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Critical Review

National Cancer Institute Workshop on Proton Therapy for Children: Considerations Regarding Brainstem Injury

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Purpose: Proton therapy can allow for superior avoidance of normal tissues. A widespread consensus has been reached that proton therapy should be used for patients with curable pediatric brain tumor to avoid critical central nervous system structures. Brainstem necrosis is a potentially devastating, but rare, complication of radiation. Recent reports of brainstem necrosis after proton therapy have raised concerns over the potential biological differences among radiation modalities. We have summarized findings from the National Cancer Institute Workshop on Proton Therapy for Children convened in May 2016 to examine brainstem injury.

Methods and Materials: Twenty-seven physicians, physicists, and researchers from 17 institutions with expertise met to discuss this issue. The definition of brainstem injury, imaging of this entity, clinical experience with photons and photons, and potential biological differences among these radiation modalities were thoroughly discussed and reviewed. The 3 largest US pediatric proton therapy centers collectively summarized the incidence of symptomatic brainstem injury and physics details (planning, dosimetry, delivery) for 671 children with focal posterior fossa tumors treated with protons from 2006 to 2016.

Results: The average rate of symptomatic brainstem toxicity from the 3 largest US pediatric proton centers was 2.38%. The actuarial rate of grade $\geq$2 brainstem toxicity was successfully reduced from 12.7% to 0% at 1 center after adopting modified radiation guidelines. Guidelines for treatment planning and current consensus brainstem constraints for proton therapy are presented. The current knowledge regarding linear energy transfer (LET) and its relationship to relative biological effectiveness (RBE) are defined. We review the current state of LET-based planning.

Conclusions: Brainstem injury is a rare complication of radiation therapy for both photons and protons. Substantial dosimetric data have been collected for brainstem injury after proton therapy, and established guidelines to allow for safe delivery of proton radiation have been defined. Increased capability exists to incorporate LET optimization; however, further research is needed to fully explore the capabilities of LET- and RBE-based planning. © 2018 Elsevier Inc. All rights reserved.

Introduction

Radiation therapy is an important component of the multimodal approach to cancer treatment. Continual, significant improvement has occurred in both photon and proton radiation therapy, with more precise dose conformality (1). Advances in technology have aimed to improve outcomes, including disease control and quality of life, the latter through a reduction of untoward effects (2). Proton therapy can significantly reduce the radiation dose to critical normal tissues, which is important for preserving functional capabilities (3-5). By reducing the unintended medium and low radiation doses in normal tissue structures, proton therapy can potentially reduce both short-term and long-term deleterious radiation effects (5).

The proton beam model policy adopted by the American Society of Radiation Oncology in 2017 supports proton therapy in primary solid neoplasms in children treated with curative intent (6). Proton beam radiation is particularly appealing for treating primary brain tumors in children. The number of pediatric patients treated with proton therapy has continued to increase significantly (5, 7), and proton therapy is now an option for many Children's Oncology Group (COG) protocols.

As more children have been treated with protons, an increasing body of data has suggested possible lower rates of treatment-related morbidities (8-14), including cognitive effects (15-19), secondary malignancies (20-23), and physical and psychosocial domains affecting patients' quality of life (24). In addition, studies have reported uncommon, but significant, morbidities, including brainstem injury in the setting of posterior fossa tumors treated with proton beam radiation (7, 25-28). Two recent commentaries summarized the concerns regarding brainstem necrosis in children after proton therapy, highlighting the limited data indicating that this rare event might be more common after proton irradiation (29, 30). The National Cancer Institute convened a Workshop on Proton Therapy for Children: Caveats and Opportunities in May 2016 to examine brainstem injury in children after proton therapy. The present report summarizes the data and

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