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Original Article

Long-term outcomes and late adverse effects of a prospective study on proton radiotherapy for patients with low-grade glioma

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ABSTRACT

Background: Patients with low-grade gliomas (LGG) can survive years with their illness. Proton radiotherapy (PRT) can reduce off-target dose and decrease the risk of treatment-related morbidity. We examined long-term morbidity following proton therapy in this updated prospective cohort of patients with LGG.

Methods: Twenty patients with LGG were enrolled prospectively and received PRT to 54 Gy(RBE) in 30 fractions. Comprehensive baseline and longitudinal assessments of toxicity, neurocognitive and neuroendocrine function, quality of life, and survival outcomes were performed up to 5 years following treatment.

Results: Six patients died (all of disease) and six had progression of disease. Median follow-up was 6.8 years for the 14 patients alive at time of reporting. Median progression-free survival (PFS) was 4.5 years. Of tumors tested for molecular markers, 71% carried the IDH1-R132H mutation and 29% had 1p/19q co-deletion. There was no overall decline in neurocognitive function; however, a subset of five patients with reported cognitive symptoms after radiation therapy had progressively worse function by neurocognitive testing. Six patients developed neuroendocrine deficiencies, five of which received Dmax $\geq$20 Gy(RBE) to the hypothalamus–pituitary axis (HPA). Most long-term toxicities developed within 2 years after radiation therapy.

Conclusions: The majority of patients with LGG who received proton therapy retained stable cognitive and neuroendocrine function. The IDH1-R132H mutation was present in the majority, while 1p/19q loss was present in a minority. A subset of patients developed neuroendocrine deficiencies and was more common in those with higher dose to the HPA.

Low-grade gliomas account for 20% of all gliomas and typically occur in young patients who survive years with their illness [1–3]. Choice of treatment must therefore weigh the goals of disease control against late adverse effects [4]. Radiation therapy has been shown to increase PFS in LGG [5], but with risk of late neurocognitive and neuroendocrine toxicity [6–8].

PRT is an alternative to standard photon-based radiation therapy that offers better dose conformity, with the potential to reduce radiation-related toxicity. Few studies have examined long-term morbidity and late adverse effects in LGG patients treated with PRT.

We previously reported on a prospective cohort of 20 LGG patients who received PRT and found a subset of patients developed neuroendocrine deficiencies and no overall cognitive decline was detected [9]. Here, we present an updated final report on this cohort with minimum follow up of 5 years following treatment on all surviving patients. Data on IDH1-R132H and 1p/19q co-deletion are provided.

Methods and materials

This study was approved by our Institutional Review Board. Patients with a diagnosis of WHO Grade II (2000/2007 criteria) glioma were enrolled into a single-cohort prospective study. They underwent comprehensive clinical, neurocognitive, neuroen-

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docrine, and quality of life assessments for 5 years following enrollment. Patients were removed from the protocol if they had disease progression based on surgical confirmation following radiographic signs, or per patient preference.

This report is an update of a previously published trial [9] now with complete data collection on all assessments through the full 60-month follow up period on all patients. An abbreviated summary of enrollment criteria, treatment and follow-up assessments is presented below. Full details are available in the initial reports [9,10].

Patients, treatment, and assessments

Patients with LGG were eligible if they had an indication for radiation therapy, either as new diagnosis or progression, age ≥18, and Karnofsky's Performance Score ≥70. Exclusion criteria included comorbidities with likely survival <5 years, baseline gross cognitive deficiencies or other barriers to neurocognitive assessment, or prior radiation therapy. Enrolled patients received PRT to 54 Gy(RBE) in 1.8 Gy(RBE) fractions. The clinical target volume was defined as a composite of T2-hyperinstense tumor, any T1-enhancing disease, surgical bed, and 1.5-cm expansion with respect to normal anatomy. Further details regarding PRT planning and dosimetry are available in the initial report [9].

Assessments included neuroendocrine testing, measures of neurocognitive performance, emotional well-being, and quality of life (QOL), and evaluation for treatment-related toxicity. Neurocognitive performance was assessed using tests covering eight cognitive domains: intellectual functioning, visuospatial ability, attention and working memory, processing speed, executive function, language, verbal memory, visual memory, and tests from the Clinical Trial Battery composite, which has been utilized in several previous studies [11]. Emotional well-being was assessed using the Beck Depression and Beck Anxiety Inventories, and QOL was assessed with the Functional Assessment of Cancer (FACT)-General, FACT-Brain, and FACT-Fatigue measures. Laboratory and neurocognitive assessments were performed at scheduled intervals following PRT (6, 12, 24, 36, 48, and 60 months) or until progression of disease. Long-term treatment related toxicities were defined as those that occurred or persisted ≥3 months after completing PRT and were tabulated and scored according to the Common Terminology Criteria for Adverse Events (version 3.0). Toxicities were reported as potentially radiation-related unless clearly attributable to another cause.

Dose–volume relationships were computed for critical structures. The rate of neuroendocrine deficiencies were compared between those patients who received Dmax ≥20 Gy(RBE) to either the pituitary or hypothalamus and those who did not. A cutoff of 20 Gy(RBE) was used as the most reasonable cutoff based on the Dmax distribution – 12 patients had Dmax dose of ≥20 Gy(RBE) to either structure (and at least 17 Gy(RBE) to both) and the remainder received doses <5 Gy(RBE) to both.

1p/19q co-deletion status was assessed using fluorescence in-situ hybridization (FISH) in 17 out of 20 patients. IDH1-R132H mutation status was assessed in 17/20 patients (a different subset from those tested for 1p/19q co-deletion) using a combination of DNA testing and immunohistochemistry. DNA from tumors of 8 patients was tested using a genotyping assay developed on the SNaPshot platform (Applied Biosystems, Foster City, CA) [12]. Tumors from another 8 patients were tested using immunohistochemistry for the IDH1-R132H mutation. Finally, one patient's tumor was tested using both SNaPshot and immunohistochemistry.

Statistics

PFS and OS were computed from the first day of radiation therapy. PFS time was censored at the date of last follow-up for patients alive with no evidence of progression. PFS and OS rates were estimated using the Kaplan–Meier method. The log-rank test was used to test for association of individual variables with PFS, and the hazard ratio (HR) between groups was estimated by the proportional hazards regression model. The risk of developing new neuroendocrine deficiency was estimated by the cumulative incidence function in the presence of disease progression and death as competing risks. A competing risks regression model was used to compare the development of new neuroendocrine deficiency between dosimetric groups and to compute the subdistribution HR. Linear mixed models were used to analyze the repeated measures of Z-scores on neurocognitive assessments, emotional inventories and self-reported QOL scores, with patient-specific intercepts and slopes modeled as random effects. Their associations with neuropsychiatric toxicity was modeled with toxicity as a fixed effect and assessed as an interaction with the slope. Baseline comparisons between patients with and without neuropsychiatric toxicity were done using the *t*-test. Patient-specific data analysis was performed using the R statistical software package (v3.3.2), with the 'OISurv' package for survival analysis, the 'lme4' and 'lmerTest' packages for mixed linear models, and the 'cmprsk' package for competing risks analysis. All *p*-values were based on a two-sided hypothesis and considered significant at alpha level of 0.05.

Results

Twenty patients were enrolled between October 2006 and May 2010 (Table 1). Six patients died of disease, at a median of 4.8 years (range 1.7–8.2 years) following start of PRT and median of 6.9 years (range 1.8–11.5 years) from first diagnosis. Median follow-up was 6.8 years from start of PRT and 9.3 years from first diagnosis for the 14 patients alive at the time of this report. Six surviving patients had progression of disease, with a median follow-up of 6.9 years (range 5.6–8.2 years) and eight had no evidence of progression, with a median follow-up of 6.6 years (range 5.1–8.2 years). Two patients had received temozolomide prior to PRT. No patients received systemic therapy (including bevacizumab) concurrent with or following PRT until disease progression. Eight patients received bevacizumab following progression.

Median PFS from time of treatment initiation was 4.5 years. Median OS could not be reliably estimated since only six deaths occurred during the follow-up period. At 6 years follow-up, PFS was 39% (Fig. 1A) and OS was 79% (Fig. 1B). At 10 years from time of first glioma diagnosis, PFS was 37% and OS was 69%. Size ≥6 cm was associated with decreased PFS (HR 6.1, $p = 0.021$). Eight (40%) had pseudoprogression, defined as new enhancement or T2/FLAIR signal that resolved or remained stable at 6–12 months [13], at a median of 4.2 months (range 2.5–23) following treatment. Three patients with pseudoprogression eventually had disease progression at 24, 48, and 53 months following pseudoprogression. One patient had radiation necrosis proven on biopsy, first noted on imaging 22 months following treatment. Six other patients had suspected radiation necrosis but were found to have disease progression.

IDH1-R132H mutation status was available for 17 tumors, of which 12 (71%) carried the mutation. 1p/19q co-deletion status was available for a different set of 17 tumors, of which 5 (29%) carried the co-deletion.

Table 1
Baseline features of cohort.

Characteristic	Number of patients (%)
Age at enrollment:	
Median (range), years	37.5 (22–56)
Sex:	
Men	13 (65)
Women	7 (35)
Histology:	
Astrocytoma	7 (35)
Oligoastrocytoma	9 (45)
Oligodendroglioma	4 (20)
Laterality:	
Right	12 (60)
Left	8 (40)
Tumor crosses midline:	
Yes	3 (15)
No	17 (85)
Dominant location	
Frontal	9 (45)
Temporal	5 (25)
Frontotemporal	3 (15)
Parietal	2 (10)
Occipital	1 (5)
Greatest tumor dimension:	
Median (range), cm	6.3 (1.4–10.0)
Ki-67:	
Median (range), %	3.3 (<1–12)
1p/19q codeletion status:	
Codeletion present	5 (25)
Codeletion absent	12 (60)
Unknown	3 (15)
IDH1 R132H mutation status:	
Mutant	12 (60)
Wild type	5 (25)
Unknown	3 (15)
Surgery:	
Gross total resection	4 (20)
Subtotal resection	12 (60)
Biopsy only	4 (20)
Number of surgeries:	
0 (biopsy only)	4 (20)
1	12 (60)
2	4 (20)
Neuroendocrine deficiency:	
Present	6 (30)
Absent	14 (70)
Prior chemotherapy (temozolomide):	
Yes	2 (10)
No	18 (90)
Symptoms at baseline	
None	3 (15)
Seizure under control	2 (10)
Seizure under control and other symptoms	4 (20)
Seizure	5 (25)
Seizure and other symptoms	6 (30)
Indication for radiation therapy:	
Newly diagnosed high-risk	8 (40)
Persistent symptoms	6
MIB-1 ≥3%	5
Tumor size ≥6 cm	3
Age ≥40 y	3
Recurrent/progressive disease	12 (60)
Radiographic only	3
New symptoms with radiographic change	8
New symptoms without radiographic change	1

Neuroendocrine outcomes

At baseline, 4 patients had growth hormone deficiency and 2 had central hypothyroidism. Six developed new neuroendocrine deficiencies, 3 involving more than one axis. Four patients developed new adrenal insufficiency, 3 developed central hypothyroidism, and 2 men developed central hypogonadism. Patients developed their first neuroendocrine deficiency at a median of 10.9 months from start of radiation therapy (range 4.8–37.8 months).

Five out of 12 patients (42%) who received Dmax ≥20 Gy(RBE) to the pituitary or hypothalamus developed a deficiency in at least one neuroendocrine axis, compared to 1/8 (13%) who received Dmax <20 Gy(RBE) to both structures. The five patients with an endocrine deficiency who received a high dose developed their deficiency at a median of 7.3 months after start of radiation therapy (range 4.8–27.9 months), compared to 37.8 months for the patient who received a low dose. Furthermore, the dose received was inversely correlated with the timing of neuroendocrine deficiency (Pearson's $r = -0.81$, $p = 0.05$). Dmax ≥20 Gy(RBE) to the pituitary or hypothalamus tended to be associated with higher likelihood of developing a new neuroendocrine deficiency (HR 4.3 [0.6–30.5]), although this relationship did not reach statistical significance ($p = 0.142$, Fig. 2).

Neurocognitive and QOL outcomes

Prior to PRT, eight patients had impairment in at least one neurocognitive domain. Median follow-up for neurocognitive assessments was 36 months (range 0–60 months). Two did not have further neurocognitive testing after their baseline assessment. Over the course of follow-up, performance in all neurocognitive domains remained stable or improved from baseline (Table 2).

Median follow-up for assessment of emotional well-being and QOL was 42 months (range 12–60 months). One patient was severely depressed on baseline assessment. Performance on these measures remained stable or improved over the course of follow-up for the cohort overall.

Treatment-related toxicity

Long-term toxicities first occurred at a median of 4.7 months (range 0–62) following PRT, and most presented within 2 years (Fig. 3A). The three most common long-term toxicities were fatigue, headache and alopecia, while neurological toxicities in aggregate formed the largest proportion (47%). Of the 85 reported toxicities presenting within 2 years of starting radiotherapy, 59% were grade 1, 32% were grade 2, 9% were grade 3. The 17 toxicities that occurred >2 years following radiation therapy were predominantly neurological (65%) and neuroendocrine (18%) in nature, and 16/17 (94%) were grade 1 with only one reported grade 2 toxicity (Fig. 3B).

A subset of five patients reported long-term toxicity of grade ≥2 affecting mood or cognition, which we hypothesized could affect their performance on neurocognitive testing. Initial onset of toxicities was during radiotherapy for one, within the first three months following radiotherapy for two, and 3–6 months following radiotherapy for the remaining two. These patients were all male, 4 of 5 had a new diagnosis of glioma at time of enrollment, and 4 of 5 had left-sided tumors. At baseline, there were no differences between these five patients and the remainder of the cohort in most neurocognitive domains (Fig. 4). Those with reported toxicities showed less improvement compared to the rest of the cohort in several neurocognitive domains (intellectual, visuospatial, attention and working memory, processing speed, and executive function domains, Clinical Trial Battery composite) and a trend toward worsened depression by Beck's Depression survey ($p = 0.077$) (Fig. 4).

Hippocampal Dmean was similar between those with and without reported toxicity, with a median Dmean of 13.9 Gy(RBE) (range 0–31) among the 5 patients with reported toxicity versus 12.2 Gy

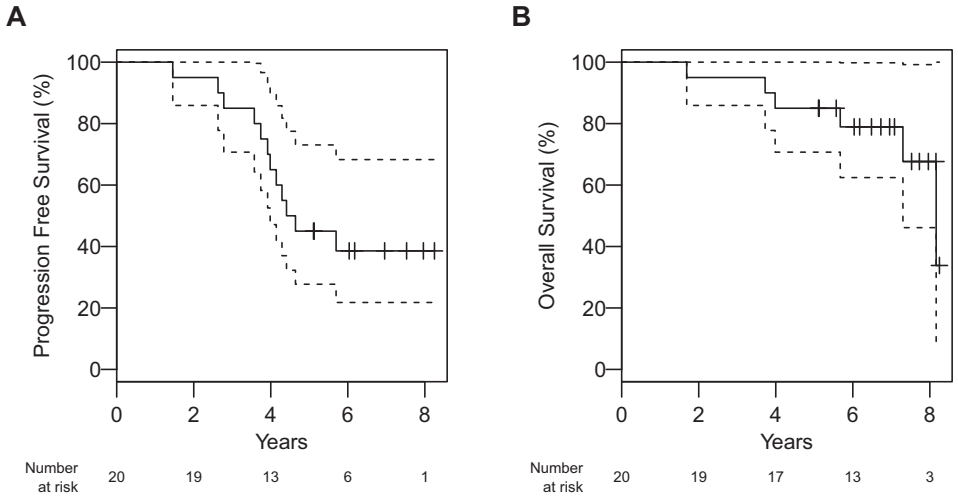

Fig. 1. Progression-free survival (A) and overall survival (B). '+' indicates censored data. Dashed lines indicate 95% confidence intervals.

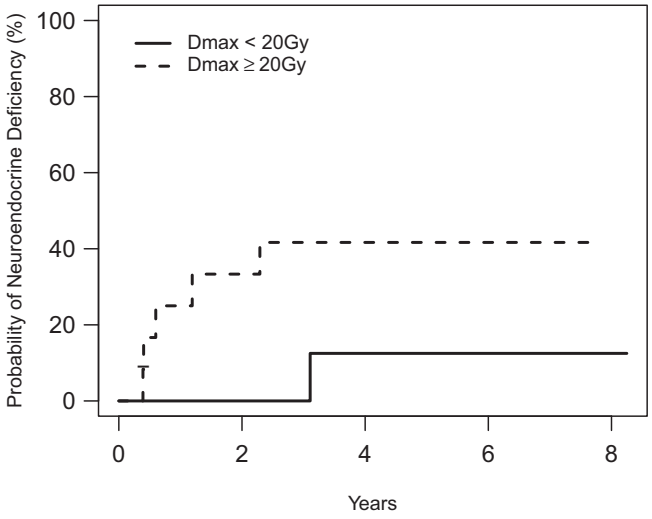

Fig. 2. Cumulative incidence of neuroendocrine deficiency in patients who received Dmax ≥20 Gy(RBE) to the pituitary or hypothalamus (dashed line) versus those who received Dmax <20 Gy(RBE) (solid line), $p = 0.142$. The first step on the dashed curve represents two patients, separated by a horizontal line. RBE = Relative Biological Effectiveness.

Table 2
Neurocognitive performance following PRT.

	Baseline ± SD	Mean change per year ± SE	*P*
Intellectual	0.47 ± 0.56	0.08 ± 0.04	0.044
Visuospatial	0.54 ± 0.69	0.14 ± 0.04	0.003
Language	−0.50 ± 2.19	0.05 ± 0.09	0.549
Attention & working memory	0.24 ± 0.49	0.03 ± 0.04	0.502
Processing speed	0.06 ± 0.83	0.10 ± 0.05	0.076
Executive function	−0.18 ± 0.62	0.13 ± 0.06	0.059
Verbal memory	−0.72 ± 1.19	0.06 ± 0.06	0.364
Visual memory	−0.81 ± 1.41	0.02 ± 0.17	0.921
Clinical Trial Battery	−0.35 ± 0.78	0.13 ± 0.05	0.025
Emotional			
Beck anxiety	8.9 ± 8.0	−0.55 ± 0.33	0.105
Beck depression	12.7 ± 9.9	−0.10 ± 0.50	0.846
Quality of life			
FACT-G	77.0 ± 18.4	1.70 ± 0.96	0.093
FACT-fatigue	32.7 ± 14.8	1.03 ± 0.42	0.017
FACT-Br	131.0 ± 28.5	1.64 ± 1.03	0.133

(RBE) (range 0–33.1) among those without. The contralateral hippocampus was spared in most patients, with a median Dmean of 0 Gy(RBE) (range 0–12.2). The ipsilateral hippocampus received median Dmean of 51 Gy(RBE) (range 0–57.4), with 10 patients receiving Dmean ≥48.6 Gy(RBE) (90% of prescribed dose). There were no statistically significant associations between risk of developing neurocognitive decline and dose to specific cranial structures. Two of 5 patients with reported neurocognitive decline had pseudoprogression, consistent with the overall rate in this cohort. Time of pseudoprogression corresponded with onset of neurocognitive toxicity in one patient and occurred 3 months following onset of symptoms in the other. Two other patients in this cohort of 5 had eventual progression of disease, at 33.8 and 45.5 months after start of PRT and well after onset of neurocognitive symptoms.

Discussion

In this study we sought to evaluate the risk of long-term neuroendocrine and neurocognitive deficiencies in patients treated with PRT as an alternative to standard photon-based radiotherapy. Survival outcomes in our cohort are consistent with previous reports and confirm survival on the order of years following radiotherapy, even with more than half of our cohort treated for recurrent disease. Our results support excellent PRT tolerance, low rates of long-term adverse effects, and radiation dose dependent neuroendocrine deficiencies that are likely reduced by superior dosimetry with protons.

Development of neuroendocrine deficiencies is a known risk of cranial irradiation and can manifest years after treatment [14–16]. Six patients (30%) developed new neuroendocrine deficiencies after PRT in our cohort, which compares favorably to rates of 38–41% in retrospective cohorts of photon therapy with median follow-up of 2.7–3.2 years [17,18], and 88% at median follow-up of 8 years [19]. Neuroendocrine deficiencies were more common in those who received ≥20 Gy(RBE) to the hypothalamus or pituitary, although this difference did not reach statistical significance. There was an inverse relationship between dose and time of onset, which supports a dose–response relationship and suggests that the risk of new neuroendocrine deficiencies decreases after the first 3 years following treatment.

Neurocognitive dysfunction has been found to be both a consequence of cranial irradiation and factors such as surgery and underlying diseases [20,21]. In this study, we took a conservative

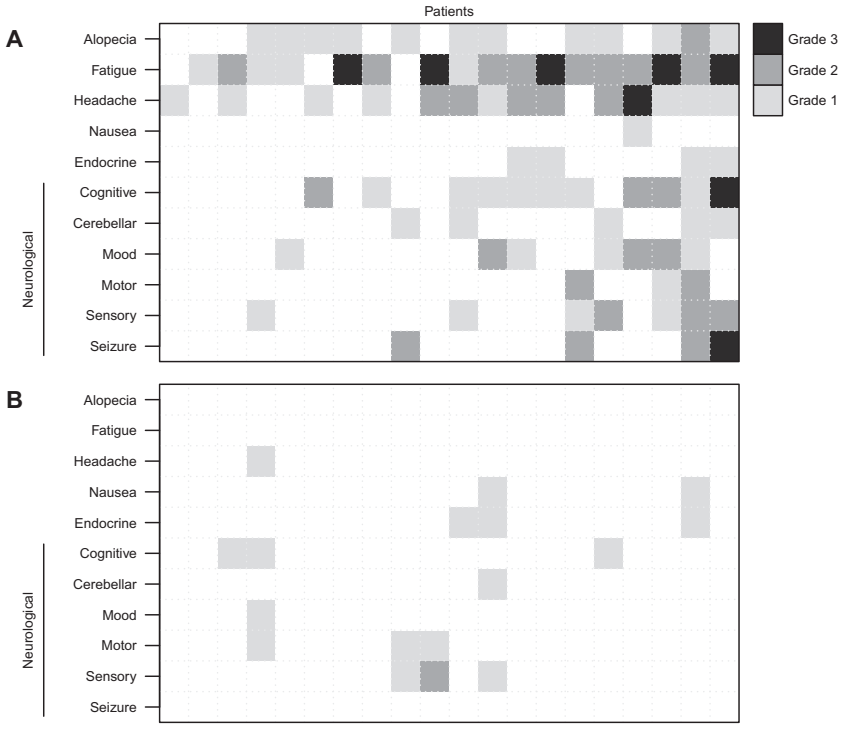

Fig. 3. Long-term toxicities that first presented ≤2 years (A) or >2 years (B) after radiation therapy. Shading corresponds to grade of toxicity. There were no toxicities of grade >3.

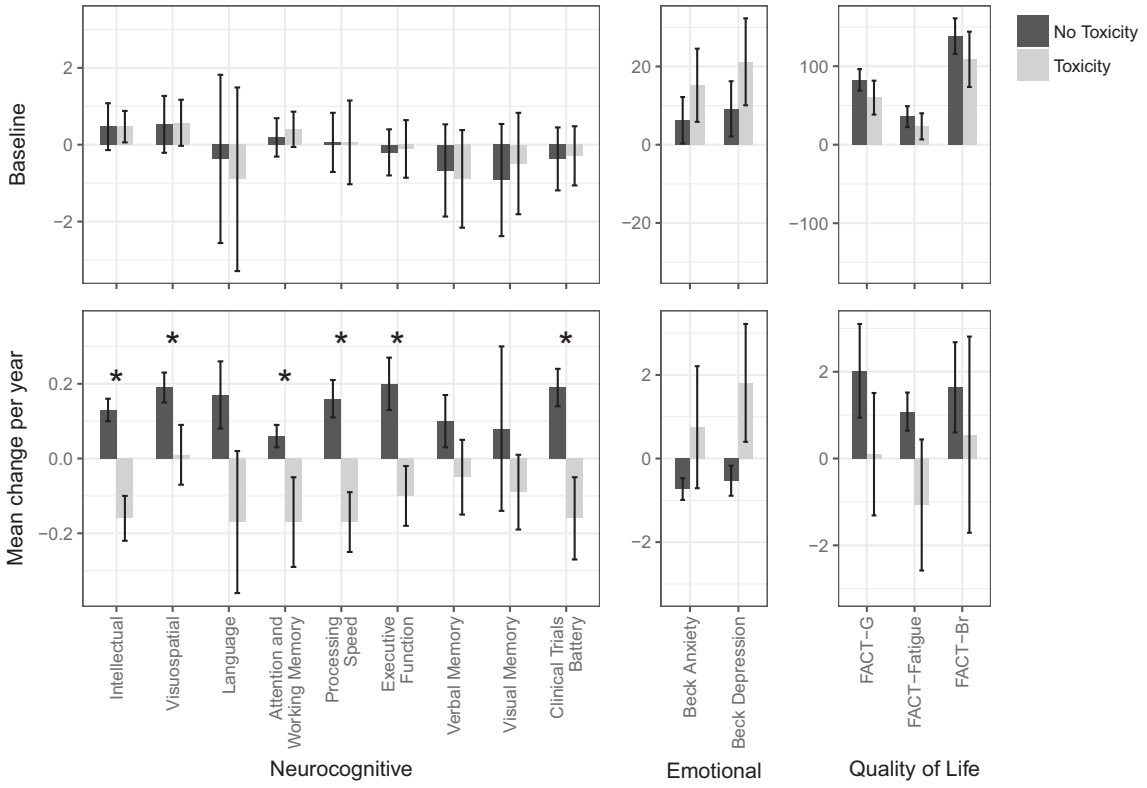

Fig. 4. Baseline and mean change per year in neurocognitive performance in patients with (gray) and without (black) self-reported mood or cognitive toxicities. Bars represent standard error. $^{*}p < 0.05$.

approach of assuming changes in neurocognition would be secondary to PRT, though there were potential other contributors including the disease itself and chemotherapy. Consistent with the initial report on this cohort, we noted no overall decline in any of the domains tested. A previous report suggested however that this improvement was less than expected after taking practice

effects into account [10,22]. We found that a minority (25%) of patients who self-reported changes in mood or cognition following treatment also showed a decline in performance on neurocognitive measures. Therefore, although PRT is overall well tolerated in terms of preservation of neurocognitive function, there may be a predictable subset of patients who are more susceptible to neurocognitive adverse effects. We did not detect a difference in hippocampal dose between the patients with reported neurocognitive toxicity and those without. The contralateral hippocampus was spared effectively using PRT in this cohort, with a median Dmean of 0 Gy(RBE) (range 0–12.2 Gy(RBE)), comparing favorably to doses achieved in contralateral hippocampal avoidance with IMRT/VMAT [23–25], such as median Dmean of 12.3 Gy (range 1.3–19.7 Gy) in [23].

The profile of toxicity in this cohort was similar to those reported in other studies [26,27]. We found that most long-term toxicities present in the first 2 years following radiation therapy. Among these, neuropsychologic toxicity is common, and can arise or persist over a span of many years, underscoring the need for long-term follow-up of these patients. Long-term follow-up of photon radiotherapy for LGG suggests that treatment-related neurotoxicity may not be appreciated until 6 or more years after radiotherapy [6]. It remains to be seen whether a similar pattern holds for PRT.

IDH1 mutation and 1p/19q loss are now part of the diagnostic criteria for LGG and inform prognosis [28–30]. In our cohort, IDH1-R132H was present in 71% of tumors tested and 1p/19q loss was present in only 29%, consistent with 80% of our cohort being of astrocytic dominant histology. In the initial publication, only 2 patients were reported to have 1p/19q loss [9] based on the assumption that untested astrocytomas are wild type for the co-deletion. However, two of our astrocytoma cases carried the co-deletion, as well as an oligodendroglioma that was not previously tested. 1p/19q co-deletion status was not tested in three astrocytomas (reported as unknown here, previously reported as intact in the initial report).

Limitations of this study include lack of a randomized design and a relatively small number of patients. Both limitations will be addressed in the currently open multicenter randomized trial of proton therapy versus photon therapy for LGG patients (NRG-BN005). In the meantime, we are not able to make direct comparisons to other treatment modalities using our assessment tools. Nonetheless, our results have some of the longest follow-up periods for proton therapy published to date and provide insight into the long-term outcomes of LGG patients treated with PRT.

Our results demonstrate that the majority of LGG patients who receive PRT maintain neurocognitive and neuroendocrine function and compare favorably to results of photon studies in terms of treatment-related morbidity. A predictable number of patients develop neuroendocrine deficiencies, and a small subset incurs neurocognitive deficiencies, with most long-term toxicities first presenting within two years following radiotherapy.

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Conflicts of interest

- Beow Y. Yeap: Abcodia Inc (Consultant), SISCAPA Assay Technologies (SAB), LunGevity Non-profit (SAB).
- Jay S. Loeffler: Advanced Oncology (Leadership), Richard Schiller (Expert Testimony).
- Helen A. Shih: prIME Oncology (educational speaker), UpToDate (Writer), Cleveland Clinic (expert testimony).
- Tracy Batchelor: Merck & Co, NXDC, Amgen, Roche, Oxigene, Foundation Medicine, Proximagen/Upsher, Genomicare (pharmaceutical consulting fees); Pfizer, AstraZeneca, Millenium (grant support); Up to Date, Research to Practice, Oakstone Medical Publishing, Imedex (work on CME material); and work with Jiahui Health and Champions Biotechnology.
- Kevin Oh: UpToDate (Writer), Merck & Co (research funding), Elekta (research funding).
- All other authors report no conflicts of interest.

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