


Neurocognitive effects of proton radiation therapy in adults with low-grade glioma

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Abstract To understand neurocognitive effects of proton radiation therapy (PRT) in patients with low-grade glioma, we evaluated 20 patients who received this therapy prospectively and over 5 years with a comprehensive neuropsychological battery. 20 patients were evaluated at baseline and at yearly intervals for up to 5 years with a battery of neuropsychological measures that assessed intellectual, attention, executive, visuospatial and memory functions as well as mood and functional status. We evaluated change in cognitive functioning over time. We analyzed the relationship between cognitive performance and tumor location and also examined whether patients' performance differed from that reported in a study of normative practice effects. Overall, patients exhibited stability in cognitive functioning. Tumor location played a role in performance; those with tumors in the left hemisphere versus in the right hemisphere were more impaired at baseline on verbal measures ($p < .05$). However, we found greater improvement in verbal memory over time in patients with left than with right

hemisphere tumors ($p < .05$). Results of our study, the first to investigate, in depth, neurocognitive effects of PRT in adults with low-grade gliomas, are promising. We hypothesize that the conformal advantage of PRT may contribute to preservation of cognitive functioning, although larger sample sizes and a longer period of study are required. Our study also highlights the need to consider normative practice effects when studying neurocognitive functioning in response to treatment over time, and the need to utilize comprehensive neuropsychological batteries given our findings that differentiate patients with left and right hemisphere tumors.

Keywords Neurocognitive function · Proton radiation therapy · Low-grade glioma · Tumor laterality · Neuropsychology

Introduction

Low-grade gliomas (LGG) are relatively slow growing brain tumors that most often occur in individuals under the age of 50. Although patients often remain stable for several years following diagnosis, they may experience neurocognitive impairments that significantly impact quality of life [1, 2]. Many factors contribute to neurocognitive deficits, including tumor characteristics (histology, tumor size and location), distal effects of the tumor on normal surrounding brain tissue, seizures, psychological distress, characteristics of the individual, including age at time of diagnosis and premorbid intellect, and effects of treatment [3–10]. While some factors are not modifiable, it is important to determine whether those that are, specifically treatment factors, might be associated with a reduction in neurocognitive deficits.

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Prior research has shown that conventional (photon) radiation therapy (RT), the standard treatment for patients with LGG, has a favorable impact on survival, but may have negative impacts on cognitive functioning [6, 11]. Findings indicate that LGG patients treated with conventional RT have greater neurocognitive deficits than those who did not receive RT and that neurocognitive deficits may be dose dependent [12]. Deficits are more apparent in certain cognitive domains, particularly memory and attention [7, 13] and onset may be delayed following treatment, with late neurocognitive effects especially deleterious [6, 7]. Neurocognitive deficits are particularly concerning for patients with LGG who are typically quite young and actively engaged in work and family.

Findings that point to greater deficits in patients who receive conventional radiation versus those who do not motivates an exploration of a relatively new form of radiation therapy, proton radiation therapy (PRT) [6, 7, 13, 14]. PRT reduces entrance dose and eliminates exit dose, with the advantage of sparing normal tissue, while having comparable biological effects on the targeted tissue as do photons [15]. Given these conformal advantages, we asked whether adult patients with LGG who received PRT would exhibit a relative preservation of cognitive functioning. In an earlier paper [16], we reported that patients tolerated this treatment well, and that their cognitive functioning remained stable over time. Similar encouraging findings regarding effects of PRT on neurocognitive functioning have been reported in children [17–19]. In this paper, we present our findings based on a more in-depth analysis of neurocognitive sequelae following PRT in adults with LGG. We prospectively and longitudinally studied cognitive functioning in adults diagnosed with LGG who received PRT. Although our study sample is relatively small, we begin to ask whether certain features of the tumor, specifically its size and location, differentially impact cognitive outcome and effects of this treatment.

Materials and methods

Study design

Patients completed a comprehensive neuropsychological battery at baseline, prior to treatment and at yearly intervals for 5 years. End points included overall survival, progression-free survival, neurocognitive function, neuroendocrine function and quality of life [16]. This study was reviewed and approved by our Institutional Review Board.

Patients

Patients included 13 men and 7 women, ages 22–56 (mean age 37.5). Mean level of education was 16.3 years (range

12–20 years) and all were native English speakers. All had pathologically confirmed WHO grade II LGG and were enrolled between October 2007 and May 2010. Characteristics of patients' tumors are described in detail elsewhere [16]. Indication for radiation therapy was either presence of one or more high risk features at time of upfront diagnosis, defined as age ≥ 40 , MIB-1 $\geq 3\%$, or tumor size ≥ 6 cm. Alternatively, patients were treated for evidence of tumor progression. Eight patients were treated upfront and 12 patients were treated for progression. Tumor types included astrocytomas (7 patients), oligoastrocytomas (9 patients) and oligodendrogliomas (4 patients). Twelve patients had right hemisphere tumors and eight left hemisphere tumors. Tumor locations were predominantly in the frontal (9), temporal (5) and frontotemporal region (3). Two patients had tumors in the parietal lobe and one had an occipital lobe tumor. Nine patients had small tumors (< 6 cm) and eleven had large tumors (≥ 6 cm). Sixteen patients had undergone tumor resection (4 gross total and 12 subtotal) and 4 had biopsies only. No patients received concurrent chemotherapy and eighteen of our patients were on concurrent anticonvulsant therapy during the time of irradiation. Inclusion criteria included age ≥ 18 , KPS ≥ 70 , no comorbidities to suspect compromise of survival less than 5 years, no prior cranial irradiation and no other medical history to potentially compromise neurocognitive performance.

Patients were removed from protocol at time of clear disease progression or if the patient desired (three patients followed for 60 months, five for 48 months, seven for 36 months, four for 24 months and one for 12 months).

Treatment

All patients were treated with fractionated proton therapy to the radiographic tumor, defined as the T2 hyperintense residual tumor, resection cavity that abutted the tumor and any potential T1 enhancing disease, with a 1.5 cm expansion beyond this volume with consideration of the surrounding anatomy. Dose delivered was 54 Gy (RBE) at 1.8 Gy (RBE) per fraction over 6 weeks.

Assessments

Comprehensive neuropsychological evaluations were conducted at baseline as defined within 8 weeks of initiating PRT, and at 12, 24, 36, 48, and 60 months from completion of PRT. An abbreviated test battery was administered at 6 months post-radiation completion. All evaluations were performed by a neuropsychologist (JCS) or trained psychometricians under the neuropsychologist's supervision. Tests included standardized measures of intellectual functioning, attention and executive functioning, language,

visuospatial functions and memory (Table 1). The battery of tests includes those from the abbreviated Clinical Trial Battery which has been utilized in numerous previous studies [e.g. 20]. Patients’ raw scores on all measures were compared to normative data and standard (z-scores) were calculated for each cognitive domain. Z-scores that were 1.5 standard deviations at or below the mean were considered impaired. Patients were also administered self-rating inventories of emotional and quality of life functioning [Beck Depression Inventory, Beck Anxiety Inventory, Functional Assessment of Cancer (FACT)-General, FACT-Brain, and FACT-Fatigue measures].

Statistics

Mixed linear models were used to analyze the repeated measures of cognitive domain scores, Beck Inventory

Table 1 Cognitive tests by domain

Domain	Test(s)
Intellectual	WAIS-III ^a Full Scale IQ
Visuospatial	WAIS-III ^a Perceptual Organization
Language	WAIS-III ^a Verbal Comprehension Boston Naming Test Auditory Naming Test
Attention/working memory	WAIS-III ^a Working Memory WMS-III ^b Spatial Span CPT-II ^c Inattention CPT-II ^c Vigilance
Processing speed	WAIS-III ^a Processing Speed Trail Making Test Part A
Executive function	Trail Making Test part B COWAT ^d F-A-S WCST ^e Errors CPT-II ^c Impulsivity
Verbal memory	HVLT-R ^f Total Recall HVLT-R ^f Delayed Recall HVLT-R ^f Retention
Visual memory	BVMT-R ^g Total Recall BVMT-R ^g Delayed Recall
Clinical trials battery	HVLT-R ^f Total Recall Trail Making Test Part A Trail Making Test Part B COWAT ^d F-A-S

^a Wechsler adult intelligence scale—3rd edition

^b Wechsler memory scale—3rd edition

^c Conners’ continuous performance test—2nd edition

^d Controlled oral word association test

^e Wisconsin card sorting test

^f Hopkins verbal learning test—revised

^g Brief visuospatial memory test—revised

scores, and FACT scores using the REML method. Patient-specific intercepts and slopes are assumed to be random effects with unstructured covariance, while standard variance components were specified within patients. Tumor location and tumor size were treated as fixed effects to compare cognitive performances between left and right-sided tumors as well as between large and small tumors. Tumor size was dichotomized as <6 versus ≥6 cm in the largest linear dimension, corresponding to the high-risk definition for early progression. Type 3 tests of fixed effects are based on the *F* statistic. Fisher’s exact test was used to assess the relationship between tumor size and laterality. Data analysis was performed using SAS 9.4 (SAS Inst Inc, Cary, NC) with p-values based on a two-sided hypothesis test. *P* < .05 was considered to be statistically significant. As subjects were evaluated at multiple time points, we also compared their performance over time to those from a published study of practice effects on the same or similar neuropsychological measures [21].

Results

Study duration and survival

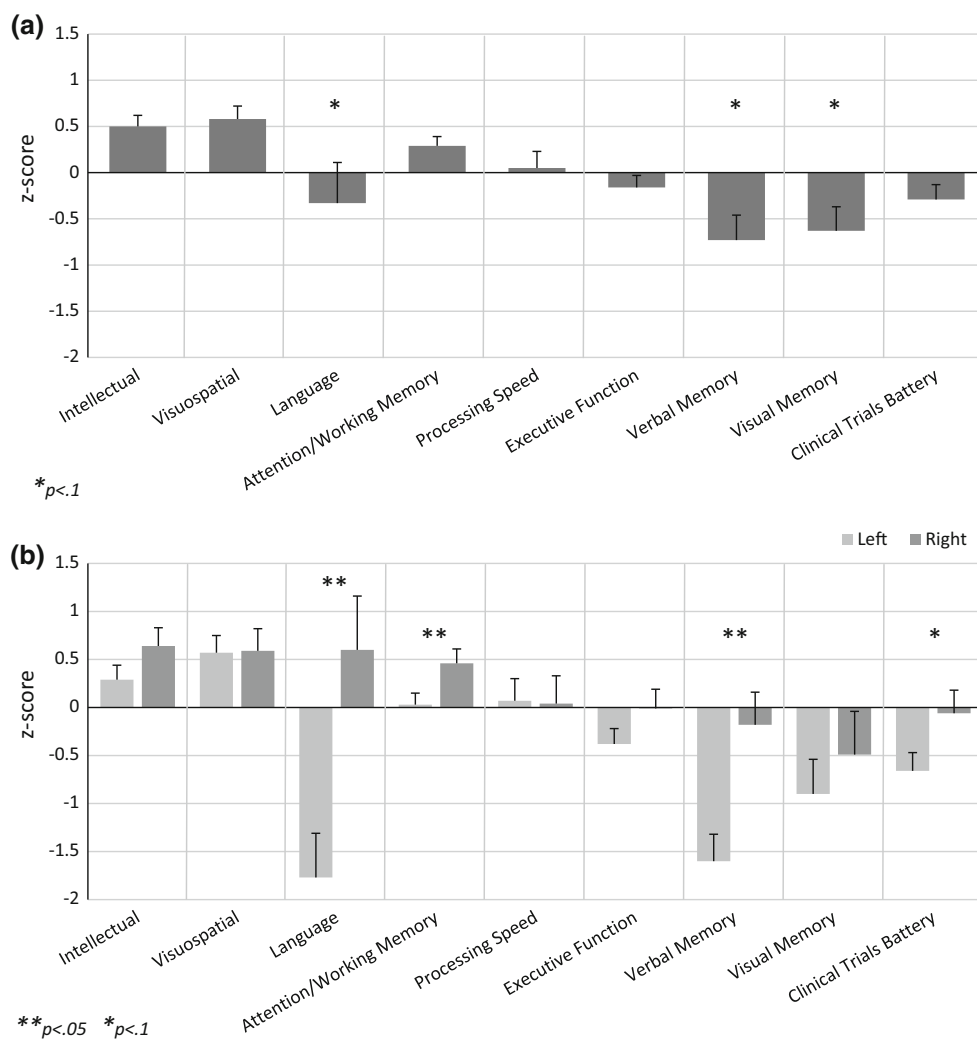
At the time of data cutoff, median follow up for the nine patients alive without progression was 5.1 years (range 3.3–5.2 years). Median follow-up for the eight patients who remained alive, but with progressive disease was 4.9 years (range 3.8–5.9 years). Survival was measured from initiation of radiation therapy. Progression-free survival (PFS) at 1, 3, and 5 years was 100, 85, and 40 %. Overall survival (OS) at 1, 3, and 5 years was 100, 95, and 84 %.

Cognitive functioning at baseline

As an entire group, patients at baseline were not significantly impaired compared to normative data in any assessed cognitive domain. However, there was greater variability and a trend towards worse performance on measures of language functioning, verbal memory, and visual memory (Fig. 1a). While the group was not impaired as a whole, seven patients were impaired in visual and/or verbal memory ($-3.0 \leq z \leq -1.6$). Three of these seven patients also exhibited severe impairments in language functioning ($-5.8 < z < -5.1$) while in four patients, language functioning was normal. One patient had moderate impairment at baseline only in processing speed ($z = -1.86$).

The variability in language and memory performances at baseline correlated with tumor location. As a group, patients with left-sided tumors performed significantly worse than patients with right-sided tumors on measures of verbal memory, language function, and attention and

Fig. 1 a Cognitive functioning at baseline. **b** Cognitive functioning by tumor location at baseline



working memory ($p < .05$) (Fig. 1b). Otherwise, tumor laterality did not have a significant impact on cognitive functioning at baseline, although it is notable that there was a borderline trend for patients with left-sided tumors to perform worse than those with right-sided tumors on the Clinical Trial Battery ($p < .1$), which includes the Controlled Oral Word Association Test (COWAT), Trail Making Test and Hopkins Verbal Learning Test-Revised (HVLTR) and has been used in several studies investigating effects of brain tumor [e.g. 20]. Cognitive performance at baseline did not significantly differ based on tumor size. Patients who had large (≥ 6 cm) and small (< 6 cm) tumors performed similarly across all cognitive domains.

Change in cognitive functioning over time

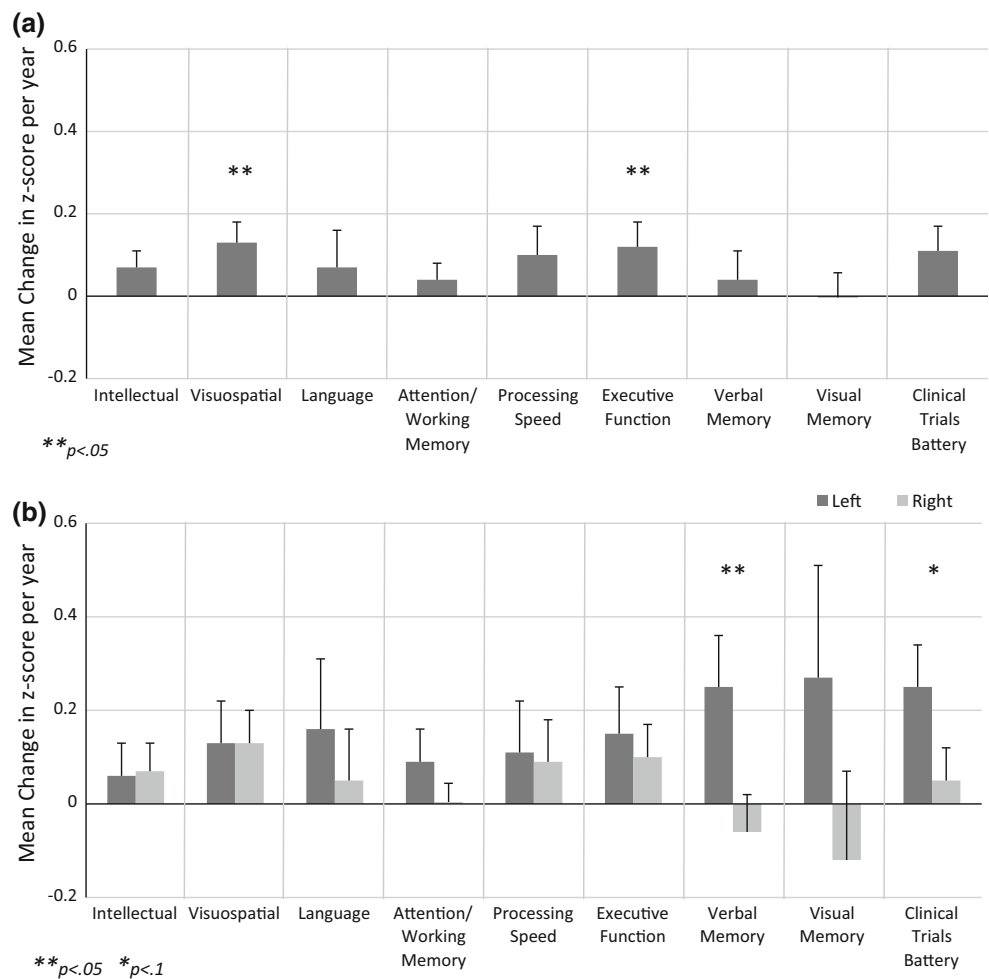
Across all patients, there was significant improvement in visuospatial and executive functioning over time ($p < .05$). Otherwise, cognitive functioning of the entire group

remained largely stable (Fig. 2a). However, there was greater improvement in verbal memory in patients with left-sided tumors than in patients with right-sided tumors ($p < .05$). Indeed, patients with right-sided tumors had stable performance on memory measures (visual and verbal) over time. There was also a trend for patients with left-sided tumors to show greater improvement on the Clinical Trial Battery compared to patients with right-sided tumors who had stable performance ($p < .1$) (Fig. 2b). Change in cognitive functioning over time did not vary depending on tumor size and there was no association between tumor size and laterality.

Comparing observed change to expected change over time

As is standard in studies of treatment effects in patients with brain tumors, our patients completed the same neuropsychological measures multiple times (when available, alternate test forms were used), typically with 12 months

Fig. 2 a Average change in functioning per year. **b** Average change in functioning by tumor location per year



between evaluations. In order to determine whether changes observed over time were consistent with practice effects, we compared our patients’ performances to expected change derived from available normative data [21]. Most measures are the same as those reported; when not the case, we substituted a similar measure. Overall, there was no significant difference in test performance over time between LGG patients and available normative data. However, there were borderline trends ($p < .1$) for LGG patients to show *less* improvement over time than normal controls on measures of processing speed, executive functions, verbal memory, and the Clinical Trial Battery (Fig. 3a). Further analysis revealed that there was no difference between patients with left-sided tumors and the normative group in terms of expected change with practice. However, patients with right-sided tumors did not show as much expected improvement in their verbal memory function and also on the Clinical Trial Battery ($p < .05$). There was also a trend for patients with right-sided tumors to show less improvement than expected in processing speed and executive functions ($p < .1$) (Fig. 3b).

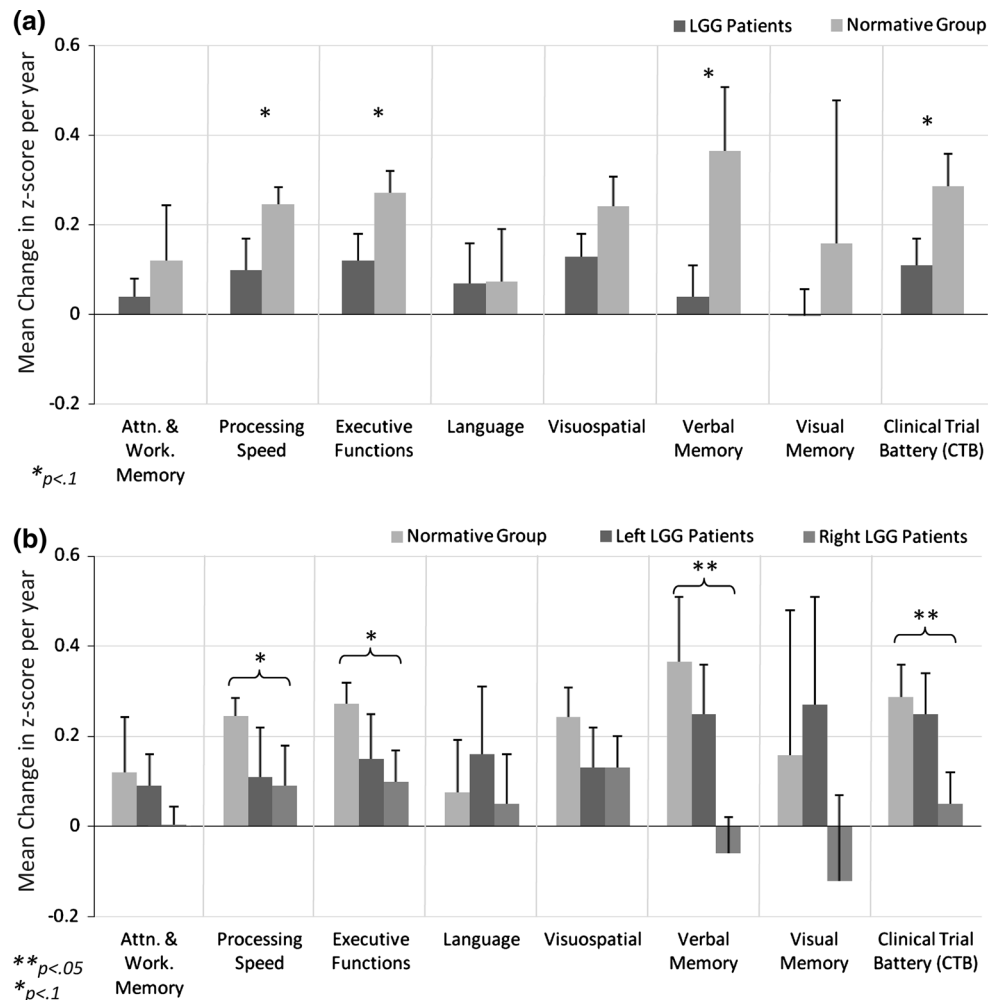
Emotional functioning and quality of life

Of the seventeen patients assessed for emotional well being with the BDI-II and BAI at baseline, one patient was severely depressed but none had severe anxiety. Four patients had moderate depression prior to irradiation, while four experienced moderate anxiety. There was no change on average in the emotional well-being of patients over time. Quality of life as determined by patient reported questionnaires demonstrated no significant decline over time following radiation therapy completion.

Discussion

Our study represents the first detailed investigation of neurocognitive functioning in adult patients with low-grade gliomas treated with PRT. We considered factors that have been previously shown to impact neurocognitive function in patients who received conventional radiation therapy, including baseline neurocognitive performance, tumor size

Fig. 3 a Comparing observed change to expected change over time. **b** Comparing observed change to expected change over time by tumor location



and location. Our study has the advantage of including a homogenous clinical sample; patients had the same tumor type, underwent the same treatment, and were of similar age and cognitive status at baseline. The rationale for treating low-grade glioma patients with proton therapy is in hopes of reducing potential radiation-associated side effects such as decrements to neurocognitive function. However, the utility of PRT in this regard would not be helpful if it comes at the expense of inferior survival. Slightly less than half of our patients were treated with the indication of upfront diagnosis of a low-grade glioma. The composite 5-year PFS was 40 % and 5-year OS was 84 %. This compares favorably to the results of Radiation Therapy Oncology Group (RTOG) study 9802, a prospective randomized study of intermediate risk low-grade glioma patients in which those patients treated with radiation alone achieved a 5-year PFS of 46 % and 5-year OS was 63 % [22].

With regard to neurocognitive assessments, we included a comprehensive battery of neuropsychological tests, allowing us to understand whether PRT may have any

generalized or specific impact on patients' neurocognitive performance. As we previously reported, patients showed preservation of overall intellectual functioning, as well as preserved language, visuospatial, attention, executive and memory functioning, a highly encouraging finding. However, there were differences between patients with left- and right-sided tumors. At baseline, patients with left-sided tumors performed significantly worse than those with right-sided tumors on measures of verbal memory, language function, attention and working memory. These findings likely reflect the left hemisphere's specialized role in language processing. Interestingly, patients with left-sided tumors showed greater improvement in verbal memory than patients with right-sided tumors. Also over time, patients with left-sided tumors showed positive changes in language function and attention and working memory while improvement in these areas in patients with right-sided tumors was more modest. These findings suggest that patients who have left-sided tumors may initially show greater cognitive impairment, at least within verbal domains, but this is likely due to tumor factors or non-

radiation treatment effects and/or the immediate impact of surgical resection that resolve over time. These findings also suggest that it is important to consider task demands when selecting neurocognitive measures for future research studies. For example, a commonly used test battery in neuro-oncology research, the Clinical Trial Battery, primarily includes verbal tasks; patients who had left-sided tumors in our study showed a trend towards improved performance on this battery while there was no change over time on this measure for patients who had right-sided tumors.

A second key finding related to tumor laterality was that patients with right-sided tumors may show greater vulnerability over time. This was not related to tumor size, as patients with left- and right-sided tumors did not differ in terms of tumor size. Specifically, patients with right-sided tumors showed stable memory performances (visual and verbal), but showed less improvement on tasks of verbal memory and the Clinical Trial Battery than expected based on repeated exposure (practice) alone. There was also a trend for patients with right-sided tumors to show less improvement in processing speed and executive functions. Altogether, these results suggest that patients who have left-sided tumors may show greater recovery and preservation of cognitive functioning over time, as evidenced by an ability to learn at rates typical of normal controls. A similar finding was also reported in a study of cognitive deficits following conventional radiation therapy in patients with low and high grade gliomas [5], suggesting that this is not specific to the type of radiation. Specifically, Raysi Dehcordi, et al. [5] found that patients with LGG in the left, but not the right hemisphere improved markedly both in verbal short-term memory and figural working memory. They hypothesize that the improved performance in patients with left hemisphere tumors could be due to greater cortico-cortical projections in the left hemisphere versus cortico-subcortical and cortico-limbic projections in the right hemisphere. They postulate that the more diffuse organization of the right than the left hemisphere may explain the greater vulnerability to effects of treatment. However, other studies have reported either worse cognitive impairment in patients with left than with right hemisphere tumors following radiation therapy [6, 13], or report no difference based on tumor side or location [8].

The findings of our study also highlight the importance of considering practice effects in neurocognitive studies of patients undergoing treatment for cancer. Generally speaking, it is possible that a ‘practice effect’ may obscure findings of decline over time. In our study, patients with left sided tumors showed an expected improvement from repeated exposure to tests; patients with right-sided tumors failed to show the same degree of expected improvement. Replication of this finding using a true control group would

be important (patients with LGG who received photon radiation therapy) as the practice effects that we considered in this study are those based on a non-clinical group of subjects. Nonetheless, we suggest that practice effects should be considered in interpreting findings from serial evaluations.

Although our patients were only followed for a median of 5 years, the current results suggest a potential advantage for PRT over conventional radiation therapy for LGG patients. Photon radiation therapy has been associated with cognitive dysfunction across a number of domains [8]; when compared to untreated patients, selective declines can be seen within the first 2–3 years [11]. In a large study, Klein et al. [13] found that LGG patients who received photon radiation had a higher rate of “cognitive disability” than patients who did not receive conventional radiation therapy and found that the degree of cognitive impairment correlated with high fraction doses.

Douw et al. [7] provide a possible explanation for these findings; in their study, patients who received radiation therapy showed worse cognitive performance than those who did not, and this was associated with radiologically detectable brain abnormalities including white matter hyperintensities and brain atrophy. Patients in their study were followed for a mean of 12 years, and RT was associated with a slow progression of radiographic abnormalities and cognitive deficits, specifically a significant increase in attentional deficits. This contrasted with stable radiologic findings and cognitive performance in patients who did not receive RT. MRI ratings in another study [6] found more severe leukoencephalopathy in patients who received radiation than those who did not, specifically in the resected hemisphere, and found that severity of leukoencephalopathy was associated with poor memory performance in the irradiated but not non-irradiated group.

Given these previous findings, which generally show that photon radiation therapy is associated with neurocognitive deficits, the findings of our study, which provide evidence for preservation of cognitive function are encouraging. This may be explained by characteristics of PRT which allow for greater precision to targeted tissue. While advances in imaging and treatment planning have led to greater precision in radiation therapy in general [15], the absence of an ‘exit dose’ associated with proton therapy allows for highly conformal dose distributions, with high levels of radiation to the tumor and reduced irradiation to normal tissue compared to matched photon fields. Similar to our study’s findings, initial studies in the pediatric brain tumor population suggest that PRT is associated with a relative preservation of neurocognitive function [17–19]. Our study further describes differences in patients with left and right hemisphere tumors, with patients with left hemisphere tumors having greater baseline cognitive

impairment but also showing greater improvement over time than patients with right hemisphere tumors. This finding may have been uncovered in our study, given the comprehensive neuropsychological battery we used, including measures of both verbal and visual abilities. If replicated in a larger sample, this finding has potential clinical applications for counseling patients regarding initial neurocognitive difficulties, and also for tailoring cognitive rehabilitation therapy depending on tumor location. In order to further investigate these findings and to more fully understand the effects of PRT on cognitive functioning, it will be important to study this relatively new treatment in a larger sample of patients with longer duration of follow-up.

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Compliance with Ethical Standards

Conflict of Interest The authors made no disclosures.

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