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Critical Review

A Road Map for Important Centers of Growth in the Pediatric Skeleton to Consider During Radiation Therapy and Associated Clinical Correlates of Radiation-Induced Growth Toxicity

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With the increasing use of advanced radiation techniques such as intensity modulated radiation therapy, stereotactic radiation therapy, and proton therapy, radiation oncologists now have the tools to mitigate radiation-associated toxicities. This is of utmost importance in the treatment of a pediatric patient. To best use these advanced techniques to mitigate radiation-induced growth abnormalities, the radiation oncologist should be equipped with a nuanced understanding of the anatomy of centers of growth. This article aims to enable the radiation oncologist to better understand, predict, and minimize radiation-mediated toxicities on growth. We review the process of bone development and radiation-induced growth abnormalities and provide an atlas for contouring important growth plates to guide radiation treatment planning. A more detailed recognition of important centers of growth may improve future treatment outcomes in children receiving radiation therapy.

Introduction

Radiation therapy (RT) can have inhibitory effects on the growth of the pediatric skeleton, leading to functionally debilitating toxicities if impaired growth results in asymmetry.[1-7] The foundational experiments to explore the impact of radiation-induced growth toxicity were performed by Hinkel.[8-10] In preclinical studies, the risk of growth stunting was related to the radiation dose delivered via a single fraction and the age of the patient at the time of

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irradiation. Subsequent in vivo studies by Eifel et al[11] demonstrated decreased injury to growth centers and improved recovery with increased fractionation. When fitted to a linear-quadratic model, the growth plate α-to-β ratio has been estimated as 4.5, suggesting an intermediate sensitivity to fractionation or, more likely, a sensitivity based on the combined impact of radiation on several varied cell populations with unique responses to radiation toxicity.

Long-term follow-up reports of early RT protocols for pediatric malignancies have provided unfortunate, yet important, clinical lessons about radiation-induced growth abnormalities. These toxicities reflect the potential impact of radiation toxicity on growth inhibition. However, most data on toxicity are generated from an era predominated by 2-dimensional (2D) treatment planning, higher prescription doses, larger treatment volumes, and less conformal techniques than used today. With the increasing use of advanced radiation techniques such as intensity modulated radiation therapy (IMRT), stereotactic RT, and proton therapy, radiation oncologists are now positioned to begin to consider musculoskeletal dose objectives that can be prioritized in a more conformal treatment-planning era. This approach is of utmost importance in the treatment of a pediatric patient.

Complexities of a Standard Dose Constraint

For several reasons, defining dose constraints for growing regions of the skeleton is a complex challenge and, as a result, current guidelines are generalizations that lack the framework to support nuanced decision making. This result is certainly not due to a lack of effort. Because most data that report growth toxicity resulting from RT are based on treatments given in the prior 2D treatment era, the field currently lacks the ability to define and validate nuanced three-dimensional (3D) dosimetric parameters to the growing skeleton. The inherent complexities of the various forms of bone growth and the implications of growth disruption based on the anatomic location of the insult also pose challenges.

A multitude of patient factors affect musculoskeletal growth, such as age, pubertal status, nutritional status, and medical comorbidities. In a child with cancer, systemic therapy and surgical insults may further contribute to growth inhibition. For example, surgery of the paraspinal region may cause damage to the musculature, exacerbating the risk of scoliosis when combined with RT. Particular chemotherapy regimens may also slow the rate of growth; however, it is thought that a period of catch-up growth follows completion of therapy in the absence of RT to reach a normal growth pattern. The long-term growth effects of intensive chemotherapy regimens are unclear. RT factors, including the total radiation dose, fractionation, dose homogeneity, beam energy, treatment volume, symmetry of the treatment volume, and nature of the irradiated growth centers, all independently influence the severity of radiation-induced abnormalities in growth.[2]

Emerging data from the 3D treatment-planning era support the complexity of both predicting the variable sensitivity of the parts of the musculoskeletal system and providing guidance to the radiation oncology community on dose parameters to the growing skeleton as an organ at risk (OAR). Krasin and colleagues from St. Jude Children's Research Hospital have proposed a model considering patient-specific and radiation plan dose-volume information to specifically predict growth of flat bones.[12] The investigators created a model that incorporated variables such as patient age, baseline volume of the OAR, and radiation dose to understand the impact of RT specifically on the development of facial and pelvic flat bones in pediatric patients. The model supported a significant effect of doses at or >35 Gy, weighted by the volume of bone treated at that specific dose, as an important dose-volume parameter incorporating a threshold and the cumulative effect of dose on risk of growth toxicity. Modeling studies hold promise to provide the type of nuanced dosimetric constraints that are likely necessary to reduce the risk and severity of radiation-induced musculoskeletal toxicity.

Currently, the field is limited to oversimplified thresholds to guide RT planning to at least provide a goal for normal tissue avoidance. Doses $\geq$15 Gy,[4] particularly those $\geq$30 Gy,[7,13-15] have been associated with clinically measurable toxicities. These observations inform the common current clinical practice to restrict asymmetrical treatment to the epiphyseal growth plates to $<$15 Gy. If this is not feasible, the entire growth region is "targeted" with a more uniform dose to avoid the risk of deformity because of asymmetrical dose across the growth center. Pediatric Normal Tissue Effects in the Clinic is a group of physicians, physicists, and epidemiologists who are striving to develop quantitative, evidence-based, dose-volume guidelines for treatment planning. This important collective will include guidelines for dose to the pediatric musculoskeletal system and is eagerly awaited.

Assessment of Skeletal Maturity and Completion of Growth

Assessment of skeletal maturity is the practice of evaluating skeletal development with respect to size, shape, and degree of mineralization of the bone to determine its nearness to full maturity. In children receiving RT, assessments of skeletal maturity can help predict the risk of inducing radiation-associated growth arrest in patients who have not yet reached full maturity. The most widely used skeletal maturity assessment techniques used today are the Greulich-Pyle and Tanner-Whitehouse 2 approaches, both involving left hand and wrist radiographs.[16-19]

For the purposes of RT treatment, the Tanner-Whitehouse 2 and Greulich-Pyle assessments of bone age are only truly useful if the patient is determined to be at

complete skeletal maturity. It is recommended that this comparison be done by an experienced reader. Because the axial skeleton matures a few years later than the remaining skeleton, consideration of a more focused assessment for spinal maturity in select patients using the Risser sign may be warranted,[20] which should be assessed by an expert pediatric radiologist.

The following sections will highlight the location of important centers of growth to consider during RT planning for patients with residual potential for growth to either reduce the risk of radiation-induced growth abnormalities by sparing highlighted regions or to improve patient counseling when treatment of the growth centers is unavoidable.

Anatomic Road Map of Important Growth Plates and Clinical Correlates of Radiation-Associated Growth Toxicity

Whole-brain radiation therapy

The human skull consists of 5 "flat" bones, the paired frontals and parietals and the unpaired interparietal, and is bound laterally by the squamous part of the temporal bone and the greater wing of the sphenoid bone (Fig. 1). All of these bones are formed by intramembranous ossification, and the predominant growth of the calvarium occurs at the interfaces, or sutures, of the bones. Sutural growth is driven by the underlying increase in intracranial hydrostatic pressure correlating with the enlarging brain volume and occurs perpendicular to the orientation of the suture, continuing throughout the period of growth of the brain.[21,22] The most rapid period of growth of the calvarium is within the first year of life, by the end of which the brain is 75% of adult size. Growth continues at a slower rate, typically until puberty.

The call for whole-brain radiation therapy (WBRT) for an infant is fortunately rare, although WBRT is at times recommended as part of a risk-based approach to children with leukemia,[23,24] with doses of 18 to 20 Gy for the patients at highest risk. A multitude of acute and long-term toxicities are associated with WBRT in the developing child. Impairments in cognitive function and hormone production (including growth hormones) are among the most common long-term toxicities. Radiation oncologists, however, should also be aware of the risk of premature growth arrest of the calvarium, or craniosynostosis, because of radiation-associated toxicity. Although infrequent, consequences are profound and may require multiple surgeries with potential for wound-healing complications.

Craniofacial radiation therapy

The challenge in avoiding radiation-associated toxicity resulting with craniofacial radiation therapy is inherent in the physiology of growth of the facial bones. The growing cartilaginous nasal septum is believed to be a primary driver in the morphogenesis of the maxilla and surrounding bones until the age of approximately 7 years as the nasal septum grows forward and down, carrying the maxilla with it and causing separation of the sutures and subsequent stimulation of bone growth. After age 7, the overall surface apposition represents the dominant mechanism of growth.[25-27] Both the maxilla and the mandible grow in a similar process of bone deposition on the posterior surfaces, with resorption from the anterior surface leading to gradual remolding and reorientation of the bone in such a way as to maintain their constant relative positions with areas of articulation and as part of the maxilla and mandible bones as a whole.[22] Table 1 depicts the percentage of craniofacial growth completed at different stages. Although most of the growth of the calvarium is complete by age 5, the remaining craniofacial growth centers continue to grow at a steady pace until the second decade of life.[28] Figure 2 highlights the locations of important centers for craniofacial growth, which should be recognized and avoided when possible in the treatment

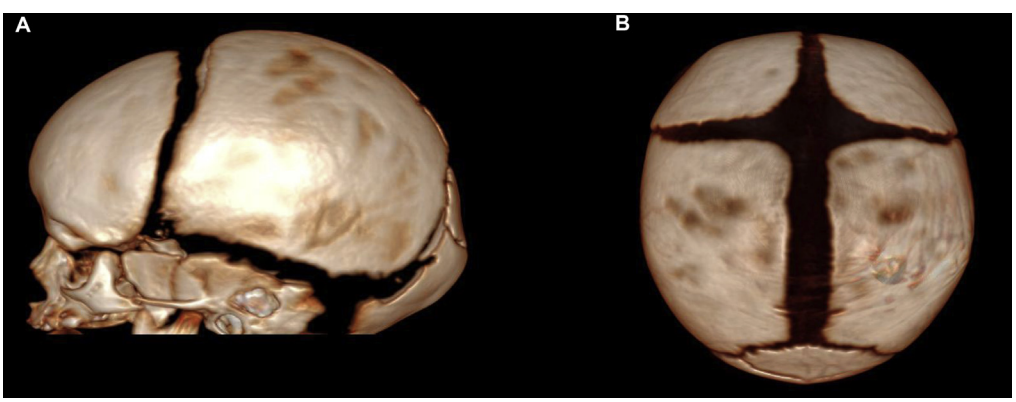

Fig. 1. Cranial sutures depicted on 3-dimensional reconstruction computed tomography images of a 7-day old male infant.

Table 1 Percentage of craniofacial growth completion by age groups

Site	Patient age (y)		
	Birth-5 (%)	6-10 (%)	11-20 (%)
Cranium	85	11	4
Maxilla	45	20	35
Mandible	40	25	35

Adapted from Phulari.[28]

plans for growing pediatric patients receiving RT to the head and neck.

Facial hypoplasia

Facial hypoplasia and asymmetry are known consequences of craniofacial irradiation, occurring as a result of damage to the growth centers of the nasomaxillary prominence, mandible, and the nasal septum.[22,29]

Growth suppression of the facial bones causing asymmetrical craniofacial appearance has been reported in up to 75% of patients treated with proton or photon radiation therapy for rhabdomyosarcoma of the head and neck.[29,30] Most commonly, toxicity manifests as hypoplasia of the maxilla or mandible. Children with nasopharyngeal cancer also experience late deformities in the cranial vault and reduced interorbital distance compared with healthy controls, albeit at a reduced frequency than patients with head and neck rhabdomyosarcoma. This result is likely because of the older age of presentation of nasopharyngeal cancer compared with rhabdomyosarcoma.[1]

The resultant physiological dysfunction in respiration, alimentation, and dentition that can result secondary to facial hypoplasia and asymmetry often requires repeated, difficult reconstructive surgeries. Such surgical procedures have challenging postoperative courses because of poor wound healing caused by postirradiation ischemia and fibrosis. Furthermore, the sequelae often lead to lifelong psychological problems.[31-33]

The limitations in avoiding craniofacial asymmetry and hypoplasia are inherent in the treatment of head and neck tumors, which most often present with a laterality. When uninvolved by tumor, avoidance of growth centers in the ipsilateral and contralateral face should be attempted. A better understanding of the radiobiology of postradiation wound-healing complications, the impact of the differential skin dose delivered using proton radiation therapy compared with photon radiation therapy, and the use of IMRT to spare the skin surface when possible is needed to reduce the burden accompanying reconstruction in the head and neck after RT. Furthermore, given the challenges in quantifying facial asymmetry, future studies comparing radiation approaches (proton vs photon), or possibly radioprotectant pharmaceuticals, should consider objective measurement approaches using 3D imaging techniques.[34]

Orbital defects

Orbital defects are a common late toxicity experienced by long-term survivors of retinoblastoma and orbital rhabdomyosarcoma cured with chemotherapy and radiation[35-37] (Fig. 3). Patients at a younger age (<6 months)[38] are at greater risk for orbital defects after radiation. Advancements in IMRT and proton therapy have improved the ability to maximize dose to the tumor while sparing the surrounding ipsilateral orbit compared with 2D radiation therapy (2D-RT), 3D conformal radiation therapy (3D-CRT), or en face electron plans.[39-41] In a study by St. Jude Children's Hospital, the doses to the orbit in 5 patients with neuroblastoma confined to the globe of the eye were compared across 4 RT techniques (IMRT, 2D-RT, 3D-CRT, and en face electrons) per patient.[41] The mean volumes of ipsilateral bony orbit

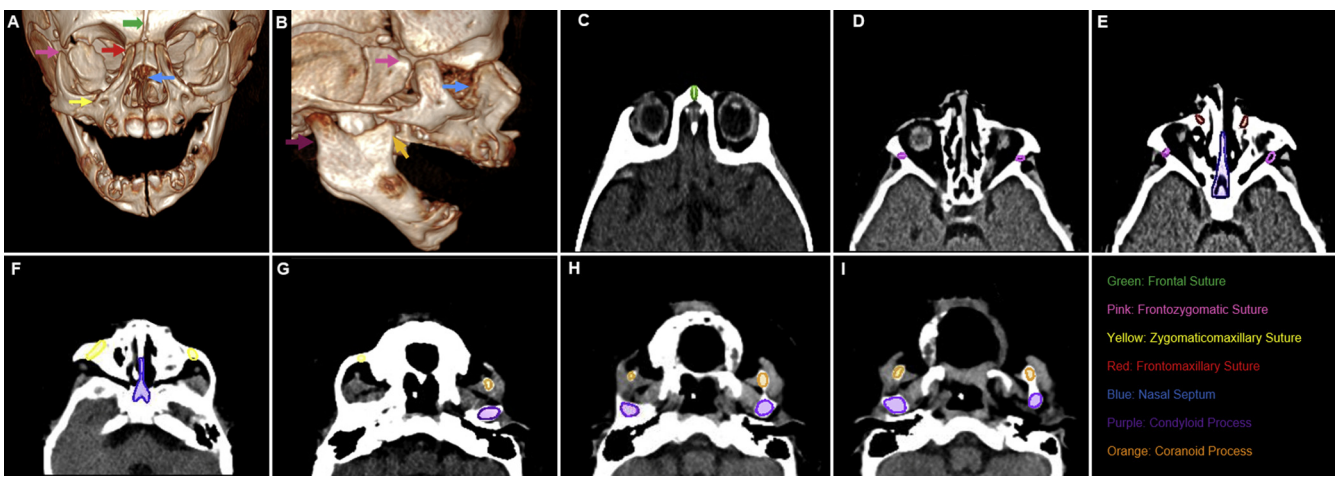

Fig. 2. Craniofacial centers of growth depicted on an anterior (A) and lateral (B) 3-dimensional reconstructed computed tomography scan of an 8-month-old female infant. Also shown are axial computed tomography slices with contours of important centers for growth (C-I), progressing in the craniocaudal direction.

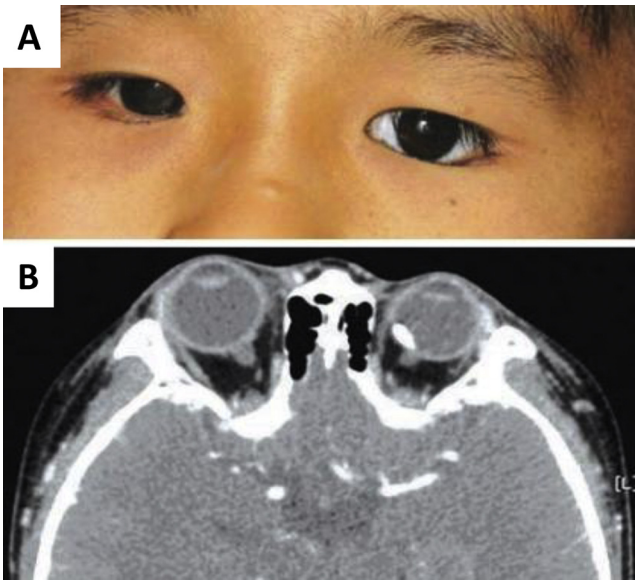

Fig. 3. (A and B). Orbital hypoplasia after radiation therapy for retinoblastoma. Reprinted from Choi et al.[37] (https://doi.org/10.3346/jkms.2010.25.4.546 is licensed under CC BY-NC 3.0).

treated above 20 Gy were 60% for IMRT compared with higher volumes of 78%, 91%, and 89% for 3D-CRT, 2D-RT, and electron plans. In a smaller study including 3 patients with retinoblastoma, the average of the mean orbital volume receiving 20 Gy or more was 22% in the IMRT plans compared with 3% in the proton plans generated, with an even more pronounced reduction in the average of the low-dose volumes receiving 5 Gy more (69% for IMRT vs 10% for proton plans).[39]

When the tumor is confined to the globe without bony orbit invasion, the orbit should be contoured as a separate OAR to guide treatment planning to reduce the dose as much as reasonably allowable. Particularly in patients at increased risk for the development of secondary malignancies, such as those with hereditary retinoblastoma, proton therapy may provide the added theoretical advantage of decreasing this risk by reducing the volume of normal tissue receiving lower doses when compared with IMRT.[40]

Shoulder and arm radiation therapy

Patients receiving RT in proximity to the shoulder girdle include children with soft tissue sarcomas (trunk, chest wall, or extremity disease), Hodgkin or non-Hodgkin lymphomas (supraclavicular, axillary, or mediastinal disease), and head and neck cancers (lower cervical/supraclavicular disease or elective coverage). When considering administering RT to this region, one must recognize the important growth plates in the clavicle and the humerus that are depicted in Figure 4 to avoid or recognize the potential toxicity if these areas are included in the RT plan.

Clavicular narrowing

Clavicular narrowing has been reported as a toxicity in children treated with extended field treatment and high-dose RT for pediatric Hodgkin disease.[4,42] The treatment approach to pediatric Hodgkin lymphoma has gradually

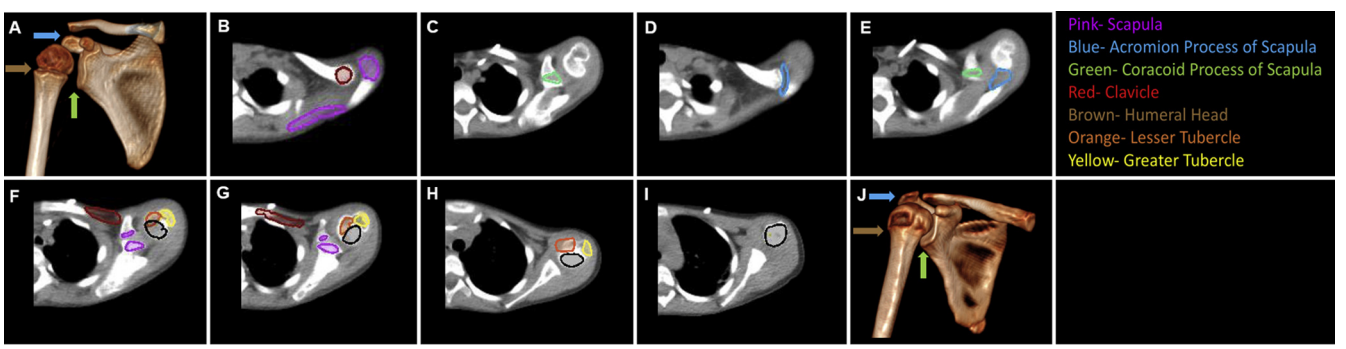

Fig. 4. Important ossification centers of the shoulder depicted on an anterior (A) 3-dimensional reconstructed computed tomography scan of a 5-year-old female patient. Axial computed tomography slices show contours of important centers for growth (B-I), progressing in the craniocaudal direction. Growth is nearly complete, with ossification centers fused, in the depicted scan from a 14-year-old male patient (J).

adapted to the use of reduced radiation dose and field size. Still, reduced clavicle growth has been observed in patients treated with only 15-Gy asymmetrical mantle irradiation for Hodgkin lymphoma involving the unilateral neck or supraclavicular region and no mediastinal involvement in a published series of 15 patients with a mean age of 12.9 years at time of radiation.[4] In the study, fully irradiated clavicles grew only 1.3 ± 0.3 cm, compared with 1.8 ± 0.4 cm of growth in partially irradiated clavicles. In addition to the effect of irradiation on the developing soft tissue, asymmetrical clavicular narrowing can contribute to subsequent asymmetry of the overlaying musculature, as shown in Figure 5.[4]

Slipped proximal humeral epiphysis

Subluxation and separation of the proximal humeral epiphysis has been reported as a rare but serious complication of irradiation to the shoulder. Both chemotherapy and RT likely contribute to the development of a slipped proximal humeral epiphysis occurring within the first 2 years of completing radiation treatment.[43-46] The pathophysiology of this toxicity is thought to be similar to that of the more commonly reported slipped capital femoral epiphysis (SCFE) after RT of the pelvis and proximal femur.

Slipped proximal humeral epiphysis is known to be an injury associated with high trauma in children without cancer. The relative laxity of the shoulder combined with the amount of stress across the joint may account for the apparent rarity of separation of the proximal humeral epiphysis after RT. Special counseling on the risk of this toxicity should be considered in patients receiving RT to the shoulder, particularly in those who engage in high-impact or repetitive-use activities.

Arm-length discrepancy

In patients with soft-tissue sarcomas, a limp-sparing approach to therapy uses mutimodality therapy or primary RT. In such patients, although the limb may be spared, the limb is at risk of significant shortening, atrophy, and pathologic fracture. Although such morbidity resulting from RT is dose dependent, adequate control of the primary tumor is essential, prohibiting significant dose reduction. Furthermore, residual arm-length discrepancy can still offer improved form and function compared with amputation, which may otherwise be required for treatment.[47] Counseling regarding the moderate morbidity that can result from arm-length discrepancy, however, is essential before RT.

Pelvic radiation therapy

Pelvic RT poses risks to the developing spine (discussed in the following sections), pelvis, and proximal femur. Figure 6 highlights several growth plates that exist in the pelvis and, if unilaterally damaged, can cause asymmetry in future growth.

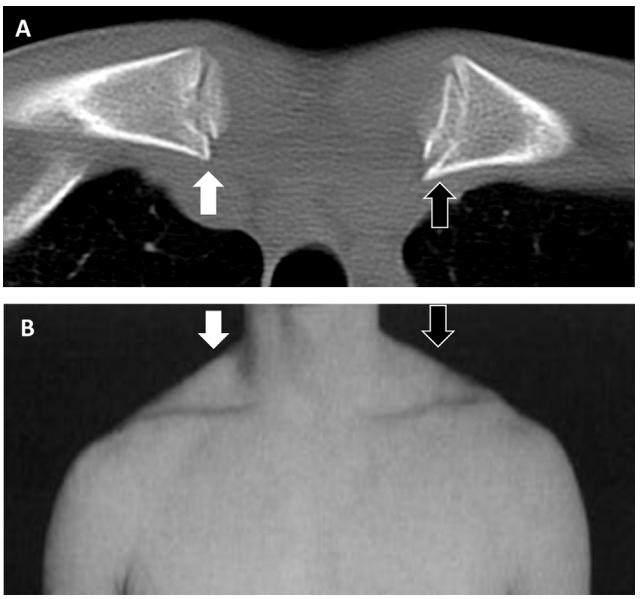

Fig. 5. The locations of the right (white arrow) and left (black arrow) clavicular physes are shown on an axial computed tomography scan of a 15-year-old female patient (A). The clinical correlate (B) depicts a slight asymmetry noted after radiation therapy to a total dose of 15 Gy to the entire right clavicle (white arrow) and partial left clavicle (black arrow) in a male patient, resulting in mild clavicular narrowing and soft tissue asymmetry in the region of the right clavicle. Figure 5B is reprinted with permission from Merchant TE, Nguyen L, Nguyen D, et al.,[4] with the only modification being the addition of the corresponding white and black arrows.

Slipped capital femoral epiphysis

In contrast to children with typical SCFE, children with RT-associated SCFE are usually thin and younger in age. In a report of 50 children younger than 15 years receiving RT to the pelvis and nonfused capital femoral epiphyseal plate, a total of 83 epiphyseal plates were at risk 4 plates (5%) developed clinically symptomatic SCFE. In the series, no cases occurred in children treated with <25 Gy; however, no dose response was noted after administration of 25 Gy. An increased risk of RT-induced SCFE was seen in children <4 years at time of RT.[48]

In a second report of 32 children with RT-associated SCFE treated across a range of doses (1000-8000 cGy), presentation and pathology were noted to be milder than in cases of routine SCFEs. Again, incidence was associated with a younger age of presentation, and delivery of higher doses of RT (>40 Gy vs ≤40 Gy)[49] did not appear to be a risk factor. Higher radiation dose was associated with a more rapid development of SCFE, with the median time between RT and diagnosis of the SCFE being 6.0 ± 3.0 years (range, 1.0-13.3 years). Given the development of RT-associated SCFE even after doses as low as 1000 cGy in a child with Wilms tumor in the series, it is prudent to take care to restrict the proximal femoral epiphysis to as low a dose as reasonably allowable when feasible.

Osteonecrosis

RT to endocrine organs involved in bone homeostasis and the bone at risk itself increases the chance of developing osteonecrosis. In patients with cancer, the femoral head, humeral head, and jaw are at highest risk of osteonecrosis.[50-52] Osteonecrosis is less common in children than in adults and is thus not likely to be a result of insult to the growing bone.[50,51] Existing reports of osteonecrosis in children treated with RT have been described in the context of a combination of chemotherapy, steroids, and surgery, and thus, incidence may be due to the contribution of multiple risk factors. In a study by Hanif et al[50] investigating patients with pediatric cancer who were treated between 1974 and 1991, femoral head osteonecrosis was seen in 15 cases of 5278 treated patients, 5 of whom were treated with RT (4 with doses ≥35 Gy). All also received chemotherapeutic agents associated with development of osteonecrosis. Although rare, osteonecrosis can be a challenging late toxicity when present in children because of the difficulty in subsequent management. Avoidance of prolonged steroid use in children receiving RT to regions at high risk (femoral head, humeral head, and mandible) could reduce the risk of this late, multifactorial toxicity.

Leg-length discrepancy

Leg-length discrepancy after RT has been reported not only after treatment to the femur, tibia, and fibula, but also to the abdomen. Figure 7 depicts the percentage of bone growth, limb growth, and average growth per year of the lower extremity.[53] In a series of patients treated with RT for Wilms tumor, 5 of 42 patients (12%) developed leg-length discrepancy, of which 2 were symptomatic.[54] Although small leg-length discrepancies can be managed with a shoe lift, treatment may require multiple corrective surgeries and, in extreme cases, even amputation to achieve adequate function.

Spinal irradiation

Currently, it is common practice to treat the whole vertebral body to avoid asymmetrical growth in a pediatric patient. Extension to the contralateral edge of the vertebral body can result in substantially higher doses to the contralateral kidney, ovaries, and liver in some cases. It is recommended to assess spinal maturity in patients who may be peripubertal or postpubertal to guide a more deliberate decision-making process in the need to include the entire vertebral body in the adolescent population. This approach

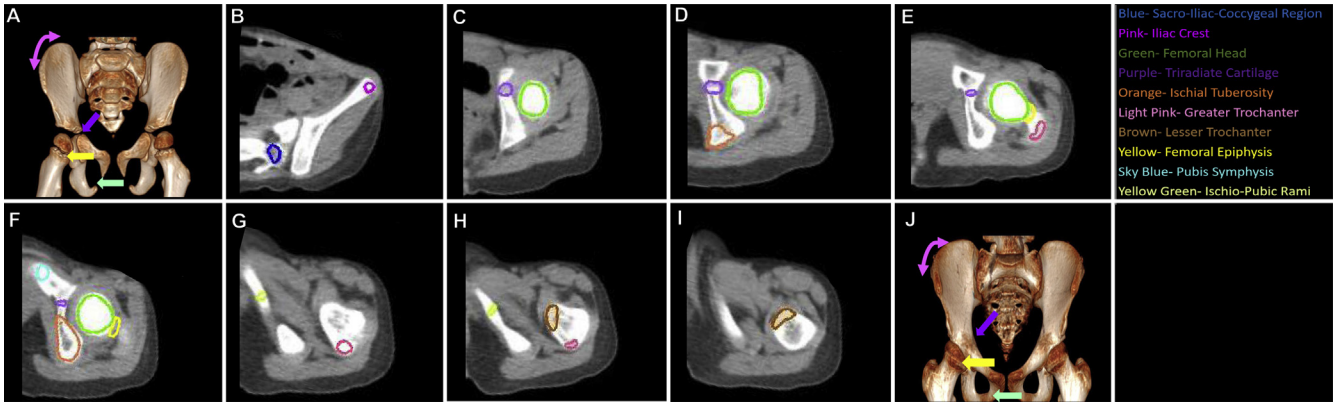

Fig. 6. Important ossification centers of the pelvis in an anterior (A), 3-dimensional, reconstructed computed tomography scan of a 2-year-old male patient, with axial computed tomography slices showing contours of the centers of growth (B-I) progressing in the craniocaudal direction. Growth is near complete, with ossification centers fused, in the depicted scan from the 12-year-old female patient (J).

is preferable to reflexively extending a radiation field to treat the whole vertebral body for symmetry in all pediatric patients.

Reduced final height

Chemotherapy has been shown to cause growth impairment in children during treatment, and often a period of catch-up growth occurs once chemotherapy is completed.[55,56] Radiation-associated growth impairment, however, cannot be overcome by a period of recovery. Probert et al first quantified radiation-associated growth impairment in children after megavoltage complete spinal irradiation.[57] The most marked abnormalities of growth were noted in patients receiving >35 Gy to the axial skeleton and who were younger than 6 years of age or between 11 and 13 years of age at the time of radiation treatment. An extension of this study was performed by Willman and colleagues, incorporating baseline height measurements on all patients, rather than comparing measurements to a population standard, as done in the initial Probert and Parker report.[7] Their results indicated that height impairment is the greatest for boys irradiated before age 11 and girls irradiated before age 9. The association between younger age at time of RT and more significant height impairment have been shown by others as well.[56,58-60] Table 2 shows the predicted height deficit (cm) at age 18 after flank RT for Wilms tumor at selected ages and doses.[61]

Silber et al[5] successfully constructed a model to predict the final adult height in children treated for cancer outside of the central nervous system, incorporating patient-specific factors (age, sex, baseline patient height, and parent height) and radiation-specific factors (dose, location within the spine, inclusion of the femoral heads, and vertical centimeters treated of specific anatomic regions), which can be used to predict the impact of RT on a more patient-specific level.

Several radiation techniques have been evaluated in attempts to reduce the magnitude of radiation-induced growth abnormalities. Hyperfractionated versus conventionally fractionated craniospinal radiation for children and young adults with standard-risk medulloblastoma was recently evaluated in the PNET4 European trial, with hyperfractionated RT being associated with reduced growth but better executive function.[62] More promisingly, retrospective data on vertebral body sparing with IMRT in children with neuroblastoma show early promise in the ability to use advanced technologies to avoid or reduce radiation-associated toxicities in growth and warrant prospective investigation.[63] Vertebral body sparing craniospinal irradiation using proton therapy is also being explored as a method to reduce bone marrow toxicity, allow increased tolerance to chemotherapy, and reduce radiation-induced growth toxicity.[64,65] Vertebral body sparing intensity modulated proton therapy may spare a significant portion of the vertebral body from radiation doses that would cause growth impairment (10-20 Gy).[64] In a report of long-term follow-up of 5 pediatric patients with medulloblastoma treated with vertebral body sparing proton therapy, 2 patients were clinically diagnosed with scoliosis and treated

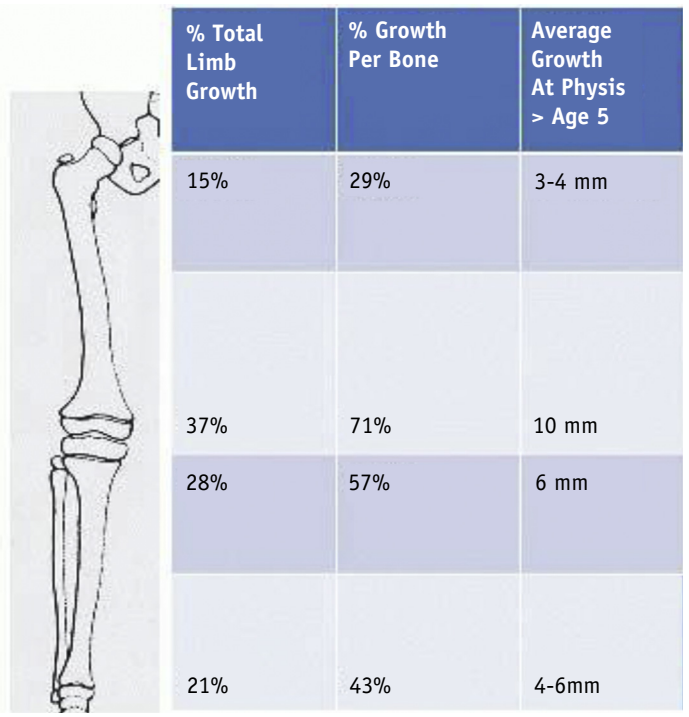

Fig. 7. Percentage of bone growth, limb growth, and average growth per year of the lower extremity. Reprinted with permission from Halanski and Noonan.[53]

Table 2 Predicted deficit in height (cm) at age 18 years after flank radiation therapy given at selected ages and doses for Wilms tumor

Age at treatment (y)	Height deficit (cm) after radiation therapy dose of		
	10 Gy	20 Gy	30 Gy
2	2.4	4.8	7.2
4	1.8	3.5	5.3
6	1.2	2.4	3.6
8	0.8	1.5	2.3

Reprinted with permission from Hogeboom et al.[61]

conservatively.[65] No patients reported chronic back pain, required spine surgery, or were noted to have thoracic lordosis; however, diminished growth of the posterior portions of the vertebral bodies was identified with an average posterior-to-anterior height ratio of 0.88. Interestingly, there was compensatory hypertrophy of the posterior intervertebral disks in all patients.

Scoliosis

Dörr et al reported the long-term sequelae of RT on bone and soft tissue from a series of 146 children whose trunk or extremities were treated, excluding patients with cranial irradiation.[66] Pathologic findings in the skeletal system and soft tissues were observed in more than 50% of patients, with respective minor cases in 59% and substantial cases in 41% of those affected. Overall, no substantial pathologic changes on the bone and soft tissue occurred in patients treated who were older than 12 years. More than 10% of patients experienced substantial scoliosis corresponding to a bending of the vertebral column of 10° to 20° and requiring corset treatment, whereas nearly 20% of children experienced minor scoliosis requiring physiotherapeutic procedures. A significant inverse dependence on age at exposure and specific incidence of kyphoscoliosis was found. For children younger than 6 years of age, dose gradients within the vertebral body of 10 Gy, 20 Gy, and 30 Gy resulted in a ~50%, 85%, and 100% incidence of substantial kyphoscoliosis, respectively.[66] Other reports support younger age as a risk factor for development of scoliosis after radiotherapy.[67] Discrepancies are found, however, in the threshold of radiation dose after which scoliosis occurs across studies. Although Door et al[66] report cases of scoliosis after treatment with EQD2 (equivalent dose in 2-Gy fractions) when $\alpha/\beta = 3$) <10 Gy, others have reported cases only in patients treated with >26 Gy[67] and >20 Gy,[68] respectively.

Although the impact of RT on the growing spine is more substantial in younger patients, the manifestation of the alternations in spinal alignment only becomes more pronounced during periods of rapid growth, particularly the adolescent growth spurt, during which close follow-up is recommended.

Conclusion and Future Directions

Progress in the treatment of pediatric malignancies has brought new hopes for long-term survivors in nearly every cancer diagnosis afflicting children. Coupled with the immense strides in systemic therapy and operative techniques, novel technologies in the field of RT are being exploited not only to eradicate disease but also to keenly mitigate toxicity. To do so for the growing skeleton, however, is a particular challenge for the radiation oncologist. The developing skeleton is a complex organ, without a clearly understood or fixed dose constraint. Overlaying the variations in genetic and environmental factors that uniquely affect a patient's sensitivity to RT is the complex, age-dependent sensitivity to radiation-induced musculoskeletal damage. Furthermore, the rate and completion of growth vary among the regions of the human skeleton.

Here, we enable the radiation oncologist to better understand, predict, and minimize the radiation-mediated toxicities on growth by reviewing the physiology of skeletal development and pathophysiology of radiation-induced growth abnormalities. The clinical cases and atlas of important anatomy involved in growth serve as a tutorial for contouring important growth plates to guide treatment planning to avoid or better anticipate musculoskeletal toxicity. This approach will lead to improved patient counseling, outcomes, and considerations for follow-up.

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