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PENTEC SPECIAL ISSUE (INVITED ONLY)

Predictive Factors Associated With Radiation Myelopathy in Pediatric Patients With Cancer: A PENTEC Comprehensive Review

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Purpose

Radiation myelitis (RM) is a rare complication of radiation therapy (RT). The Pediatric Normal Tissue Effects in the Clinic spinal cord task force aimed to identify RT dose effects and assess risk factors for RM in children. Through systematic review, we analyzed RT dose, fraction size, latency between completion of RT and toxicity, chemotherapy use, age when irradiated, and sex.

Methods and Materials

We conducted literature searches of peer-reviewed manuscripts published from 1964 to June 2017 evaluating RM among children. Normality of variables was assessed with Kolmogorov-Smirnov or Shapiro-Wilk tests. Spearman's rank correlation coefficients were used to test correlations between RT dose/fraction size and latency between RT and development of toxicity.

Results

Of 1329 identified and screened reports, 144 reports were fully reviewed and determined to have adequate data for analysis; 16 of these reports had a total of 33 cases of RM with a median age of 13 years (range, 0.2-18) at the time of RT. The most common primary tumor histologies were rhabdomyosarcoma (n = 9), medulloblastoma (n = 5), and Hodgkin lymphoma (n = 2); the most common chemotherapy agents given were vincristine (n = 15), intrathecal methotrexate (n = 12), and intrathecal cytarabine (n = 10). The median RT dose and fraction size were 40 Gy (range, 24-57.4 Gy) and 1.8 Gy (range, 1.3-2.6 Gy), respectively. RT dose resulting in RM in patients who also received chemotherapy was lower than in those not receiving chemotherapy (mean 39.6 vs 49.7 Gy; $P = .04$). There was no association of age with RT dose. The median latency period was 7 months (range, 1-29). Higher RT dose was correlated with longer latency periods ($P = .03$) to RM whereas sex, age, fraction size, and chemotherapy use were not. Two of 17 patients with adequate follow-up recovered from RM; unfortunately, it was fatal in 6 of 15 evaluable patients. Complication probability modeling was not possible because of the rarity of events.

Conclusions

This report demonstrates a relatively short latency from RT (with or without chemotherapy) to RM and a wide range of doses (including fraction sizes) associated with RM. No apparent association with age at the time of RT could be discerned. Chemotherapy appears to reduce spinal cord tolerance. Recovery from RM is rare, and it is often fatal.

Section snippets

Clinical Significance

Radiation therapy (RT) is a critical component of the management of pediatric patients with tumors of the central nervous system.[1] Additionally, appropriate radiotherapeutic treatment of malignancies of the bone, paraspinal soft tissues, thorax, hematologic/lymphatic system, abdomen, and pelvis can result in the spinal cord and sacral nerve roots being exposed to potentially damaging doses of radiation. Radiation myelopathy is the most severe side effect of radiation exposure to the spinal…

Endpoints and Toxicity Scoring

For the purposes of this manuscript, we defined myelitis as Common Terminology Criteria for Adverse Events version 5.0 grade 2 or higher.[12] This corresponds to moderate weakness or sensory loss that limits performing activities of daily living. Specifically, we did not include grade 1 toxicity, for which patients are largely asymptomatic. These patients may demonstrate Babinski reflex, Lhermitte's sign, or only asymptomatic imaging-defined spinal cord changes. Many of the cases of RM identified …

Anatomy and Developmental Dynamics

The spinal cord develops from the 3 cellular layers of the neural tube: the ventricular zone, intermediate zone, and the marginal zone. The ventricular zone gives rise to neuroblasts, which will ultimately become nerve cells and glioblasts, which develop into supporting cells. By week 8 of embryologic development, the spinal cord extends the entire length of the vertebral canal. At birth, the conus medullaris extends to the level of the third lumbar vertebra. As children grow, the transition…

Defining Volumes: Pediatric Imaging Issues

The transition point between the brain stem contour and the cervical spinal cord contour in RT is often at the inferior extent of the foramen magnum. The spinal cord is then contoured caudally until the true cord gives way to the cauda equina at the conus medullaris at the L1-L2 level. The cauda equina is contoured caudally to the bottom of the thecal sac (S1-S2). The spinal canal is defined by the vertebral foramen and includes epidural space fat, dura, cerebrospinal fluid, and so forth. The…

Review of Dose Volume Response Data and Risk Factors

The Pediatric Normal Tissue Effects in the Clinic systematic review of RM was undertaken to ascertain the dose response of the pediatric spinal cord in childhood cancer survivors.…

Mathematical Models

There were insufficient data providing both per patient incidence of radiation myelopathy and reliable spinal cord dose estimation to form a predictive model for toxicity risks. For the subset of publications not reporting RM and additionally providing at least minimal information on the distribution (eg, mean ± SD or max/min) of cord doses in their cohort, the distribution was modeled as an incomplete gamma function using the mean and SD of the doses in each cohort. Shown by the dashed dark…

Recommendations for Nominal Dose Volume Goals

It has been over 20 years since the last case of RM was reported in the pediatric population. Treatment delivery techniques and accuracy of dose estimates have matured substantially in the era since RM was last reported. These improvements substantially reduced the probability of treatment delivery related errors affecting delivered dose. With the available information, it is not possible to differentiate or quantitatively analyze the potential contributory role of those effects.

Additionally,…

Toxicity Scoring Recommendations

For reporting RM in pediatric patients with cancer, we recommend using the most recent Common Terminology Criteria for Adverse Events toxicity scoring system (Table E3), as it is commonly applied in clinical practice and conveniently groups patients into those with and without limitations to their activities of daily living.…

Data Reporting Standards Specific to This Organ

RM is rare, and dosimetry of patients who do not develop complications is not usually reported. To facilitate pooled analyses on risks of myelitis, we recommend consistent reporting of data on number of patients treated, patient demographics, cancer diagnosis, and dosimetry as listed in the following for all studies where the patient cohort includes those with spinal cord Max[equivalent dose in 2 Gy fractions Gy; a/b = 2] > 50. It would be necessary to indicate those patients who have and those …

Contrast Pediatric and Adult Normal Tissue Complication Probability Data

Adult radiation dose-effects data specific to RM were published as part of the QUANTEC effort.[4] Given that malignancy in adults is much more common than in the pediatric population, they were able to identify 10 times more cases of RM in the literature (a decade ago) than we had available for our analyses. With only 32

clinically relevant cases of RM identified, we were unable to perform any normal tissue complication modeling. However, given the rarity of the events observed there are no signs …

Future Investigations

RM is a rare event in children irradiated for cancer, with few cases reported in the literature. This rarity of events prohibited normal tissue complication probability modeling. There was evidence that IT chemotherapy could increase the risk of myelitis, as has been anecdotally observed by other investigators.[18] With only 32 cases identified in this systematic literature review, it is tempting to consider dose escalation in patients with diseases where local recurrences are common,…

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