



Pediatric proton therapy

Attention, processing speed, and executive functioning in pediatric brain tumor survivors treated with proton beam radiation therapy



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ABSTRACT

Background and purpose: This study examines attention, processing speed, and executive functioning in pediatric brain tumor survivors treated with proton beam radiation therapy (PBRT).

Material and methods: We examined 39 survivors (age 6–19 years) who were 3.61 years post-PBRT on average. Craniospinal (CSI; $n = 21$) and focal ($n = 18$) subgroups were analyzed. Attention, processing speed, and executive functioning scores were compared to population norms, and clinical/demographic risk factors were examined.

Results: As a group, survivors treated with focal PBRT exhibited attention, processing speed, and executive functioning that did not differ from population norms (all $p > 0.05$). Performance in the CSI group across attention scales was normative (all $p > 0.05$), but areas of relative weakness were identified on one executive functioning subtest and several processing speed subtests (all $p < 0.01$).

Conclusions: Survivors treated with PBRT may exhibit relative resilience in cognitive domains traditionally associated with radiation late effects. Attention, processing speed, and executive functioning remained intact and within normal limits for survivors treated with focal PBRT. Among survivors treated with CSI, a score pattern emerged that was suggestive of difficulties in underlying component skills (i.e., processing speed) rather than true executive dysfunction. No evidence of profound cognitive impairment was found in either group.

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Neurocognitive late effects are commonly reported in long-term survivors of pediatric brain tumors. Domains of particular vulnerability to CNS-directed treatment include attention [1,2], processing speed [3–5], and executive functions, including working memory [2], task efficiency [6], inhibitory control [7], and organization [6]. Understanding the range of attention and executive function outcomes expected following treatment for pediatric brain tumors is important, as impairments in these neurocognitive domains are associated with lasting difficulties in social functioning, educational attainment, employment, and reduced income potential [6,8].

While cranial radiation therapy (RT) is often an essential treatment for pediatric brain tumors, it is associated with

neurocognitive impairment [9], with higher radiation doses linked to greater cognitive decline [10,11]. In an effort to mitigate treatment late effects, proton beam radiation therapy (PBRT) is being used more frequently in the treatment of pediatric brain tumors. Compared to conventional photon RT (XRT), PBRT eliminates exit dose, thus minimizing irradiation of healthy brain tissue [12]. As such, there is optimism that PBRT will better preserve cognitive functioning in pediatric brain tumor patients while providing equivalent tumor control. Still, research examining neurocognitive outcomes in patients treated with PBRT is sparse given its historically limited availability.

Thus far, empirical support for the neuroprotective benefits of PBRT is not definitive. In a large retrospective comparison of survivors of pediatric brain tumors, we found no statistically significant IQ decline or impairment in survivors treated with PBRT ($n = 90$; mean (M) follow-up = 2.7 years), while survivors treated with XRT showed statistically significant IQ decline ($n = 60$; M follow-up = 5.4 years); yet, the IQ trajectories (i.e., the slope or

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the amount of IQ change over time) did not differ between groups [13]. Another recent study examining intellectual ability in 43 pediatric survivors of medulloblastoma treated with PBRT-based craniospinal irradiation (CSI; M follow-up = 5.2 years) found significant decline in processing speed and verbal comprehension, with global IQ decline observed only in patients younger than 8 years old at treatment [14]. Finally, Pulsifer et al. [15] identified significant decline in processing speed, but not in global IQ, in a sample of survivors of pediatric brain tumors treated with PBRT ($n = 60$; M follow-up = 2.5 years). Together, these early studies seem to show that patients treated with PBRT, as a group, are not exhibiting profound cognitive changes in early survivorship, although areas of cognitive vulnerability (e.g., processing speed) and clinical risk factors (e.g., younger age at treatment) are emerging.

In sum, uncertainty lingers with respect to the neurocognitive impact (and potential neuroprotective benefits) of PBRT, and the few available studies to date have focused on changes in global intelligence or broad intellectual domains. The aim of the current study was to expand our knowledge of the impact of PBRT by examining measures of attention, processing speed, and executive functioning in survivors of pediatric brain tumors treated with PBRT. Since attention, processing, and executive functions are cognitive domains known to be at particular risk following treatment with XRT, we hypothesized that survivors treated with PBRT would underperform in these cognitive domains relative to population norms.

Materials and methods

Procedure and participants

Data presented here are part of a larger ongoing study examining long-term outcomes in pediatric brain tumor survivors. With approval from the Institutional Review Board, eligible study participants were identified by medical chart review and consecutively enrolled. Informed written consent was obtained prior to participation.

Eligible survivors were between the ages of 6 and 19 years with a history of a brain tumor treated with PBRT at least one year prior to enrollment and with no evidence of active disease. Patients diagnosed with brain stem gliomas, high-grade gliomas, and atypical teratoid/rhabdoid tumors were excluded from participation due to our interest in long-term outcomes. The present study reports on the 39 survivors who completed the neuropsychological measures of interest at a single time point between 2011 and 2014 (88.9% participation rate). Two patients were excluded from analysis due to disease progression identified following enrollment.

Measures

Conners' Continuous Performance Test-II (CPT-II)

The CPT-II [16] is a computerized assessment of sustained attention. Seven performance indicators were included in the present study: *Omission Errors*, *Commission Errors*, *Mean Reaction Time*, *Reaction Time Standard Error*, *Variability*, *Attentiveness*, and *Perseverations*. Age-norm derived T-scores ($M = 50$, $SD = 10$) are reported. Higher scores indicate worse performance, with scores >65 considered to fall in the clinically significant range. On two scales, however, atypically low scores are also interpreted as problematic: *Mean Reaction Time* (low score = impulsive responding, high score = slow responding) and *Perseverations* (low score = slow responding, high score = impulsive or random responding). T-scores <35 on these two scales were also categorized as clinically significant.

Delis-Kaplan Executive Function System (D-KEFS)

The D-KEFS [17] is a collection of standardized tests of executive functions using a cognitive process measurement approach. Three timed D-KEFS tests were included in the present study: Color-Word Interference, Trail Making Test, and Verbal Fluency. Each test includes several subtests. Some subtests measure higher level executive functioning while others measure processing speed, a lower level cognitive skill. Taken together, these scores provide a better understanding of whether weak performance on an executive functioning subtest is due to true executive dysfunction or due to a deficit in processing speed that also contributes to performance on the task. Age-normed scores are reported as scaled scores ($M = 10$, $SD = 3$), with lower scores indicating worse performance. Scaled scores <5.5 (or 1.5 SD below the normative mean) were considered clinically significant in the current study. Of note, since D-KEFS tests are normed for ages 8–89 years, the one patient in the sample who was less than 8 years old at testing was excluded from analyses of D-KEFS scores.

The D-KEFS Color-Word Interference test includes four timed subtests. Two subtests assess processing speed: *Color Naming* (speed of naming colors) and *Word Reading* (speed of reading words). Higher level executive functioning is assessed on two subtests: *Inhibition* (speed of naming the ink color while not reading the printed word), and *Inhibition/Switching* (speed of naming the ink color or reading the printed word depending on a rule). We also examined the *Inhibition/Switching Errors* score, which assesses the accuracy of performance on the executive functioning task.

We included three timed subtests from the D-KEFS Trail Making Test. Two subtests assess processing speed: *Number Sequencing* (speed of drawing a line to connect numbers in order) and *Letter Sequencing* (speed of drawing a line to connect letters in order). Higher level executive functioning is assessed on one subtest: *Number-Letter Switching* (speed of drawing a line to alternately connect numbers and letters in order). We also examined the *Number-Letter Switching Errors* score, which assesses accuracy of performance on the *Number-Letter Switching* executive functioning task.

The D-KEFS Verbal Fluency Test includes four timed subtests. Two subtests assess processing speed: *Letter Fluency* (the number of words produced beginning with a specified letter) and *Category Fluency* (the number of words produced from specified categories). Two subtests assess higher level executive functioning: *Category Switching* (the number of words produced that belong to alternating categories) and *Category Switching Accuracy* (the number of successful category switches). We also examined the *Percent Switching Accuracy* score, which assesses error frequency on the executive functioning task.

Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) – Sixth Edition

The VMI [18] examines visual-motor integration. Two subtests were included to explore the possible contribution of visual (*Visual Perception*) and/or fine motor functioning (*Motor Coordination*) on D-KEFS Trail Making Test performance. Age-normed scores are reported as standard scores ($M = 100$, $SD = 15$), with lower scores indicative of worse performance. We defined clinical scores on this measure as those <77.5 (or 1.5 SD below the normative mean).

Analyses

CSI and Focal groups were compared on demographic and medical characteristics using t -tests and χ^2 tests. These groups were analyzed separately for all remaining analyses. One-sample t -tests compared normative means (i.e., the means from the tests'

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