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Proton Beam Radiation Therapy: The Future May Prove Brighter for Pediatric Patients With Brain Tumors

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Multiple meta-analyses have demonstrated significant deficits in overall intellectual abilities, academic functioning, and specific cognitive skills, including attention, processing speed, and executive function, among pediatric brain tumor survivors treated with photon radiotherapy (XRT).[1–4] The physical characteristics of heavy proton particles used in proton beam radiation therapy (PBRT), which permits delivery of maximal dose at the desired depth of tissue penetration while minimizing the exit dose of radiation to healthy surrounding tissue, have been well described.[5] What has been missing from the literature is the extent to which proton radiation therapy (RT) differs from XRT in terms of cognitive, academic, visual, auditory, endocrine, vascular, and skin late effects.

In the article that accompanies this editorial, Kahalley et al[6] have evaluated a large retrospective sample of pediatric patients with brain tumors (n = 150) previously treated with either XRT between the years 2002 and 2007 (n = 60) or PBRT between the years 2007 and 2012 (n = 90) at the Texas Children's Hospital/MD Anderson Proton Therapy Center. Overall, the survivors treated with PBRT did not demonstrate a significant decline on average in Full Scale Intelligence Quotient (FSIQ), whereas those treated with XRT evidenced, on average, a statistically significant decline of 1.1 FSIQ points per year. The FSIQ slopes between these two groups, however, did not differ significantly, as the trajectories of both groups declined over time.

Upon further analysis by field of irradiation, the PBRT and XRT groups who received craniospinal irradiation evidenced stable FSIQ over time, and the slopes between the groups, once again, did not significantly differ. In contrast, a statistically significant difference between the two groups was displayed after receipt of focal RT. The FSIQ was stable for the PBRT group but significantly declined for the XRT group by an average of 1.57 points per year, whereas the trajectory of FSIQ slopes over time between the two groups did not significantly differ. One might be surprised that the focal XRT group significantly declined over time on FSIQ, given that narrower volume of RT has been demonstrated to be less neurotoxic to the CNS. From a different perspective, however, perhaps focal/local RT is the optimal scenario in which the physics of PBRT manifests maximal benefits by minimizing

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the scatter of radiation to the surrounding healthy brain tissue, as opposed to craniospinal irradiation, in which the entire brain and spine are treated.

Kahalley et al[6] cite the few published late-effects studies of pediatric brain tumor survivors treated with PBRT who received pre- and posttreatment IQ assessments for diagnoses that included low-grade gliomas,[7] ependymoma,[8] and high-risk medulloblastoma or supratentorial primitive neuroectodermal tumors.[9] Although the sample sizes in these three studies were small (from five to 14 survivors), and the 2-year length of follow-up brief, the results indicate stable FSIQ, with the exception of patients with low-grade glioma who were either younger than age 7 years at the time of PBRT or who received a dose of ≥15 Gy relative biological effectiveness to 20% of the volume of the left temporal lobe or hippocampus.[7] Although prior research has documented that children treated for brain tumors with XRT display declines in FSIQ over time,[10–15] further research has documented this decline in overall intelligence to primarily be the direct result of the diminution of two of the four IQ index scores that assess working memory (Working Memory Index) and processing speed (Processing Speed Index).[16–22]

Newer studies evaluating the neurocognitive late effects of the treatment of pediatric brain tumors with PBRT indicate that, on average, verbal comprehension, perceptual reasoning, and working memory remain stable, whereas processing speed can still be negatively impacted and declines over time after PBRT. As an illustration, a recently published follow-up study of 60 pediatric patients with brain tumors who were treated with PBRT at a mean age of 12 years and were retested after an average follow-up of 2.5 years reported no significant change in mean FSIQ, although the authors clearly portray the variable impact treatment can have upon individual survivors: FSIQ scores improved for 33 patients (55%) and declined for 24 patients (40%).[23] Furthermore, this study analyzed the four constituent index scores that compose FSIQ and reported no significant change in verbal comprehension, perceptual reasoning, or working memory; however, processing speed significantly declined by a mean of 5.2 points, with subjects younger than 12 years at baseline displaying a decline of 8.8 points.[23] This specific pattern of cognitive late effects arising from the treatment of pediatric brain tumors with PBRT is further supported by another recent follow-up study of 15 pediatric patients with brain tumors who were treated with PBRT at the mean age of 8 years old and re-evaluated approximately 3 years post-PBRT, and who also demonstrated stable FSIQ over time, with the exception of declining processing speed.[24] Additionally, by administering a range of neuropsychological measures, a group mean profile emerged that revealed intelligence, attention, problem solving, visual memory, and story memory to be within the average range, whereas delayed verbal list learning and visual scanning were within the low average range, along with impaired fine motor/graphomotor abilities.[24]

The potential stabilization of the Working Memory Index is encouraging because working memory (the ability to sustain one's attention and concentration when presented with new material and to manipulate that information to formulate a response) precedes learning and memory, and has been the primary focus of intervention trials.[25] The negative impact of PBRT upon the Processing Speed Index, a critically important and broad skill that directly relates to one's overall cognitive processing speed on a range of everyday tasks such as

thinking, problem solving, reading, and writing, is consistent with the late effects of XRT and has been correlated with impairment in the growth of normal-appearing white matter.[26–28]

The scientific ability to document late effects arising from the treatment of pediatric patients with brain tumors can often be limited by missing data when obtaining baseline and serial followup assessments, whereas the variation in age ranges of patients can commonly result in the use of different test measures. It should be noted that this retrospective study from the Texas Children's Hospital/MD Anderson Proton Therapy Center was able to obtain copies of previous testing for 75% of all eligible patients who were assessed with either the Leiter International Performance Scale (19%), the Wechsler Scale of Intelligence (71%), or the Woodcock-Johnson Tests of Cognitive Ability (10%). Whereas the majority (86%) of patients had the same test after RT and at follow-up, the use of the Leiter test, which is a nonverbal measure of IQ that does not require a spoken or written word from the examiner or the child, was associated with significantly lower FSIQ scores.

In response to these common serial assessment challenges, along with the scientific need to move beyond a singular measurement of IQ, the Behavioral Science Committee of the Children's Oncology Group (COG) developed the ALTE07C1 protocol, a battery of well-validated measures administered during three postdiagnosis evaluation windows (at 9 ± 3 months, 30 ± 3 months, and 60 ± 3 months) to provide psychometrically robust data about a child's neurocognitive functioning—estimated IQ, processing speed, attention and concentration, and memory—while also examining the child's functional abilities, behavior, executive functioning, and quality of life in approximately 1.5 hours.[29,30] The ALTE07C1 study is currently open at 162 COG institutions and is paired with seven COG CNS studies with a variety of brain tumor diagnoses and treatment regimens. Additionally, ALTE07C1 has enrolled more than 600 patients since study activation in September 2008 and has been successful in reaching the goal of a greater than 90% compliance rate for postdiagnosis evaluation time 1, greater than 80% for time 2, and greater than 70% for time 3.[31] It is eagerly anticipated that the uniform and prospective data from ALTE07C1 will be able to more accurately assess, for a range of diagnoses, the impact of CNS tumor therapies that include lower craniospinal doses and narrower margins to the posterior fossa or tumor bed, focal/local RT, or surgery only.

XRT has improved over the years to now include intensity modulated RT and more advanced forms of three-dimensional conformal RT to provide more precise radiation dose delivery to target areas.[32] According to Kahalley et al, advanced XRT delivery methods, such as those used in their study, may account for improved long-term outcomes. The authors should be commended for their prudence in concluding that insofar as a significant difference in the change of FSIQ over time was not identified between the two groups, the study does not provide clear evidence that PBRT results in clinically meaningful sparing of global IQ significantly exceeding that of modern XRT protocols. This is particularly relevant given that the patients who underwent XRT were significantly different from the PBRT group in terms of many medical variables that are commonly associated with worse neurocognitive outcomes. Specifically, the XRT group consisted of more patients with medulloblastoma/primitive neuroectodermal tumors, more patients with ventriculoperitoneal

shunts, a larger proportion of patients with Lansky or Karnofsky scores of less than 80 at their first postdiagnosis visit, higher total RT dose administered, and longer follow-up postirradiation compared with the PBRT group (5.4 years ± 3.3 *v* 2.7 years ± 1.9, respectively). It is important to also appreciate that proton delivery methods are evolving from first-generation (three-dimensional conformal proton therapy) to second-generation (intensity-modulated proton therapy) systems and are similarly expected to improve over the ensuing years to further reduce dose to normal tissues and increase conformity of the prescription dose to the targeted volume. As an illustration, pencil-beam scanning (or spot scanning) proton therapy has emerged in which a single, narrow proton beam is magnetically scanned across each layer of the tumor's thickness to irradiate the tumor in three dimensions. This is performed layer by layer, spot by spot, thereby curtailing the falloff of dose distal and lateral to the target but also to the proximal side of the tumor. Kahalley et al suggest that perhaps in the future, when more subjects are treated with PBRT and assessed beyond a singular measure of intelligence for a longer follow-up period, the anticipated preservation of cognitive functioning from PBRT may be realized.

At present, answers to these important questions remain elusive, given the extremely limited number of academic medical centers currently providing PBRT for pediatric brain tumors. While we eagerly await the forthcoming publication of late-effects studies from these centers, it should be noted that these sites are administering different batteries of neuropsychological test measures at different collection time points for nonrandomly assigned patients, including those who possess the time and funds to travel for 6 weeks of RT but, unfortunately, do not always return to that medical center for long-term follow-up, thereby limiting access to reassessment data. In terms of future direction, 15 evidence-based standards of psychosocial care of children with cancer and their families have recently been developed and include the standard that patients with brain tumors should be monitored for neuropsychological deficits during and after treatment.[33] Furthermore, a recently published manuscript outlines the rationale for insurance reimbursement for neuropsychological assessment of pediatric patients with brain tumors on research protocols,[34] which, hopefully, will address salient barriers for follow-up. Therefore, it is incumbent upon all those working with pediatric patients with brain tumors to ensure that baseline and serial follow-up neuropsychological assessments are obtained consistent with a standardized battery, such as COG ALTE07C1, along with any additional test measures and late-effects data that a specific site or consortium may wish to collect. In this manner, it is anticipated that such prospectively collected uniform data and time points will enable the scientific community, as well as concerned patients and families, to better understand the anticipated late effects that may arise from our continued efforts to minimize the toxicity of curative radiation therapies for pediatric patients with brain tumors.

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