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CLINICAL STUDY

Radiation-induced brain injury in patients with meningioma treated with proton or photon therapy

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Abstract

Introduction Radiation therapy is often used to treat meningioma with adverse features or when unresectable. Proton therapy has advantages over photon therapy in reducing integral dose to the brain. This study compared the incidence of radiological and clinical adverse events after photon versus proton therapy in the treatment of meningioma.

Methods A retrospective review was conducted on patients with meningioma treated with proton or photon therapy at two high-volume tertiary cancer centers. Patients with a history of prior radiation therapy (RT) or less than 3 months of follow-up were excluded. Post-RT imaging changes were categorized into abnormal T2 signal intensities (T2 changes) or abnormal T1 post-contrast and T2 signal intensities (T1c+T2 changes) on magnetic resonance imaging (MRI). Clinical outcomes of adverse events and survival were compared between the proton and photon therapies.

Results Among the total of 77 patients, 38 patients received proton therapy and 39 patients received photon therapy. The median age at diagnosis was 55 years and median follow-up was 2.2 years. No significant differences in symptomatic adverse events were observed between the two groups: grade ≥ 2 adverse events were seen in 4 (10.5%) patients in the proton group and 3 (7.7%) patients in the photon group ($p=0.67$). The 2-year cumulative incidences of T2 changes were 38.3% after proton therapy and 47.7% after photon therapy ($p=0.53$) and the 2-year cumulative incidences of T1c+T2 changes were 26.8% after proton therapy and 5.3% after photon therapy ($p=0.02$). One patient experienced grade ≥ 4 adverse event in each group ($p=0.99$). Estimated 2-year progression-free survival was 79.5% (proton therapy 76.0% vs. photon therapy 81.3%, $p=0.66$) and 2-year overall survival was 89.7% (proton therapy 86.6% vs. photon therapy 89.3%, $p=0.65$).

Conclusions Following RT, high rates of T2 changes were seen in meningioma patients regardless of treatment modality. Proton therapy was associated with significantly higher rates of T1c+T2 changes compared with photon therapy, but severe adverse events were uncommon in both groups and survival outcomes were comparable between the two groups. Future studies will aim at correlating the MRI changes with models that can be incorporated into RT planning to avoid toxicity.

Keywords Meningioma · Radiation necrosis · Brain injury · Proton therapy

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Introduction

Meningiomas are the most common intracranial neoplasm in adults, representing approximately 35% of central nervous system (CNS) tumors [1]. The majority are benign, World Health Organization (WHO) grade I in histology [2]. However, since the re-classification of meningiomas in 2000, more tumors have been identified as atypical (WHO grade II) or malignant (WHO grade III) [3–5]. Recent studies have suggested that 35% of meningiomas may reach criteria for grade II, under the new WHO classification [6].

Multiple retrospective series have shown a significant improvement in recurrence- and progression-free survival outcomes with the addition of adjuvant radiation therapy (RT) to surgical resection in those with subtotal resection (STR), or atypical or malignant histology [7–9]. However, RT is not without potential significant long-term complications such as RT-induced brain injury, neurocognitive function decline and hypopituitarism [10, 11]. These treatment-related toxicities can be debilitating and have a significant impact on quality of life, while most patients with meningioma have relatively favorable survival outcomes after treatment [12]. In contrast, the benefit is less pronounced in patients with gross tumor resection (GTR) of benign tumors, in which observation remains a valid management option [13–15].

In order to minimize the late effects of treatment, proton therapy has been increasingly utilized for patients with meningioma, whereby lower integral doses are achieved in the brain parenchyma and other critical structures, such as hippocampi, pituitary gland, optic apparatus and cochleae. This lower integral dose is made possible by the Bragg peak phenomenon from the lower beam entrance dose and minimal exit dose [16–18]. However, at the end of the spread-out Bragg peak (SOBP), the dose heterogeneity with proton therapy could result in a relative biological effectiveness (RBE) that may be higher than what is currently modeled [19]. This issue, combined with varying reports on the incidence of brain injury after proton therapy, particularly in pediatric patients [20], has led to some concern regarding the increasing use of proton therapy.

In the current literature, there exists a paucity of clear data on the radiological and clinical outcomes of RT-induced brain injuries between proton and photon therapies in the treatment of meningioma. We aimed to characterize and compare the radiological and clinical outcomes of brain injuries between these two modalities.

Methods and materials

Study design and patient selection

Institutional Review Board approval was obtained prior to commencement of the study. A retrospective review was conducted on patients with meningioma of any grade, who received standard fractionated RT with proton therapy between 2014 and 2017 at University of Washington/Seattle Cancer Center Alliance, where all meningioma patients are treated with proton therapy, or photon therapy between 2008 and 2018 at The Ottawa Hospital, where all meningioma patients are treated with photon therapy, both high-volume tertiary cancer centers in North America. No proton therapy is available at The Ottawa Hospital and was thus selected as the institution for comparator arm of photon therapy. Patients with a history of previous treatment with RT, or less than 3 months follow-up were excluded.

Data collection

Data on patient demographics, tumor characteristics and treatments were collected, including tumor grade, extent of surgical resection (Simpson grade I–V) and dosimetric parameters of RT. Data on RT-induced brain injuries were also collected, which were categorized into abnormal "T2 changes" suggestive of white matter lesions, or "T1c+T2 changes" suggestive of radiation necrosis (RN), on post-treatment magnetic resonance imaging (MRI). T2 changes were defined as lesions with abnormal hyperintensities on T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences. T1c+T2 changes were defined as any areas with contrast-enhancement and distinct margins best seen on T1 post-contrast sequence, often associated with surrounding abnormal T2 hyperintensity. (Fig. 1) No pathological confirmation for diagnosis of radiation necrosis was required.

Follow-up MRI was obtained every 3 months from completion of treatment for 1 year, then every 6–12 months until 5 years, and then annually thereafter, where almost all patients were adherent with the follow-up. All images were reviewed by an experienced neuro-radiologist (JF). Abnormal images were then reviewed after fusion with the initial RT plans. Adverse events were graded as per the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, where patients were categorized into radiographic changes only (i.e., grade 1 adverse event) or symptomatic radiation injury (i.e., grade 2 or higher adverse event) [21]. Those patients with T1c+T2 changes without any symptoms were defined as grade 1 RN.

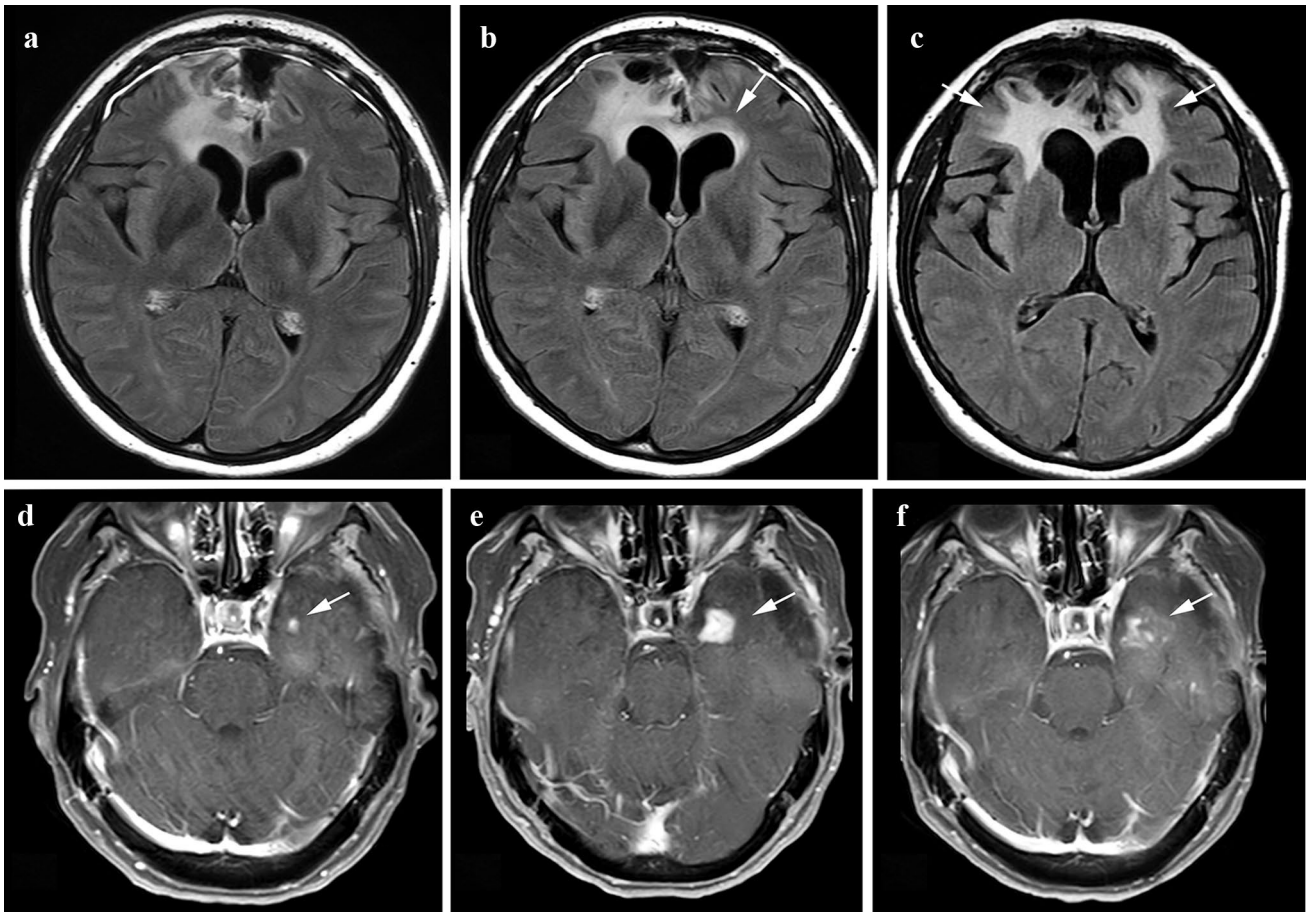

Fig. 1 Examples of radiation-induced radiographic changes in brain. The top row (**a**–**c**) demonstrates serial T2 fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) for a 48-year-old woman treated with adjuvant proton therapy after gross total resection (GTR) of World Health Organization (WHO) grade 2 meningioma. Before radiation therapy (RT), confluent T2 signal hyperintensity is seen in the right frontal lobe (**a**). Six months after RT, there is a new T2 signal hyperintensity in the genu of the corpus callosum and surrounding the left frontal horn (arrow, **b**), and 33 months after RT there is an expansion of confluent T2 hyperintensity within both frontal lobes (arrows, **c**). The bottom row (**d**–**f**) demonstrates serial T1 post-contrast MRI for a 58-year-old woman treated with adjuvant proton therapy after GTR of WHO grade 2 meningioma. Twenty-four months after RT, there is a new contrast enhancing lesion in the left temporal lobe (arrow, **d**). This increased in size at 30 months after RT (arrow, **e**) and became less confluent at 39 months after RT (arrow, **f**)

Statistical analysis

Statistical analysis was performed using IBM® SPSS Statistics 27.0 (Armonk, NY, USA). Survival curves were generated with the Kaplan–Meier method, and the log-rank test was used to compare the differences in cumulative incidence rates of RT-induced brain injury and survival outcomes between the proton and photon groups. Univariate and bivariate analyses were performed using Cox regression analysis. Independent factors that are radiation treatment-related and thus would have potential impact on radiographic changes, including disease involvement of brain, maximum dose to brain and size of clinical target volume (CTV), were selected for the analysis. Primary endpoints were symptomatic radiation injury and secondary endpoints were asymptomatic radiation injury, either T2 changes or T1c+T2 changes. Survival outcomes were analyzed in 2-year progression-free survival (PFS) and 2-year overall survival (OS). PFS was defined as the time interval between the last date of RT and the date of disease recurrence or progression, or death from any cause, whichever occurred first. OS was defined as the time interval between the last date of RT and death from any cause.

Results

Patient demographics and tumor characteristics

A total of 86 patients were identified from the database. Nine patients had previous RT and were excluded, leaving 77 patients for final analysis. Median age at diagnosis was 55 years (range 14–80 years) and median follow-up was 2.2 years (proton group 1.7 years, photon group 3.1 years). Grade II histology was the most common (62.3%), followed by grade I (23.4%) and grade III (9.1%). The majority of patients (62.3%) had de novo disease and 37.7% of patients had recurrent disease. There were no significant differences in WHO grade, RT dose, size of CTV, performance status or comorbidities between the two groups (Table 1).

Surgery and radiotherapy

Among the entire cohort of 77 patients, 38 (49.4%) patients received proton therapy and 39 (50.6%) patients received photon therapy. The following target volume delineation method was used in both groups: Gross tumor volume (GTV) generally included gross residual disease after surgery for grade I tumors, and gross residual and tumor bed for grade II and III tumors. Clinical target volume (CTV) expansion was determined at the discretion of the treating radiation oncologist and generally was 0–1.0 cm depending

Table 1 Patient demographics and tumor characteristics

	All patients (n = 77)	Proton therapy (n = 38)	Photon therapy (n = 39)	P
Median age at diagnosis, years (range)	55 (14–80)	51 (14–73)	55 (19–80)	0.167
Sex, n (%)				0.104
Male	25 (32.5)	9 (23.7)	16 (41.0)	
Female	52 (67.6)	29 (76.3)	23 (59.0)	
Pre-treatment Karnofsky performance score, n (%)				0.780
> 70	66 (85.7)	33 (86.8)	33 (84.6)	
≤ 70	11 (14.3)	5 (13.2)	6 (15.4)	
History of diabetes, n (%)	15 (19.5)	6 (15.8)	9 (23.1)	0.420
History of CVA, n (%)	2 (2.6)	2 (5.3)	0 (0.0)	0.147
Status of tumor, n (%)				0.277
De novo disease	48 (62.3)	26 (68.4)	22 (56.4)	
Recurrent	29 (37.7)	12 (31.6)	17 (43.6)	
Location of tumor, n (%)				0.157
Frontal lobe	32 (41.6)	13 (34.2)	19 (48.7)	
Parietal lobe	6 (7.8)	4 (10.5)	2 (5.1)	
Temporal lobe	4 (5.2)	2 (5.3)	2 (5.1)	
Occipital lobe	3 (3.9)	0 (0.0)	1 (2.6)	
Base of skull	18 (23.4)	6 (15.8)	12 (30.8)	
Optic nerve	6 (7.8)	5 (13.2)	1 (2.6)	
Brainstem/posterior fossa	8 (10.4)	6 (15.8)	2 (5.1)	
Largest diameter of tumor, cm, median ± SD (range)	3.7 ± 2.0 (0.7–12.0)	3.7 ± 2.3 (0.7–12.0)	3.8 ± 1.6 (0.7–7.6)	0.686
WHO grade, n (%)				0.328
1	18 (23.4)	8 (21.1)	10 (25.6)	
2	48 (62.3)	24 (63.2)	24 (61.5)	
3	7 (9.1)	3 (7.9)	4 (10.3)	
Unknown	4 (5.2)	3 (7.9)	1 (2.6)	
Mitosis # in HPF, median ± SD	5 ± 5.1	5 ± 5.9	5 ± 4.2	0.961
Brain involvement, n (%)				0.913
Yes	22 (28.6)	11 (28.9)	11 (28.2)	
No	36 (46.8)	15 (39.5)	21 (53.8)	
Unknown	19 (24.7)	12 (31.6)	7 (17.9)	

CVA cerebrovascular accident, *SD* standard deviation, *WHO* World Health Organization, *HPF* high-power field

on the grade. PTV expansion was 3–5 mm from CTV to account for set-up uncertainty.

RT qualities were similar between the proton and photon groups, including intent of RT, median dose and CTV. However, 52.6% of patients underwent preoperative embolization in the proton group, compared with only 1 (2.6%) patient in the photon group. In addition, 36.8% of patients underwent GTR in the proton group, whereas 59.0% of patients underwent GTR in the photon group. These differences were statistically significant. In the photon group, 9 (23.1%) patients received additional radiosurgical boost to the surgical cavity following the fractionated RT, whereas no patient received boost in the proton group. (Table 2).

A larger volume of the brain received integral dose in the photon group than in the proton group and the differences between the two groups were greater in the lower dose range (Fig. 2; Table 2).

One (1.3%) patient in the photon group received systemic therapy (temozolomide) after disease progression following salvage radiation therapy and no patient received systemic therapy in the proton group.

Radiation-induced brain injury

Both proton and photon therapies were associated with low numbers of symptomatic radiation injury and the treatments were generally well tolerated by patients in both groups. No significant differences in toxicity were observed between the two groups: grade ≥ 2 adverse events were seen in 4 (10.5%) patients in the proton group and 3 (7.7%) patients in the photon group ($p = 0.67$). Only one patient experienced a grade ≥ 4 adverse event in each group ($p = 0.99$). Among the 4 patients with grade ≥ 2 adverse events in the proton group, 3 patients had T1c+T2 changes and 1 patient had T2 changes, while among the 3 patients with grade ≥ 2 adverse events in the photon group, 1 patient had T1c+T2 changes and 2 patients had T2 changes.

The 2-year cumulative incidences of T2 changes were 38.3% after proton therapy and 47.7% after photon therapy ($p = 0.53$), and the 2-year cumulative incidences of T1c+T2 changes were 26.8% after proton therapy and 5.3% after photon therapy ($p = 0.02$) (Fig. 3). The median time to T2 changes from the end of RT was 169 days and the median time to T1c+T2 changes was 368 days. Among the 9 patients with T1c+T2 changes in both groups, 4 patients showed symptoms, where 2 patients were treated with systemic steroids, 2 patients with bevacizumab, 1 patient with surgical resection and 4 patients with conservative management. One patient received systemic steroids despite the absence of any symptoms.

Univariate analysis identified that RT modality was significantly associated with T1c+T2 changes ($p = 0.03$), but not with T2 changes ($p = 0.53$). Brain invasion, brain dose (D_{max}) and CTV volume were not associated with either T2 changes or T1c+T2 changes. Prior preoperative embolization ($p = 0.15$ and $p = 0.66$ for T2 and T1c+T2 changes, respectively) or prescribed dose ($p = 0.42$ and $p = 0.17$ for T2 and T1c+T2 changes, respectively) was not associated with radiographic changes. Bivariate analysis showed that the RT modality was not significantly associated with T2 changes when brain invasion ($p = 0.48$), brain dose (D_{max}) ($p = 0.62$) or CTV volume ($p = 0.53$) were taken into account, but the RT modality was significantly associated with T1c+T2 changes when brain invasion ($p = 0.042$), brain dose (D_{max}) ($p = 0.017$) or CTV volume ($p = 0.030$) were taken into account (Table 3).

Clinical outcomes

A total of 10 (13.0%) patients recurred after RT (5 patients in each group). Median time-to-recurrence was 14.4 months (range 0.4–22.0 months) in the entire cohort (14.2 months in the proton group and 14.5 months in the photon group).

No patients died of meningioma in the proton group, but all 5 patients who died in the photon group died of the disease or from treatment-related causes: 3 patients died from disease progression, 1 patient died from aspiration pneumonia secondary to cognitive functional decline and 1 patient died from status epilepticus.

Survival outcomes were similar between the two groups: 2-year PFS was 76.0% in the proton group and 81.3% in the photon group ($p = 0.66$), and 2-year OS was 86.6% in the proton group and 89.3% in the photon group ($p = 0.65$) (Fig. 4).

Discussion

Our study compared the clinical and radiological outcomes of RT-induced brain injury from proton or photon therapy in meningioma. As described, T2 changes in the brain parenchyma were frequently observed following either modality, while a trend towards higher rates of T1c+T2 changes were seen with proton therapy compared with photon therapy ($p = 0.02$). The rates of symptomatic brain injury were uncommon in both groups. The results of the study add to the current literature investigating whether or not proton therapy is associated with increased brain injury compared with photon therapy.

Brain injury is one of the most significant side effects of RT for CNS tumors, although a true understanding of its incidence and etiology is difficult due to several factors. The current definition of brain injury has been inconsistently described and reported upon in the literature. Among the studies of brain injury after proton therapy, endpoints have included radiological endpoints alone [22–25] or with

Table 2 Description of surgical resection and radiation therapy

	All patients (n = 77)	Proton therapy (n = 38)	Photon therapy (n = 39)	P
Preoperative embolization, n (%)				< 0.001*
Yes	21 (27.3)	20 (52.6)	1 (2.6)	
No	47 (61.0)	10 (26.3)	37 (94.9)	
Unknown/no resection	9 (11.7)	8 (21.1)	1 (2.6)	
Extent of surgical resection (Simpson grade), n (%)				0.002*
GTR (1–2)	38 (48.1)	14 (36.8)	23 (59.0)	
NTR (3)	10 (13.0)	7 (18.4)	3 (7.7)	
STR (4–5)	25 (32.5)	13 (34.2)	12 (30.8)	
Unknown	2 (2.6)	1 (2.6)	1 (2.6)	
No resection/biopsy only	3 (3.9)	3 (7.9)	0 (0)	
Intent of radiotherapy**, n (%)				0.556
Adjuvant	45 (48.4)	23 (60.5)	22 (56.4)	
Salvage	29 (37.7)	12 (31.6)	17 (43.6)	
Definitive	3 (3.9)	3 (7.9)	0 (0)	
Median dose, GyRBE (proton) or Gy (photon) (range)	54 (50–60)	54 (50.4–60)	54 (50–60)	0.238
Median number of fraction (range)	30 (25–33)	30 (28–33)	27 (25–33)	0.401
Median dose per fraction, GyRBE (proton) or Gy (photon) (range)	1.8 (1.8–2.3)	1.8 (1.8–2)	2 (1.8–2.3)	0.187
Radiosurgical boost, n (%)				n/a
Yes	9 (11.7)	0 (0)	9 (23.1)	
No	28 (88.3)	38 (100)	30 (76.9)	
Delivery technique, n (%)				n/a
VMAT	32 (41.6)	0 (0.0)	32 (82.1)	
Tomotherapy	7 (9.1)	0 (0.0)	7 (17.9)	
Pencil-beam scanning	23 (29.9)	23 (60.5)	0 (0.0)	
Uniform scanning	15 (19.5)	15 (39.5)	0 (0.0)	
Median CTV, cm^2 (range)	65 (3–535)	68.6 (5–360)	57 (3–535)	0.633
Dose to brain				
Median D_{max}, GyRBE (proton) or Gy (photon) (range)	57.0 (48.5–66.1)	56.5 (48.5–62.6)	57.3 (52.8–66.1)	0.882
V60, mean % of brain ± SEM	1.6 ± 0.4	1.7 ± 0.6	1.5 ± 0.6	0.659
V54, mean % of brain ± SEM	7.2 ± 0.8	7.2 ± 1.1	7.2 ± 1.1	0.693
V50, mean % of brain ± SEM	10.0 ± 0.9	9.2 ± 1.2	10.8 ± 1.3	0.651
V40, mean % of brain ± SEM	13.6 ± 1.0	11.5 ± 1.3	15.6 ± 1.5	0.429
V30, mean % of brain ± SEM	16.9 ± 1.3	13.0 ± 1.3	21.5 ± 2.3	0.010*
V20, mean % of brain ± SEM	23.3 ± 1.9	16.1 ± 1.5	31.9 ± 3.3	0.001*
V10, mean % of brain ± SEM	34.2 ± 2.5	22.2 ± 1.7	48.4 ± 3.7	0.016*

GTR gross total resection, *NTR* near total resection, *STR* sub-total resection, *VMAT* volumetric-arc therapy, *CTV* clinical target volume, *SEM* standard error mean, D_{max} maximum dose, *D50%* dose delivered to at least 50% of target volume, n/a not applicable

*Statistically significant; **Adjuvant radiotherapy indicates treatment without any evidence of disease progression or recurrence following surgery and salvage radiotherapy indicates treatment in the presence of disease progression or recurrence following surgery

symptoms [26, 27]. Terms used include "radionecrosis" (RN) [22], "late contrast-enhancing brain lesions" [23], or "contrast-enhancing treatment related changes" [24], that are generally asymptomatic. Since RN is a histological diagnosis, it is not clear that all T1 contrast-enhancing lesions are associated with true RN. Other series have noted that the term RN should only be used when associated with neurological symptoms or resulting in surgery or bevacizumab use [26, 27]. Pseudoprogression has also been described, mostly in the context of the treatment of gliomas where it is difficult to distinguish between the effects of RT and true tumor progression [28–30]. Furthermore, the timeframe for imaging findings is variable and may be dependent on the extent of follow-up amongst studies. In their systematic review, Lawrence et al. reported 5% and 10% incidence rates of RN from an extrapolation of patients treated with BED higher than 120 Gy and 150 Gy, respectively, in standard fraction size, and a steep increase in the incidence rate of RN after

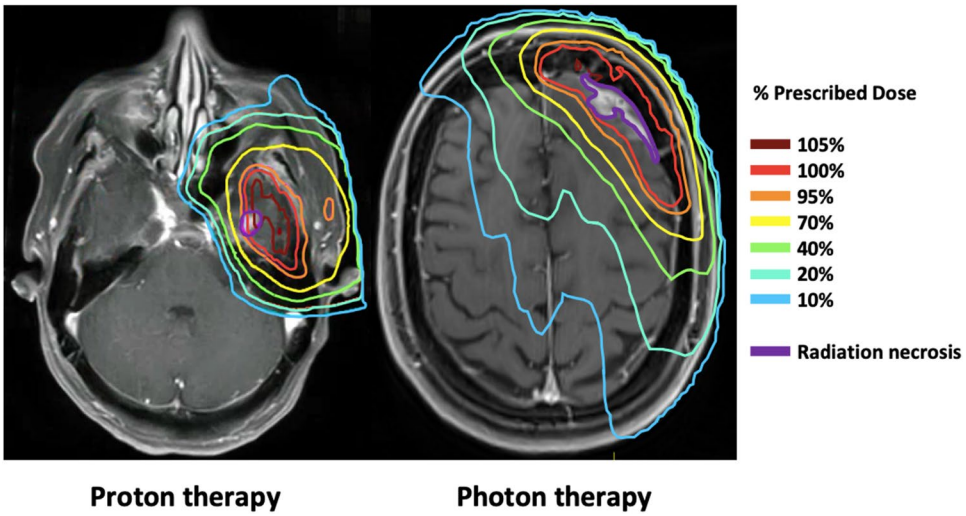

Fig. 2 Examples of the relationship between imaging changes and dose distribution. On the left is a new enhancing lesion after proton therapy and on the right is a new enhancing lesion after photon therapy. Isodose lines are shown as the percentage of prescribed dose and are overlayed on the T1 post-contrast magnetic resonance imaging

80 Gy for those treated with twice-daily fractions [31]. Some studies have suggested a correlation between incremental RT dose [32, 33] and volume [34], as well as other factors including prior RT exposure [35], chemotherapy [36] and tumor histology [37], and the incidence rates of RN, but no consensus has been established due to the heterogeneous nature of CNS tumors and their treatments.

As a heavy particle, protons rapidly lose energy within the last few millimeters of tissue penetration, yielding a sharply localized peak of dose known as the Bragg peak. By modulating the proton energy, the Bragg peak can be precisely placed at different depths, which can be used to create the SOBP covering the entire target of interest. Beyond the peak, no additional dose is deposited. The terminal portion of the SOBP may have variable RBE as high as 1.2 or 1.3, though most centers use a generic RBE of 1.1 for dose calculations. Therefore, there is concern that in the brain, the RBE could be higher at the end of range causing an increased risk of brain injury. Our results indeed showed higher rates of new T1 post-contrast enhancements in the proton group compared with the photon group, although the rates of symptomatic brain injury were not significantly different between the two groups.

Multiple studies have reported on this finding of T1 post-contrast enhancing lesions at the end of range. Bojaxhiu et al. [22] reported that 29 (17%) of 171 pediatric patients treated with proton therapy for brain tumors had new T1 post-contrast enhancing changes, with 7 (24%) of those being asymptomatic. Bahn et al. [23] reported similar rates of 23 (21%) of 110 patients with late contrast enhancing brain lesions after proton therapy for low-grade glioma. Others have reported increased risk for these lesions in the periventricular regions [24] as well as areas of high linear energy transfer (LET) [25]. Whether these post-contrast enhancing lesions lead to clinically significant brain injury, however, remains unknown. The controversy is perhaps best seen in evaluating brainstem injury in children treated with proton therapy for posterior fossa tumors where high injury rates were initially suggested [38]. In addition, a comparative study of imaging changes following proton therapy or intensity-modulated RT (IMRT) for children with ependymoma found increased rates of post-RT changes after proton therapy. However, once a consensus amongst pediatric radiation oncologists regarding appropriate dose constraints for proton therapy to the posterior fossa was created, studies have shown similarly low rates of brainstem injury compared to photons. [20, 39].

Our toxicity findings are consistent with previously published studies on meningioma treated with photon therapy. A report on 48 patients with intermediate-risk meningioma treated with IMRT (54 Gy in 30 fractions) on RTOG 0539 found no grade 3 or higher events [40]. For the 51 high-risk patients treated with IMRT utilizing a simultaneous integrated boost technique (54–60 Gy), 1 (1.9%) patient experienced a late grade 5 necrosis-related adverse event and 2 (3.3%) patients experienced grade 2 necrosis. [41] Another phase II study (EORTC 22,042–26,042) on 56 patients with non-benign (WHO grade II and III) meningioma following GTR showed that the addition of adjuvant RT (median dose 60 Gy in 30 fractions) resulted in 14.3% grade ≥ 3 toxicity with one patient with grade 3 ischemia within the irradiated brain [32]. A prospective trial with long term follow-up (median 17.1 years) of 44 patients with benign meningioma randomized to 55.8 GyRBE or 63 GyRBE with combined protons and photons reported asymptomatic brain necrosis in 1/22 cases in the lower dose arm and in 2/22 cases in the higher dose arm [18]. A retrospective study of 96 patients with meningioma treated with pencil beam scanning proton

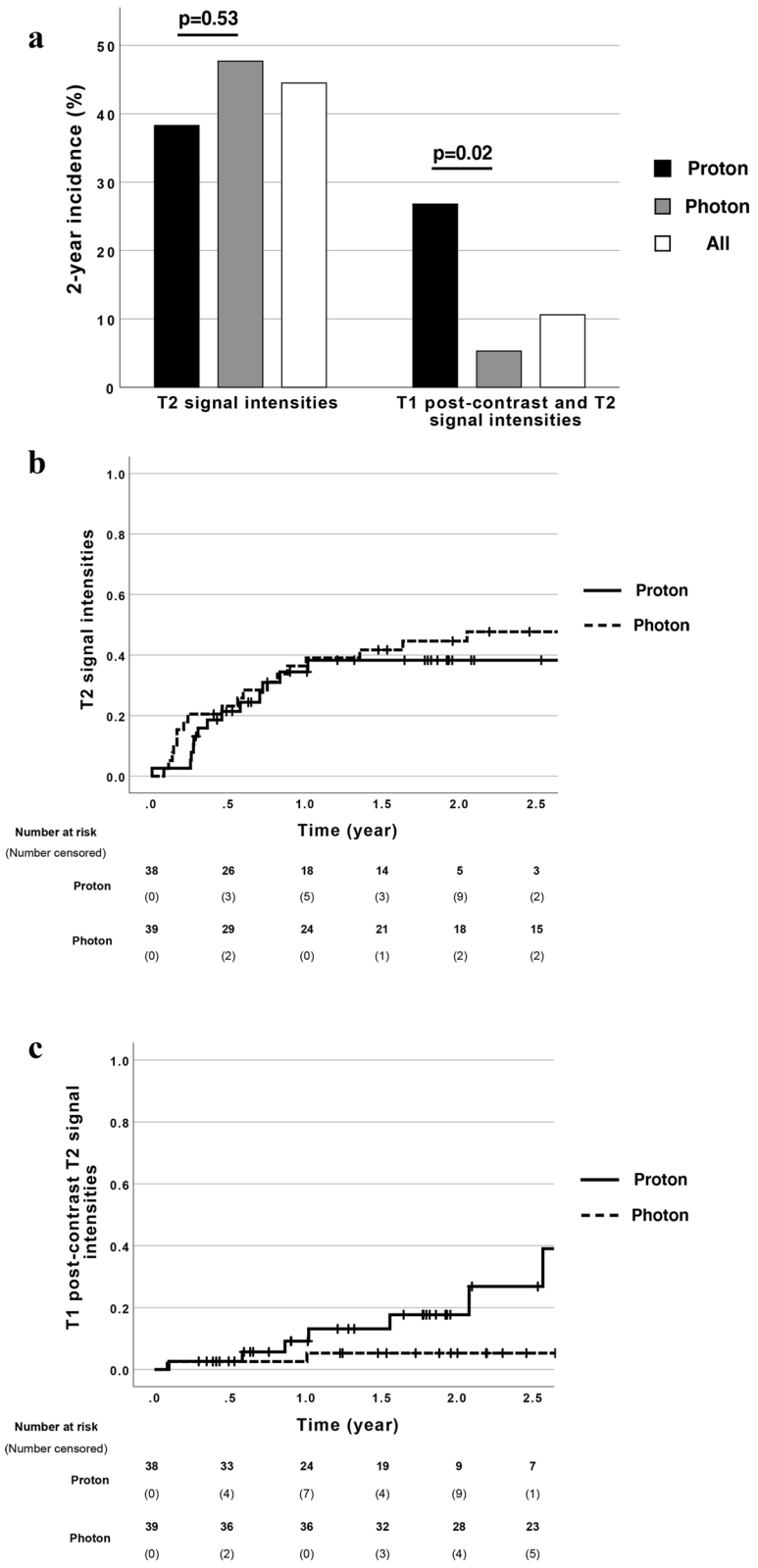

Fig. 3 Rates of radiation-induced radiographic changes. Estimated 2-year incidence rates of new T2 signal hyperintensity on T2 fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) and new enhancing lesions on T1 post-contrast MRI in conjunction with new T2 signal hyperintensity on T2 FLAIR MRI (**a**). Cumulative incidences of new T2 signal hyperintensity on T2 FLAIR MRI (**b**). Cumulative incidences of new enhancing lesions on T1 post-contrast MRI in conjunction with new T2 signal hyperintensity on T2 FLAIR MRI (**c**)

Table 3 (a) Univariate and (b) bivariate analysis on abnormal T2 signal intensities (T2 changes) and abnormal T1 post-contrast and T2 signal intensities (T1c+T2 changes)

	T2 changes		T1c+T2 changes	
	HR (95% CI)	P	HR (95% CI)	P
(a)				
RT modality (proton vs. photon)	0.795 (0.389–1.625)	0.529	5.872 (1.182–29.167)	0.030*
Brain invasion (invasion vs. no invasion)	1.072 (0.698–1.646)	0.751	1.544 (0.692–3.444)	0.289
Brain dose (D_{max})	1.001 (1.000–1.002)	0.172	1.001 (0.999–1.003)	0.289
Size of CTV (cm^3)	1.000 (0.996–1.004)	0.978	0.999 (0.991–1.008)	0.866
(b)				
RT modality (proton vs. photon)	0.770 (0.372–1.597)	0.483	5.405 (1.064–27.468)	0.042*
Brain invasion (invasion vs. no invasion)	1.105 (0.712–1.717)	0.655	1.279 (0.569–2.876)	0.551
RT modality (proton vs. photon)	0.835 (0.406–1.717)	0.624	7.262 (1.419–37.151)	0.017*
Brain dose (D_{max})	1.001 (1.000–1.002)	0.191	1.001 (1.000–1.003)	0.132
RT modality (proton vs. photon)	0.795 (0.389–1.625)	0.529	5.885 (1.184–29.251)	0.030*
Size of CTV (cm^3)	1.000 (0.996–1.004)	0.982	0.999 (0.990–1.008)	0.844

Preoperative embolization (p = 0.16 for T2 and p = 0.66 for T1c+T2 changes) and prescribed dose (p = 0.42 for T2 and p = 0.17 for T1c+T2 changes) were not associated with radiographic changes

HR hazard ratio, *CI* confidence interval, *RT* radiation therapy, D_{max}, maximum dose, *CTV* clinical target volume

*Statistically significant

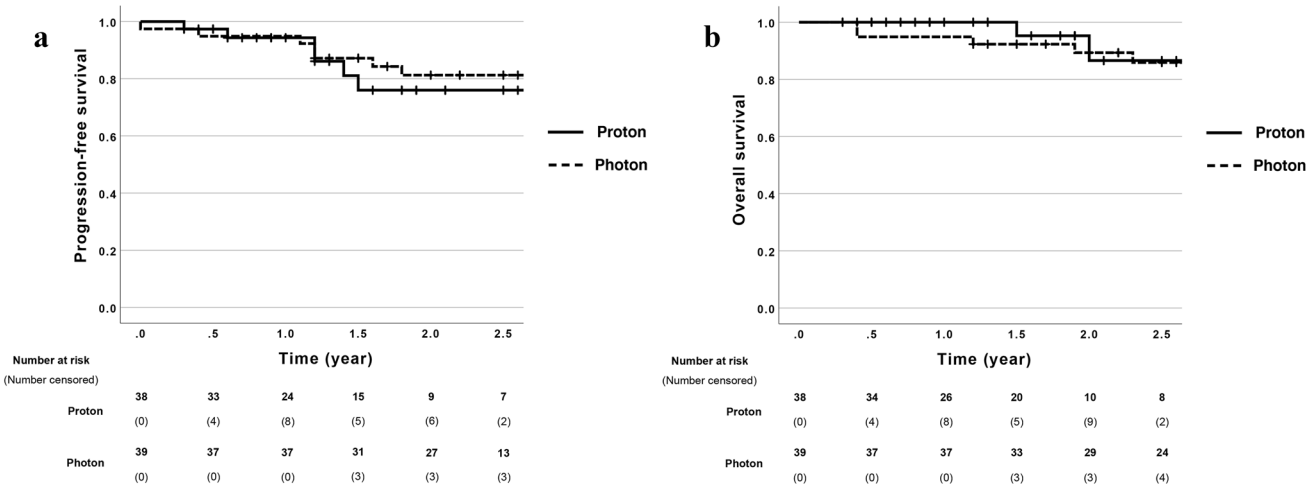

Fig. 4 Clinical outcomes. Kaplan–Meier survival plots of comparing the progression-free survival (**a**) and overall survival (**b**) of the two treatment cohorts

therapy (median 54 GyRBE for grade I and 62 GyRBE for grade II/III) reported two cases of brain necrosis [16]. Overall, with a median follow-up 56.9 months, there was 10% grade ≥ 3 toxicity in this large series.

Proton therapy, when compared with photon therapy, can achieve dose reductions in OARs and the integral dose to the brain [17, 42]. A dosimetric analysis on 10 meningioma patients treated at Massachusetts General Hospital demonstrated significant dose reductions in various intracranial structures, including brain, brainstem, hippocampi, temporal lobes, pituitary gland, optic nerves and cochleae, and estimated a significant reduction in secondary malignancies with proton therapy compared to photon therapy (p < 0.002) [43]. Given the maturing data on the effect of even low doses to the bilateral hippocampi on long-term neurocognitive function, proton therapy may lead to decreased risks of late effects in meningioma patients. However, this needs to be balanced with availability of proton therapy and any associated increased toxicity.

Strengths of our study include the well-balanced patient demographics and tumor characteristics between the proton and photon groups. In addition, all post-treatment images were interpreted by a single neuroradiologist, who was

blinded to the treatment modality, thus eliminating potential inter-observer bias.

However, a higher proportion of patients had received preoperative embolization in the proton group (52.6%) than in the photon group (2.6%). Preoperative embolization is often used and favored by some neurosurgeons to reduce intraoperative hemorrhage. Although multiple studies have shown higher rates of postoperative complications associated with preoperative embolization in treatment of meningioma, including cranial nerve dysfunction, [44–47] ischemic event, [48, 49] hemorrhage [44, 46, 48, 49] and even death [44, 45], the procedure is generally deemed safe, while postoperative complications are limited to a small number of patients [50]. Although preoperative embolization was not shown to be associated with T2 or T1c+T2 changes in our study, no study to date has identified preoperative embolization and its association with post-RT changes or tumor recurrence, and therefore its potential impact on higher rates of T1c+T2 changes seen in the proton group of our study remains uncertain and further study is required.

In addition, there were higher rates of near total resection (NTR, Simpson grade 3), STR (Simpson grade 4–5) and no surgery/biopsy only in the proton group (60.5%) than in the photon group (38.5%). Despite no significant differences between the median doses of the proton and photon groups, patients with NTR, STR or no surgery/biopsy only, especially in the proton group, may have received a higher radiation dose resulting in higher rates of T1c+T2 changes, which was not captured in our statistical analysis of median dose in each group.

Other limitations of the study include the retrospective nature of the study introducing potential confounding bias. In addition, patients were studied at two different time periods at two different institutions, where significant degrees of variations in surgical and radiation techniques may exist, resulting in outcomes seen in our study. Most importantly, the median follow-up of 2.2 years, especially the shorter follow-up of 1.7 years in the proton group, may not have been long enough to capture all post-RT radiographic changes and disease recurrences, while we continued to observe T1c+T2 changes even 2 years after completion of treatment in the proton group. Multiple studies with long follow-up have demonstrated that meningiomas many years after completion of treatment continue to recur, while the recurrent disease becomes more aggressive in its disease course, less responsive to treatment and is associated with higher mortality [14, 51, 52].

Ongoing efforts at several proton therapy centers are aimed at better understanding the true biologic dose at the end of range. Incorporating LET values in intensity-modulated proton therapy (IMPT) has been investigated for several years, though decreasing LET in critical structures may lead to higher overall doses to the critical structures. [53] Voxel level image change data has been correlated with increasing LET to support this [54]. The lack of biological data to predict variable RBE in tissues, however, has limited RBE-based planning. Mayo Clinic Cancer Center recently published their results correlating T2-FLAIR changes after spot-scanning IMPT with an in-house biological dose model and are starting to employ this model to avoid hot spots in critical structures [25]. However, the consensus remains that further study into this area is required.

Conclusion

Although the rates of symptomatic RT-induced brain injury remained low and comparable between proton and photon therapies in treatment of meningioma, significantly higher rates of T1c+T2 changes on post-treatment MRI were observed with proton therapy compared with photon therapy. While advances in our physical and biological understanding of proton therapy are ongoing, it is equally important to establish our clinical outcomes to focus further research. Future studies will aim at correlating the MRI changes with models that can be incorporated into RT planning to avoid increased toxicity.

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Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Availability of data and material Available upon request.

Ethical approval Institutional Review Board approval was obtained prior to commencement of the study.

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