Four Ways to Decrease Late Toxicity From pelvic Radiation Therapy in Children and Young Adults

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Received 5 April 2021; revised 6 July 2021; accepted 7 July 2021

Abstract

The use of curative-intent multimodality therapy with chemotherapy, surgery, and radiation results in late toxicities in almost two-thirds of patients with pediatric cancer. When pelvic radiation is used for pediatric malignancies such as rhabdomyosarcoma, lymphoma, neuroblastoma, Ewing sarcoma, and Wilms tumor, the associated late toxicities can affect many normal tissues and may include growth asymmetries, cystitis, infertility, and sexual dysfunction. We describe 4 recommendations of how to prevent or minimize late toxicities from pelvic radiation and review the literature of these pediatric late toxicities.

Introduction

Three out of five pediatric patients develop late effects from their cancer treatment, some of which can have a lasting effect on their quality of life, with 30% of pediatric patients experiencing a grade 3 to 4 late effect.1,2 Pelvic radiation is used to help provide local and regional disease control for a variety of pediatric malignancies including rhabdomyosarcoma, lymphoma, neuroblastoma, Ewing sarcoma, and Wilms tumor. In this article, we review the late toxicities of pelvic radiation and discuss 4 practical approaches to consider when delivering pelvic radiation to a young patient with the goal of decreasing serious late complications from radiation damage to normal tissues.

1. Target the entire vertebral body and minimize dose to the femoral heads

Radiation therapy is associated with multiple late effects on the skeletal system, including spinal malalignment, skeletal hypoplasia and limb length discrepancy, avascular necrosis, slipped capital femoral epiphysis, and insufficiency fractures.3 Younger age during treatment and higher radiation dose are particularly associated with the skeletal late effects.4-7 Spinal malalignment, either as kyphosis or scoliosis, has a prevalence ranging from 2% to 80%, with younger age and radiation dose affecting the prevalence.3 Modern radiation techniques emphasize an even distribution of radiation dose across the vertebral body, decreasing the risk for spinal malalignment (Fig 1).8 Skeletal hypoplasia or growth asymmetry is another late effect of radiation.3 Skeletal hypoplasia was found in 9 of 16 patients (56%) treated with doses greater than 25 Gy.9 Furthermore, after pelvic radiation, low bone-mineral density resulting in osteoporosis or insufficiency fractures can occur.10 Slipped capital femoral epiphysis after radiation has a reported incidence of 10% to 18% and is noted to occur at a younger age than expected—mean age, 10.4 years—in patients who received prior pelvic radiation.11-13 Avascular necrosis of the femoral head also can occur after pelvic radiation, particularly after high doses.14 Femoral head blocking, which minimizes the risk for late toxicity both to the femurs and to the surrounding hip musculature, is shown in Fig 2.
2. Treat with the bladder as full as possible to reduce dose to the bladder and bowel

Late effects of pelvic radiation on the urinary system include chronic cystitis and bladder fibrosis. Chronic cystitis can be characterized by irritative voiding symptoms of urinary frequency, urinary urgency, and dysuria. Radiation-induced cystitis can also be hemorrhagic, with irritation of the lining of the bladder exposing submucosal blood vessels with chronic bleeding. Radiation doses of more than 30 Gy to the entire bladder or more than 60 Gy to a portion of the bladder are risk factors for hemorrhagic cystitis. Bladder fibrosis can result in reduced bladder distensibility and capacity. Yeung et al found that 7 of 7 pediatric patients with rhabdomyosarcoma involving the bladder or prostate who underwent postoperative radiation developed abnormal voiding patterns, and 4 of the 7 (57%) showed reduced bladder capacity. Neurogenic urinary incontinence is uncommon after pelvic radiation and generally occurs after radiation doses of 45 Gy or more to the sacral spine or cauda equina.

In addition to late genitourinary effects, late gastrointestinal effects can occur and include bowel obstruction,
chronic enteritis, and fistula.\textsuperscript{17,18} Depending on the pelvic fields, radiation may have a greater effect on the small bowel or large bowel. The rates of late gastrointestinal toxicities such as bowel obstruction are confounded by prior surgery in addition to radiation.\textsuperscript{17}

Thus, using radiation techniques to minimize dose to reduce the volume of the bowel irradiated can help minimize the additive effects of multimodality therapy. Figure 3 shows the use of bladder filling to displace the bowel cephalad away from the radiation fields and to push uninvolved portions of the bladder away from the target volume to minimize late gastrointestinal and urinary effects. In cases where daily anesthesia is required, the bladder filling technique is as follows: at each fraction, a Foley catheter is inserted with sterile technique into the bladder and the bladder is filled with sterile saline to the same volume each day (volume dependent on patient size); the Foley is clamped during treatment, and after treatment, the bladder is drained and the Foley is removed.
3. Shield the scrotum and minimize dose to the ovaries

Pelvic radiation therapy can cause late effects in the reproductive system in both males and females, including hypogonadism, infertility, and sexual dysfunction. In males, radiation doses of 20 Gy or greater to the testicles can result in primary hypoandrogenism from Leydig cell failure. Subclinical Leydig cell insufficiency resulting in low testosterone can occur at lower radiation doses. In addition, prepubertal males are more sensitive to radiation, with hypoandrogenism occurring after 24 Gy, whereas postpubertal males experience hypoandrogenism at a dose of 30 Gy or greater. Infertility, as either oligospermia or azoospermia, occurs at radiation doses as low as 0.1 Gy, and more than 3 Gy to the testicles can result in permanent azoospermia. To prevent these late effects, radiation fields should be designed to exclude the testicles unless they are the targeted, involved tissue. In addition, gonadal shielding with lead clamshells or other devices is recommended whenever possible to decrease the dose to the testicles from external scatter and leakage from the primary source (Fig 4). This shielding will not prevent internal scatter. Sperm banking via cryopreservation should be discussed with male postpubertal patients.

In females, late effects from pelvic radiation include hypogonadism with low ovarian production of progesterone and estrogen, infertility and birth complications such as preterm labor and low birth weights, and sexual dysfunction. Radiation to the ovaries can cause either acute ovarian failure, occurring within 5 years of cancer diagnosis, or primary ovarian failure resulting in premature menopause. The dose of radiation resulting in ovarian failure decreases with age, likely owing to a smaller oocyte pool responding to radiation damage. Wallace et al calculated the following dose limits to cause immediate ovarian failure: 20.3 Gy at birth, 18.4 Gy at 10 years, and 16.5 Gy at 20 years. However, doses of 5 Gy in postpubertal females and 10 Gy in prepubertal females can impair ovarian function including hormone production. If pelvic radiation fields may result in a dose to the ovaries sufficient to cause immediate or premature ovarian failure, ovarian transposition can be used to reduce ovarian dose by moving the ovaries outside the pelvic radiation fields (Fig 5). In addition, oocyte

Figure 3  Treat with bladder as full as possible. A 3-year-old boy with stage 3, clinical group III embryonal rhabdomyosarcoma of the prostate, intermediate-risk categorization, underwent radiation delivering 50.4 Gy in 28 fractions. At each fraction, a foley catheter was placed, and his bladder was filled with an equal volume of saline. Filling his bladder ensured accurate dosing and allowed for sparing of some normal bladder. At his 8-year follow-up, he had no evidence of disease, but he did have mild daytime enuresis requiring a pad.

Figure 4  Scrotal shielding. A 4-year-old boy was diagnosed with high-risk neuroblastoma, stage M, of the lumbosacral spine. He underwent radiation therapy delivering 21.6 Gy in 12 fractions to the lumbosacral spine and presacral tissues (volume shown by red line) with scrotal shields in place (testicles shown in orange). The scrotal shields allowed for the prevention of external radiation scatter dose.
Figure 5  Avoidance of transposed ovary. A 10-year-old girl was diagnosed with Ewing sarcoma of the right hemipelvis and proximal femur. She had bilateral ovarian transposition (right ovary outlined in light pink, left ovary outlined in dark pink). She underwent consolidative radiation delivering a total dose of 55.8 Gy in 31 fractions. Her radiation fields were designed to minimize the dose to the bilateral transposed ovaries (isodose lines displayed). The maximum dose to the left ovary was 1.97 Gy, and the maximum dose to the right ovary was 4.55 Gy.

Figure 6  Minimize dose to vagina and vulva. A 10-year-old girl with Ewing sarcoma of the right hemipelvis and proximal femur underwent consolidative radiation to a total dose of 55.8 Gy in 31 fractions. Her radiation fields are shown, with the vagina (light blue outline) receiving 56 Gy to 40 Gy and the vulva (dark blue outline) receiving 56 Gy to 30 Gy. Attempts were made to prevent high-dose radiation to the entirety of the vagina and vulva; however, she was unable to consistently tolerate dilators, and she required examinations under anesthesia with lysis of vulvar and vaginal adhesions every 3 to 4 months.
harvesting should be discussed with postpubertal female patients and their families. In prepubertal patients, a newer technique of cryopreservation of ovarian tissue for later transplantation after completion of cancer therapies may be possible.

Radiation also can alter the reproductive system hormonally and anatomically through ovarian failure and through fibrosis and altered blood flow in the uterus. \(^{21,24}\) Radiation of more than 5 Gy to the uterus is associated with preterm birth, small size for gestational age, and low birthweight; however, prior pelvic radiation was not associated with congenital malformations. \(^{23,25}\)

4. Contour the vagina and vulva as avoidance structures

Radiation to the vagina and vulva can cause reduced vascularity and increased fibrosis, resulting in stenosis and sexual dysfunction. \(^{21,26}\) In addition, premature ovarian failure can result in vaginal dryness and atrophy. \(^{21}\) In a study of 26 girls with pelvic rhabdomyosarcoma, 15 (58%) had late gynecologic toxicity, with 4 patients having grade 3 or greater vaginal stenosis. \(^{26}\) In addition to efforts to minimize the dose to the ovaries and uterus, it is important to try to minimize irradiation of the vagina and vulva by contouring them as organs at risk or using an avoidance structure. Figure 6 shows an example of avoiding irradiation of the full circumference of the vagina. Although outside the scope of this article, post-treatment use of a vaginal dilator is recommended to reduce vaginal agglutination when complete avoidance of vaginal or vulvar irradiation is not possible owing to proximity to the target volume. \(^{27}\) Briefly, vaginal dilation should commence approximately 2 to 4 weeks after completing radiation (once all acute dermatitis and mucositis has resolved). A water-soluble lubricant should be placed on the dilator, and the dilator should be gently inserted into the vagina as deeply as is comfortable. The dilator should then be rotated and moved for 1 to 3 minutes and then withdrawn. This should be done 3 to 5 times weekly for approximately 12 months after radiation, but a longer duration may be necessary. The radiation oncologist should provide appropriately sized dilators and may recommend increasing dilator size as the months progress.

Conclusion

Survivors of childhood cancer are significantly more likely to report adverse general health, functional impairment, activity limitations, and mental health compared with their siblings. \(^{2}\) Pelvic radiation can cause growth asymmetries, proctitis, cystitis, infertility, and sexual dysfunction. Reproductive late effects in particular may have significant negative outcomes for patients’ quality of life, owing to their effect on psychosocial function as well as physical health.

Pediatric Normal Tissue Effects in the Clinic is a national collaboration working to develop quantitative, evidence-based dose and volume guidelines for radiation treatment planning. This effort is critical to improve the treatment of pediatric patients, because much of the current understanding of toxicities is based on decades-old techniques and fractionations.

An awareness of the potential late toxicities and recognition of the pelvic tissues at risk is crucial when treating pediatric patients. Incorporation of the approaches detailed in this article as well as further investigation of other radiation techniques such as proton therapy may help prevent or mitigate these toxicities and improve outcomes for survivors of pediatric cancer.

Acknowledgments

We thank our Department of Human Oncology research staff.

References


