Neuro-Oncology
21(7), 830–831, 2019 | doi:10.1093/neuonc/noz085 | Advance Access date 13 May 2019

Proton beam therapy in pediatric brain tumor patients: improved radiation delivery techniques improve neurocognitive outcomes

Rakesh Jalali and Jayant S. Goda

Neuro Oncology Cancer Management Team, Apollo Proton Cancer Centre, Chennai, India (R.J.); Department of Radiation Oncology, Tata Memorial Centre, Homi Bhaba National Institute, Mumbai, India (J.S.G.)

Corresponding Author: Rakesh Jalali, MD, Apollo Proton Cancer Centre, 100 Feet Road, Taramani, Chennai, India. 600 041 (rjalali@apollohospitals.com).

See the article by Gross et al. in this issue, pp. 934–943.

While radiation therapy continues to be an integral component in the multimodal curative management of a range of brain tumors, its role is tempered with the potential risk of developing a spectrum of radiation-induced long-term morbid complications that have a considerable impact on the physical, social, neuropsychological, and emotional well-being of these survivors. In brain tumor patients in the pediatric and young adult population, this could have impact on their academic performances and quality of life, leading to significant challenges in their social integration.[1] Multiple meta-analyses have demonstrated deficits across various neurocognitive domains among pediatric brain tumor survivors treated with photon radiotherapy (XRT). Therefore the focus of contemporary therapeutic approaches is shifting from a far more radical approach of "cure at any cost" to a more conservative approach of "cure with long-term safety" both in surgical and radiotherapy practices.

Several longitudinal studies have demonstrated the correlation between the volume of normal brain tissue irradiated and the consequent impact on neurocognitive functions.[2] Technological refinement in radiotherapy techniques enable us now to deliver intended radiation doses to the tumor target precisely, and at the same time reduce the volume of exposure of the surrounding brain parenchyma. Modern photon techniques of intensity modulated radiotherapy with image guidance or under stereotactic guidance have been shown conclusively to minimize several domains of long-term neurocognitive functions in several prospective phase II trials and a relatively large well-conducted randomized trial where the emphasis was on the reduction of irradiated volume beyond the tumor.[3–5] We are, however, cognizant that photon techniques may still expose fairly large volumes of normal brain to low and intermediate dose washes. Proton beam therapy (PBT), on the other hand, because of its inherent physical properties of minimal exit doses, can potentially further reduce the doses to the normal brain tissue. Further technical refinement in modern proton beam delivery incorporating pencil-beam scanning (or spot scanning)—where a narrow proton beam magnetically scans each layer of the tumor thickness spot by spot and layer by layer to irradiate the tumor in 3 dimensions—results in sparing of the doses not only to normal tissues distal to the tumor target but also proximal and lateral to it. While such encouraging dosimetric and technical superiority of PBT over XRT has been known, what was lacking in the literature is the magnitude to which PBT and in particular proton beam intensity modulated therapy compare with contemporary XRT in evaluating its benefit in terms of clinically meaningful endpoints of neurocognitive domains including intellectual, memory, academic, and adaptive functions while maintaining local tumor control and expected survival. The study by Gross et al published in the current issue of *Neuro-Oncology*[6] addresses this need and is a significant contribution to the field. The study of a cohort of 125 pediatric brain tumor patients treated with XRT or PBT since 2004 at their institution demonstrates that PBT has significantly favorable long-term neurocognitive function compared with XRT. The superior neurocognitive outcome in the PBT group was particularly seen in domains of full-scale IQ and processing speed with a trend toward higher verbal IQ and general adaptive functioning, which also achieved statistical significance after planned sensitivity analysis on a truncated patient cohort with equal neuropsychological follow-up intervals compared with children treated with XRT. A further subgroup analysis based on the volume of irradiation (neurocognitive outcomes compared between focal XRT vs focal PBT and craniospinal irradiation [CSI] XRT vs CSI PBT) showed significantly better outcomes across some

of the neurocognitive domains in children treated with PBT. The study substantiates the encouraging results generated by a few similar studies done on a relatively small number of patients.[7,8] Gross and colleagues need to be commended for taking up this challenging task of collecting neurocognitive data, analyzing complex data, and finally comparing the neurocognitive outcomes using a comprehensive and extensive battery of tests across different domains of neurocognitive functions. Within the limitations of a retrospective nature and mixed histologies of patients treated with varying radiation therapy volumes, results of the study are nevertheless a very valuable contribution to our understanding of the potential benefits of modern PBT and will help formulate evolving treatment paradigms for both pediatric neuro-oncology radiation communities. One of the challenges in the conduct of such studies is the missing data while obtaining the baseline and serial follow-up assessments over a long period of follow-up time as experienced by our own group while carrying out the Stereotactic Conformal Radiotherapy (SCRT) trial[4] and the Children's Oncology Group's ALTE07C1 prospective trial of 600 children investigating child's neurocognitive functioning using a battery of well-validated measures administered over 5 years, where the compliance rates dropped from >90% at 1 year to about 70% by the end of the fifth year.[9]

Evaluating health technology advances including newer radiotherapy techniques continues to be a challenge. Conducting randomized trials at each site is likely to be extremely difficult to perform, and therefore a more pragmatic option could be a prospective collection of clinical data, meticulous measurement of dosimetric data, and regular audits. An honest interpretation of the results of even smaller phase II studies with clinically relevant endpoints can give us a wealth of information on their implementation feasibility. As more and more proton centers are getting operational across the world, very informative data as presented by Gross et al would hopefully stimulate the process of conducting appropriately designed and well-powered prospective studies with the requisite scientific rigor to generate quality evidence. Also besides neurocognitive function, other equally pertinent long-term endpoints—such as endocrine functions, vascular events, and second malignant neoplasms like high-grade gliomas, meningiomas, or sarcomas, which take at least 10 to 15 years to manifest and are considered to be frequent and important life-threatening adverse events associated with radiotherapy—as well as possibly social endpoints of survivorship need to be incorporated in PBT studies to comprehensively evaluate its full therapeutic potential. Contemporary PBT techniques can also in appropriate cases significantly spare and meet with the dose constraints for specific organs at risk such as hippocampi, frontal lobes, hypothalamic-pituitary axis, etc to further improve some of these survivorship endpoints.[5,10]

Author's statement. No funding or conflict of interests declared.

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