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Protons for pediatric ependymoma: Where are we now?

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Unquestionably, one of the greatest "game-changers" in the irradiation of pediatric CNS malignancies has been the rapid development of technologies that allow for more targeted delivery of radiation therapy. Proton therapy, the oldest of these strategies, has come to the forefront due to dose distributions which allow for substantial sparing of uninvolved tissue. Ependymoma is an ideal site for the use of protons given its frequent location in the posterior fossa adjacent to eloquent structures. However, it is exactly this proximity, specifically to the brainstem, which mandates careful consideration of potential toxicity.

Early reports of the use of protons for pediatric ependymoma from Loma Linda University Medical Center[1] and the Francis H. Burr Proton Facility Therapy Center and Harvard Cyclotron Laboratory[2] documented normal tissue sparing and disease control which compared favorably with the literature of the time. Concurrent with the advent of protons was the recognition that conformal volumes were appropriate for the irradiation of non-disseminated ependymoma, and the large body of work from St. Jude Children's Hospital demonstrating excellent local control (LC)[3] and the potential for decreased late effects[4,5] informed the adoption of increasingly conformal radiotherapy (RT) fields.[6] In 2013, MacDonald et al reported the results of proton treatment of 70 pediatric patients with localized ependymoma. At a median follow-up of 46 months, 3-year LC, progression-free survival (PFS), and overall survival (OS) were 83%, 76%, and 95%, respectively.[7] Subsequent publications from that group and others continued to demonstrate good outcome.

In a recent issue of *Neuro-Oncology*, Peters et al from the West German Proton Therapy Center Essen share their experience of using protons in the treatment of 105 pediatric patients with ependymoma.[8] The importance of this study lies in its prospective collection of data and in that it reports outcome in the *modern* proton era. However, as a registry study of children treated on a variety of different protocols, caution is warranted in interpreting the outcomes for the entire group given the inherent variability of treatment mandated by both national and international protocols, including variability in the use of chemotherapy. Furthermore, the cohort included 13 patients treated for salvage or tumor progression, thus potentially confounding some survival data. Additionally, it is difficult to draw strong conclusions related to dose comparisons in that we know that treating physicians generally chose to use lower dose in younger children and higher doses for gross disease: the median dose delivered was 59.4 (range 54-62 Gy), but there was no prospective randomization to lower and higher doses. The authors report no significant difference in LC or PFS in patients receiving radiation doses of <59 or >59 Gy on univariate analysis, but it is hard to understand the relatively poor 3-year PFS of 47.6% in patients with GTR (gross total resection)/NTR (near-total resection) who received <59 Gy. Multivariate analysis was performed for PFS and only showed a relationship to the number of surgeries performed; it is unclear why this was the only significant factor, but with longer follow-up and continued analysis, this may become clearer.

Despite the above concerns, this European experience adds to the body of literature describing protons for pediatric ependymoma and is reassuring in terms of the lack of untoward toxicities. Last year, the largest series to date reporting the outcome of children with intracranial ependymoma treated with proton therapy was reported from the University of Florida and Harvard Medical School.[9] The median RT dose of 55.8 Gy (RBE [relative biological effectiveness]) resulted in a 7-year LC, PFS, and OS of 77.0%, 63.8%, and 82.2%, respectively. At a median follow-up of 5 years, late toxicity was remarkably low.

The path to the widespread adoption of protons for pediatric ependymoma has not been without its challenges. For this disease, doses exceeding 54 Gy (RBE) are commonly used and reports of brainstem necrosis, while still rare for proton series, appeared higher than photon therapy when 54 Gy (RBE) was exceeded, prompting a NCI workshop and subsequent guidelines for brainstem constraints for protons that are slightly less than for photons.[10] In the joint University of Florida/Harvard Medical

School series, the cumulative incidence of grade 2+ brain stem toxicity was 4% and occurred more often in patients who received >54 Gy (RBE), comparable to published rates in the literature for photon therapy. While difficult to draw conclusions, this slight difference may be related to a slightly higher biological effectiveness of protons. While known and accounted for since the early days of proton delivery in the 1960s, it is acknowledged that this biological effect varies in different areas of the beam and thanks to reports of these toxicities, refinements in treatment planning have and will continue to improve the therapeutic ratio for proton therapy. The low risk of >grade 2 brainstem toxicity report by Peters et al likely reflects these changes.

Proton therapy now is available in 40 centers in the United States and 89 centers worldwide. As competitive engineering allows for smaller, less expensive machines, access to protons will increase. The physical properties of protons are undoubtedly superior for almost all radiation plans, and pediatric ependymoma represents one of the most ideal disease sites for its use. The young age at diagnosis and frequent infratentorial location combined with the adoption of conformal fields may allow for sparing of the temporal lobes, cochleae, hypothalamus, and pituitary gland, thereby mitigating the risks of growth hormone deficiency, hearing loss, and neurocognitive function. The hope is that avoidance of late effects makes possible a "normal" life and may be cost-beneficial or even cost-saving. The recent publication from the Essen group adds to a growing body of literature describing protons in the treatment of pediatric ependymoma. We eagerly await mature data from this and other groups and look forward to findings from large comprehensive prospective trials and databases such as the Pediatric Proton Consortium Registry.

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