribute to the risk of kyphoscoliosis for which these studies largely do not account. Unilateral abdominal tethering that occurs with decreased muscle development resulting from surgery or irradiation, as often

occurs in Wilms tumors and neuroblastoma, may contribute to spinal deformities.[54] Postoperative spinal deformities might develop in the sagittal or coronal plane following laminectomies or other spinal surgeries.[55] Pathologic bone destruction can also increase the propensity of spinal deformities and make the spine more susceptible to postoperative deficits.[56] Chemotherapy may affect musculoskeletal development, likely due to effects on a molecular level, although the mechanisms are not completely understood.[57-59] Finally, there is a possibility of a correlation between height loss of vertebral bodies resulting in spinal instability and therefore spinal deformities; however, the available data do not presently allow such analyses. This may be an area of future investigation. Future studies should also investigate the impact of these confounders on the risk of spinal deformities.

We also lack detailed information regarding the use of growth hormone and gonadotropin hormone replacement in patients receiving craniospinal irradiation in terms of rates of or timing of delivery. This information would certainly impact the degree of growth stunting in this vulnerable population.[41,60,61] In addition, certain chemotherapeutic agents and supportive medications (eg, steroids) can contribute to bone hypoplasia both directly and indirectly, but the extent of impact on growth remains unclear. Poor nutrition and low activity levels because of side effects of treatment can also contribute to poor growth.

Finally, it should be cautioned that there were limited studies for infants and older children and adolescents; therefore, the impact of radiation dose on these outcomes cannot be accurately assessed nor can the rates of spinal deformities or growth impairment be determined at this time.

Summary of recommendations

Table 1 summarizes the aforementioned data and recommendations. Where possible, the spine dose should be limited to 20 Gy, especially in young children, and in infants under age 2, the spine dose should be as low as possible (eg, ≤10 Gy ideally although not typically achievable for many clinical scenarios; <15 Gy is likely acceptable) to limit the risk of kyphoscoliosis and growth stunting. In children 6 years of age and younger, doses >20 Gy can result in clinically significant kyphoscoliosis and growth impairment. Although the prevalence is unclear, based on clinical observations, there is a significant risk of spine deformities and growth stunting at doses exceeding 30 Gy for most children who have not achieved skeletal maturity. We suggest that the gradient should be limited to less than 10 Gy (especially in the lateral direction) but as low as reasonably achievable in the context of target volume coverage and prioritization of critical organs at risk. We also recommend irradiation of as few vertebral bodies as possible, while respecting dose limits to surrounding organs and target volume coverage.

In the case of craniospinal irradiation, we recommend including the full spinal column and vertebral bodies in the initial volume to no more than 20 Gy and then treating the thecal sac only to the remaining dose (typically up to 23.4-36 Gy). This approach is similar to the SIOPE consensus recommendations, which recommend limiting the dose gradient to ≤5 Gy for low-dose craniospinal irradiation. These recommendations are also consistent with Children's Oncology Group (COG) protocol guidelines, which recommend that 18 Gy be delivered to the full vertebral body for the initial phase but accept any gradient necessary to achieve full target volume coverage. For higher doses of craniospinal

Table 1 Summary of key findings and recommendations

Endpoints	Age at irradiation (y)	Dose effects (Gy)	Volume effect	Mitigation strategies
Clinically significant spine deformities and growth impairment	0-2 2-6 >6 Frequency and degree of spine deformities are inversely proportional to age at irradiation The effect of radiation therapy on growth impairments diminishes around age 12-14 (based on sex)	>10-15 >20 >30 Frequency and degree of spine deformities are dependent on dose and start to plateau around 40 Gy Dose gradient, especially in the lateral direction, is expected to have an impact on the development of scoliosis	The degree of spine deformities is dependent on the volume of the spine and of each vertebral body and the number of vertebral bodies irradiated	Limit the number of vertebral bodies exposed to high dose Avoid beams going through the vertebral body, when feasible Use highly conformal techniques, when available Reduce the dose to the vertebral body while treating nearby clinical targets with differential dosing methods (eg, simultaneous integrated boost) Minimize the dose gradient to be as low as feasible to avoid deformities

irradiation, we also recommend limiting the dose to the vertebral bodies to 20 Gy. This may result in a larger gradient. However, only 1 study has specifically addressed the effect of dose gradient on the severity of scoliosis. We do not feel comfortable recommending a higher dose to the spine to minimize the dose gradient until further data become available. However, the gradient should be limited to the maximum extent possible, again while respecting target volume coverage and prioritization of other surrounding critical organs.

Survivors should be followed past puberty to ascertain ultimate kyphoscoliosis outcomes. These recommendations need to be taken in the context of the patient's overall situation (ie, it is often necessary to deviate from these recommendations to adequately irradiate the target tissues). The balance between tumor control and late effects is especially challenging in children.

Toxicity Scoring Recommendations

Prospective longitudinal monitoring of skeletal outcomes through full skeletal maturity and beyond, including toxicity scoring, is important to allow better understanding of dose effects on the spine and to generate more reliable models, especially in the contemporary era of radiation therapy.

We recommend CTCAE version 5.0 criteria for scoring of scoliosis/kyphosis and growth stunting (Table E1). Long-term follow-up of children subjected to skeletal irradiation is paramount to determining ultimate outcomes. Although there is no strong evidence to suggest the optimal frequency of these evaluations, routine follow-up every 6 months with measurements including height using the methods described in the Endpoints and Toxicity Scoring section provides an easy assessment of growth velocity. Patients should be screened for spinal deformities at these visits as well. Ultimate height attainment and deformities scoring using CTCAE version 5.0 should be recorded at least once past full skeletal maturity.

Data Reporting Standards Specific to the Musculoskeletal System

We propose that the following data be collected and reported in future studies to improve our understanding of radiation effects on the pediatric musculoskeletal system and to facilitate more rigorous and quantitative meta-analyses:

- Patient demographic and clinical data, including whether skeletal maturity has been attained. We suggest evaluation by a pediatric endocrinologist when clinically indicated.
- Prescribed target volume dose, fractionation, and radiation modality.
- Identification/labeling of cervical versus thoracic versus lumbar vertebral bodies during treatment planning.
- Maximum, mean, and minimal dose delivered to the vertebral body and arch in the vicinity of the target volume.
- Dose gradient as determined by the differential in the lateral and anterior-posterior directions.
- Total attained height and sitting height (presence of stunting and CTCAE version 5.0 grading) at final follow-up.
- Presence and severity of scoliosis, kyphosis, and lordosis at baseline and during follow-up (using CTCAE version 5.0).
- Any other skeletal toxicities, such as bone fracture.
- Use of, including timing of, hormone replacement therapy.

Future Investigations

More complete and detailed data are needed to better understand the impact of radiation therapy on spine outcomes in the pediatric population and to facilitate modeling. There are limited data for very young and adolescent patients. Furthermore, additional data are needed on the dose gradient effect in the contemporary radiation era, especially with highly conformal photon and proton irradiation techniques, including vertebral body–sparing strategies. Based on the available data, the anterior-posterior gradient seems to be of less concern, but this should be evaluated in future studies involving vertebral body–sparing craniospinal irradiation. Doses to the specific components of the vertebral bodies that may contribute to these outcomes, such as the neurocentral synchondroses, ossification centers, posterior elements, and supporting musculature lateral to the spine, may also be important to determine as highly conformal techniques evolve. In fact, it is possible that the incidental irradiation of the muscles lateral to the spine, in addition to uneven irradiation of the ossification centers, may be contributing to greater incidences of scoliosis rather than kyphosis/lordosis. In addition, the majority of studies involve the lumbar spine, but there are limited data on cervical and thoracic spine outcomes when irradiated in isolation (ie, not involving entire spinal irradiation). Additional approaches (eg, using artificial intelligence) may be helpful in improving the accuracy of modeling. More powerful models might be instrumental in guiding treatment planning decisions and in determining the impact of various radiation techniques, beam arrangements, and so on. This information might allow for a more personalized, risk-adapted approach to radiation therapy and follow-up plans and interventions for these children.

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