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Overview

# Proton Beam Therapy in the Reirradiation Setting of Brain and Base of Skull Tumour Recurrences

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## Abstract

The therapeutic management of local tumour recurrence after a first course of radical radiotherapy is always complex. Surgery and reirradiation carry increased morbidity due to radiation-induced tissue changes. Proton beam therapy (PBT) might be advantageous in the reirradiation setting, thanks to its distinct physical characteristics. Here we systematically reviewed the use of PBT in the management of recurrent central nervous system (CNS) and base of skull (BoS) tumours, as published in the literature. The research question was framed following the Population, Intervention, Comparison and Outcomes (PICO) criteria: the population of the study was cancer patients with local disease recurrence in the CNS or BoS; the intervention was radiation treatment with PBT; the outcomes of the study focused on the clinical outcomes of PBT in the reirradiation setting of local tumour recurrences of the CNS or BoS. The identification stage resulted in 222 records in Embase and 79 in Medline as of March 2023. Sixty-eight duplicates were excluded at this stage and 56 were excluded after screening as not relevant, not in English or not full-text articles. Twelve full-text articles were included in the review and are presented according to the site of disease, namely BoS, brain or both brain and BoS. This review showed that reirradiation of brain/BoS tumour recurrences with PBT can provide good local control with acceptable toxicity rates. However, reirradiation of tumour recurrences in the CNS or BoS setting needs to consider several factors that can increase the risk of toxicities. Therefore, patient selection is crucial. Randomised evidence is needed to select the best radiation modality in this group of patients.


*Keywords:* Base of skull; brain; proton therapy; reirradiation; salvage treatments

## Statement of Search Strategies Used and Sources of Information

The following search strategy was run in EMBASE and Medline with the support of the Christie library and the returned records were screened for relevance: (Proton Therapy/or (“proton therap*" or “proton beam therap*" or protontherap* or “proton beam radiation therap*" or “proton radiotherap*"). mp) and ((reirradiat* or “re irradiat*"). ab, ti or *Re-Irradiation/) and (neoplasm recurrence, local/or recurrence/or neoplasm, residual/or recurrent disease/or (“local failure*" or recurrence* or relapse*). mp).

## Introduction

The therapeutic management of local tumour recurrence after a first course of radical radiotherapy is always complex [1]. Surgery and reirradiation carry increased

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morbidity due to radiation-induced tissue changes (i.e. fibrosis, hypoxia, altered vascularisation) [2]. Reirradiation is a delicate balance between safety and efficacy, with the potential for decreased efficacy and increased burden of toxicity compared with first-time irradiation [3]. On a dose–response curve, this is often described as a narrower therapeutic window, with tumour control probability and normal tissue complication probability curves close together. The decision to perform reirradiation should consider many factors: the time interval between the two irradiation courses, the late effects from first irradiation, tumour recurrence histology, volume and its location, normal tissue architecture (serial or parallel), as well as the existence of other treatment options [4]. An accurate estimate of the risks from reirradiation cannot disregard radiobiological considerations, as described by the linear quadratic model. The central nervous system (CNS) is the classic example of a late-responding tissue, with slow renewal capability and high sensitivity to fractionation (low $\alpha/\beta$ ratio) [5]. In the reirradiation setting, the cumulative dose from the two radiotherapy treatments can be estimated by converting the dose into the biologically equivalent dose in 2 Gy per fraction (EQD2) if different fractionation schedules are used. The 'historical' threshold of a 5% risk of severe complications at 5 years described by QUANTEC to identify organs at risk (OAR) constraints is hardly applicable in the reirradiation setting [6]. Even though many OARs in the brain have a serial architecture with increased risk of toxicity above a maximum point dose (Dmax), the summation of the Dmax from multiple treatments does not take into account a recovery factor or the increased sensitivity of tissues that have previously been irradiated. Reirradiation is also technically challenging, as it requires the reconstruction of previous radiotherapy volumes and the accurate estimate of treatment overlap [4].

In reality, there will always be recurrences and a rational and evidence-based approach to their management is therefore of benefit to patients. In the base of skull (BoS) and brain many tumours are relatively radioresistant and some patients are not cured because dose is limited by the proximity and tolerance of normal tissue structures (OARs). Moreover, a few patients will develop second tumours as a result of treatment with cranial radiotherapy often combined with clastogenic chemotherapy agents.

Proton beam therapy (PBT) might be advantageous in the reirradiation setting thanks to its distinct physical characteristics, provided that physical and biological uncertainties (linear energy transfer, radiobiological effectiveness) are recognised and uncertainty scenarios are integrated into the proton plan [7]. The use of the most advanced pencil beam scanning (PBS) PBT, together with multifield optimisation, allows highly conformal dose painting and steep dose gradients. Some authors suggest that out-of-field and marginal relapses could be ideal situations for PBT, as previously irradiated healthy tissues would be optimally spared (reduced low–intermediate dose bath), whereas in-field recurrences would be best managed with conventional photon radiotherapy (XRT), due to radiobiological effectiveness uncertainties at the distal edge of the beam path that could potentially increase the risk of toxicities. There may, however, be advantages for the use of PBT for in-field relapses, to reduce dose to adjacent and dose-limiting OARs. We systematically reviewed the use of PBT in the management of recurrent CNS and BoS tumours, as published in the literature.

## Methods

To facilitate the identification of relevant information, the research question was framed following the Population, Intervention, Comparison and Outcomes (PICO) criteria [8].

The study population was cancer patients with local disease recurrence in the CNS or BoS. The intervention was radiation treatment with PBT. There was no specific comparison for this study; a comparison with conventional XRT was outside the scope of this review. The outcomes of the study focused on clinical outcomes of PBT in the reirradiation setting of local tumour recurrences of the CNS or BoS. The search strategy was framed as follows.

(Proton Therapy/or ("proton therap*" or "proton beam therap*" or protontherap* or "proton beam radiation therap*" or "proton radiotherap*"). mp) and ((reirradiat* or "re irradiat*"). ab, ti or *Re-Irradiation/) and (neoplasm recurrence, local/or recurrence/or neoplasm, residual/or recurrent disease/or ("local failure*" or recurrence* or relapse*). mp)

The process of obtaining the relevant papers for this study can be shown in the PRISMA diagram (Figure 1).

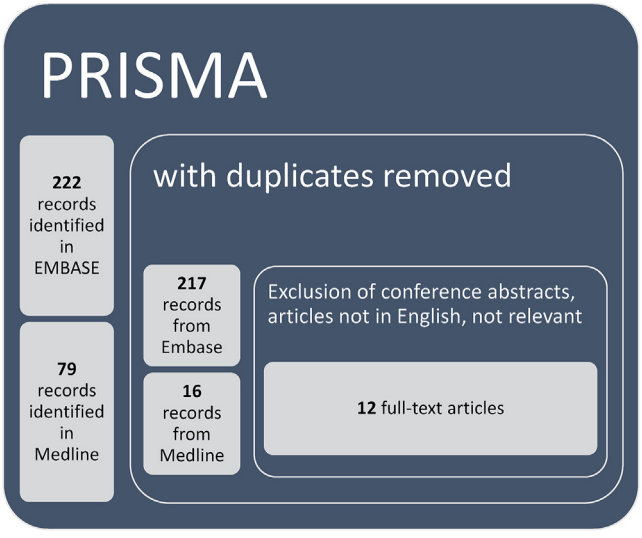


**Fig 1.** A Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart. The identification stage resulted in 222 records in Embase and 79 in Medline as of March 2023. Sixty-eight duplicates were excluded at this stage and 56 were excluded after screening as not relevant, not in English or not full-text articles.

## Results

The selected articles will be presented here according to the individual studies' inclusion criteria regarding the site of disease, namely BoS, (2) brain or both brain and BoS (Table 1).

### *Base of Skull*

Ng *et al.* [9] described a cohort of patients treated for small BoS tumour recurrences [of mixed histology squamous cell carcinoma (SCC) and non-SCC] treated with either intensity-modulated radiotherapy (IMRT), stereotactic body radiotherapy or PBT. The 2-year local control rate for the 15 patients treated with PBT was 59%. Despite the differences in patient characteristics among techniques (there was a higher proportion of non-SCC histology in the PBT subgroup), univariate analysis showed no significant differences in local control, overall survival rates or toxicity incidence between techniques. There were three grade 3 Common Terminology Criteria for Adverse Events acute toxicity events in the PBT subgroup (consisting of mucositis or dermatitis) and four grade 3 late toxicity events (osteoradionecrosis and dysphagia requiring percutaneous endoscopic gastrostomy, glaucoma, trismus and skin fibrosis), without any grade 4 or 5 reported toxicity events.

McDonald *et al.* [10] presented the outcomes of 16 patients reirradiated with radical PBT doses for BoS or spinal chordomas. Of these, eight were BoS (clival). The median doses from the first and second courses of radiotherapy are reported in Table 1, as well as the median time interval between the two and the gross tumour volumes (GTV) at the time of reirradiation (reported for the whole cohort, including spinal chordomas). All but two were treated with conventional fractionation (1.8–2 Gy), with the two exceptions being recurrent tumours abutting the brainstem not amenable to surgery, which received hyperfractionated schedules (1 and 1.2 Gy per fraction twice daily). The 2-year reported overall survival rate was 80% for the whole cohort, with a 2-year local control rate for the BoS subgroup of 85% (the majority of local failures being in-field). A GTV (with a threshold of more than 30 $cm^3$) was found to be associated with a higher risk of distant metastases and decreased chordoma-specific survival. With regards to moderate to severe toxicities, one patient developed acute grade 4 obstruction of the fourth ventricle, one experienced late grade 3 radiation necrosis and one had grade 4 cerebrospinal fluid leak with meningitis. The authors concluded that high-dose PBT in recurrent chordomas provides encouraging results in terms of tumour control, but that any expected survival benefit needs to be balanced against the higher risk of moderate–severe toxicities.

Nangia *et al.* [11] reported the results of three patients reirradiated for BoS recurrences of adenoid cystic carcinomas and suggested that for each of these radioresistant tumours, which have a high propensity for locally aggressive behaviour, image-guided pencil beam scanning (PBS) PBT achieved superior outcomes compared with XRT techniques, with no additional moderate–severe toxicities (no acute nor late grade $\geq$3 toxicities reported).

### *Brain*

Eaton *et al.* [12] reported the results of a cohort of 20 patients retreated for recurrent or metastatic ependymomas, 11 of whom were re-treated for a local, two for a local + distant and seven for a distant recurrence. After a median follow-up of 30.9 months after reirradiation (1.7–98), five of the 11 patients with isolated local failure experienced a second local failure; of the nine patients with distant failure, six experienced a second distant failure. The pattern of second failure after reirradiation was directly related to the pattern of first failure and overall survival was significantly improved with surgical resection of recurrent disease, with 3-year overall survival rates of 78.6%. Three of the 13 patients locally re-treated experienced grade 2 radiation-associated toxicity, but no grade $\geq$3 toxicities were toxicity attributable to PBT treatment. Therefore, Eaton *et al.* [12] concluded that PBT is safe and effective for the re-treatment of recurrent intracranial ependymoma.

The use of PBT for the reirradiation of highly aggressive primary brain tumours, such as glioblastomas (GBM), has been considered in two prospective series [13,14]. Both concluded that PBT is potentially effective in delaying further tumour progression. They reported either a low incidence of late grade 3 toxicities or no grade >3 toxicity events, respectively. In addition, Scartoni *et al.* [14] suggested that PBT could potentially help preserve health-related quality of life until the time of disease progression. Gulidov *et al.* [15], based on the results from a retrospective cohort of mixed low- and high-grade gliomas, suggested that reirradiation of recurrent brain gliomas with PBT can achieve reasonable tumour control with low adverse events rate, with overall survival rates being correlated to the initial pathological diagnosis.

Mizumoto *et al.* [16] examined the efficacy of reirradiation, including conventional XRT, stereotactic radiotherapy and PBT, in 26 patients with recurrent malignant brain tumours of various histologies, concluding that all these techniques had acceptable toxicity profiles, with local control/overall survival rates related to tumour histology. However, due to its increased costs, the authors' opinion is that PBT should be reserved for the treatment of large or irregularly shaped lesions that are difficult to treat with hypofractionation.

By exploiting the physical characteristics of PBT (lack of exit dose), McDonald *et al.* [17] developed a technique for salvage craniospinal irradiation with PBT, which can be adopted to provide optimal sparing of previously irradiated OARs, of particular importance when cumulative dose is a concern. In this technique, lateral PBT field apertures block the structures of concern while inverse apertures treat the portion of target brain, lateral to the OAR, that would otherwise be underdosed with XRT techniques. However, the implementation of intensity-modulated PBT since the

**Table 1**
Reirradiation studies presented in the review

| First author, year [reference] | Country | Primary tumour | Site | Age | No. patients/ reirradiation courses | Time to reirradiation (median, range) | Tumour volume | Type of study | Total dose first radiotherapy course (Gy: Median, range) | Total dose second radiotherapy course (GyRBE: Median, range) | No. fractions | Dose per fraction (GyRBE) | Local control/ overall survival rates | Acute and late toxicities |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Brain** | | | | | | | | | | | | | | |
| Saeed, 2022 [13] | USA | GBM | Brain | Adult | 45 | 20 months (3–77) | NS | Prospective | 60 (25–60) | 46.2 (25–60) | NS | 2.2 (1.2–4) | Median PFS 13.9 months; median OS 14.2 months | AT: 3 grade 3; LT: 4 grade 3 |
| Scartoni, 2020 [14] | Italy | GBM | Brain | Adult | 33 | 21.3 months (5–96) | Median CTV 75 $cm^3$ | Prospective | 60 | 36 | 18 | NS | Median PFS 5.9 months; median OS 8.7 months | AT: 3 grade 2 |
| Gulidov, 2021 [15] | Russia | Glioma | Brain | Adult | 44 | 28 months (12–173) | Median GTV 62.7 $cm^3$ | Retrospective | Median BED 93.3 (83.3–100) | 55 | NS | 2 or 3 | Median OS 12 months; median PFS 9 months | LT: 3 grade 3 (6.8%) |
| Eaton, 2015 [12] | USA | Ependymoma | Brain | Paediatric | 20/14 | 32.6 months (11.4–126.3) | | Retrospective | 55.8 | 50.4 (35–55.8) | NS | NS | 3-year OS 78.6%; 3-year PFS 28.1% | AT/LT: 3 grade 2 |
| Mizumoto, 2013 [16] | Japan | Various | Brain | Adult | 8 | NS | Median GTV 77.2 ml (14.3–135.3) | Retrospective | Median 60 (34.5–94.4) | Median 42.3 (30–60) | NS | | Median survival 18.3 months; median LC 9.3 months | No grade ≥3 toxicities in the PBT subgroup |
| McDonald, 2013 [10] | USA | N/A | Craniospinal | N/A | 2 | NS | NS | Comparative planning | NS | NS | NS | NS | NS | NS |
| **Base of skull** | | | | | | | | | | | | | | |
| McDonald, 2013 [17] | USA | Chordoma | Base of skull | Adult | 16 | 37 months (12–63) | 71 $cm^3$ (0–701) | Retrospective | Median 75.2 Gy (40–79.2) | Median 75.6 (71.2–79.2) | NS | Median 1.8 (1–2) | 2-year LC 85%; 2-year OS 80% | AT: 1 grade 4 ventricle obstruction. LT: 1 grade 3 radionecrosis; 1 grade 4 meningitis (CSF leak). |
| Nangia, 2022 [11] | India | ACC | Base of skull | Adult | 3 | 32 months (26–82) | NS | Retrospective | NS | Median 66 (60.5–70.2) | Median 30 (28–33) | Median 2.16 (2.13–2.2) | LC 100% at median follow-up 11 months (8–24) | AT: no grade ≥3 toxicities LT: no grade ≥3 toxicities |
| Ng, 2020 [9] | USA | SCC/non-SCC | Base of skull | Adult | 15 | 41 months (3–446) | 28.3 $cm^3$ (2.9–59.8) | Retrospective | 60 (30–74) | 66 | 33 | 2 | 2-year LC 59% | AT: 3 grade 3; LT: 4 grade 3 |
| **Brain/base of skull** | | | | | | | | | | | | | | |
| Imber, 2019 [18] | USA | Meningioma | Brain | Adult | 16 | 5.8 years (0.7–18.7) | Median PTV 76 (8–249) | Retrospective | 54 (13–65.5) | 60 (30–66.6) | NS | 1.8 or 2 | 1- and 2-year PFS 80% and 43%; 1- and 2-year OS 94% and 73% | LT: 5 grade 3 (31%) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Poel, 2019 [20] | Switzerland | Meningioma | Brain | Adult | 9 | NS | NS | Comparative planning | NS | NS | NS | NS | NS |
| El Shafie, 2018 [19] | Germany | Meningioma | Brain | Adult | 8 PBT + 34 carbons | NS | Median PTV 75.1 ml (Q1 –Q3 = 37.1 –126.2) | Retrospective | 3DCRT median 54 (50.5–58.8); SRS median 12.1 (12–17) | Median 52.2 (40–57.6) | NS | 1.8 (1.5 –2) | 1- and 2-year PFS 71% and 56.5%; 1- and 2-year OS 89.6% and 71.4% | LT: 3 grade 3 radionecrosis |

3DCRT, three-dimensional conformal radiotherapy; ACC, adenoid cystic carcinoma; AT, acute toxicities; BED, biologically effective dose; CSF, cerebrospinal fluid; CTV, clinical target volume; GBM, glioblastoma; GTV, gross tumour volume; LC, local control; LT, late toxicities; N/A, not applicable; NS, not specified; OS, overall survival; PBT, proton beam therapy; PFS, progression-free survival; PTV, planning target volume; RBE, relative biological effectiveness; SCC, squamous cell carcinoma; SRS, radiosurgery.

publication of this article (2013) has allowed for the generation of similar regions of dose avoidance without the requirement of patient-specific hardware used in this technique. The resultant dose distribution was favourable compared with utilising lateral XRT fields or nine coplanar IMRT fields. The complete sparing of previously irradiated OARs allowed with this technique would be difficult to achieve, even with helical or arc techniques (tomotherapy, volumetric modulated arc therapy), due to their intrinsic low-bath doses.

*Brain/Base of Skull*

Recurrent intracranial meningiomas are a therapeutic challenge, due to the difficult balance between delivering sufficient dose to achieve local control and respecting the dose constraints of previously irradiated critical structures, in patients with a life expectancy that is long enough to manifest the late toxicities related to reirradiation. To date, two retrospective series have been published. Imber *et al.* [18] reported on 16 patients reirradiated with PBT for recurrent meningiomas of any grade, a median of 5.8 years (0.7–18.7) after conventional XRT. The median progression-free survival (PFS) was 22.6 months, which was correlated with meningioma grade (improved for grade 1 disease, $P = 0.03$) and the time interval from the previous radiotherapy (a longer interval predicted improved PFS, $P = 0.03$). The incidence of grade 3 late toxicity was high at 31% (five patients), with hydrocephalus, symptomatic radionecrosis and cerebrovascular ischaemia being reported in these cases. Similar conclusions were drawn by El Shafie *et al.* [19], who, despite the larger proportion of high-grade histologies (74%), reported a median PFS of 34.3 months in a cohort of 42 patients treated with particle radiotherapy for recurrent intracranial meningiomas (eight with PBT and 34 with carbon ions), with two grade 3 radionecrosis and no severe (grade 4–5) toxicities observed.

Poel *et al.* [20] conducted the first in-silico planning study to compare XRT versus PBT for the reirradiation of recurrent intracranial meningiomas to evaluate dosimetric differences between volumetric modulated arc therapy and PBS-PBT. They concluded that the optimal treatment modality needs to be assessed on an individual basis. In fact, in most cases, no clinically relevant differences in doses to OARs were seen between XRT and PBT, with the only obvious advantage of PBT in all cases being the reduction in the integral dose.

## Discussion

PBT has drawn interest in the reirradiation arena of diseases of the brain and BoS that present a unique challenge due to the limits of reirradiation and reoperation [21]. Not only is local failure of BoS tumours the most common cause of death in these patients, but it also causes significant debilitating morbidity, due to the early involvement of surrounding critical structures (particularly cranial nerves) [22]. Furthermore, a lack of effective systemic therapy

options for recurrent BoS tumours means that reirradiation is often used following treatment failure. The retreatment of a local tumour recurrence of the BoS in a previously irradiated area poses a therapeutic challenge. These recurrences are usually inoperable and, historically, radiotherapy has only been considered with palliative intent because of the prior dose received by critical structures. However, recent advances in radiotherapy techniques have allowed a paradigm shift, as the delivery of a highly conformal dose to the tumour is now possible [23]. On the basis of published clinical data, the recently released ASTRO model policies support the use of PBT for reirradiation cases and have included these in Group 1 indications [24]. This means that there is no need for comparative effectiveness analyses for using PBT in these cases, being its use justified by the reduction in cumulative dose to critical organs.

In specific clinical scenarios, such as high-grade gliomas (including GBM) that have a high rate of recurrence, the interval between the radical treatment and reirradiation is often short, and toxicity is a major concern. Nevertheless, reirradiation remains an option in selected patients who have failed second-line treatment with a systemic agent, where operation is not possible. A recent phase II trial showed improved PFS at 6 months – but no overall survival benefit – when reirradiation was used in combination with bevacizumab as compared with bevacizumab alone in recurrent GBM [25], with an acceptable toxicity profile. In this setting, PBT could be appropriate for minimising integral dose to previously irradiated tissue. Despite not being a comparative XRT versus PBT study, the prospective study published by Scartoni *et al.* [14] suggests that PBT is an acceptable option to treat GBM recurrences, highlighting that the reduction of the integral dose can potentially mitigate the detrimental impact of reirradiation on neurocognition and preserve the health-related quality of life until the time of disease progression. The severity of late toxicities (particularly radionecrosis) seems to be higher when reirradiation doses are higher, as reported in the retrospective PBT series by Saeed *et al.* [13] (who delivered reirradiation doses of up to 60 Gy depending on the tumour World Health Organization grade). These preliminary data suggest that the rationale for the use of PBT in this setting is the reduction of acute and late side-effects through the reduction of integral doses, rather than overcoming the radioresistance of high-grade gliomas through dose escalation, which comes at a cost of increased toxicity. This is in line with the results of two phase I–II randomised trials of dose escalation in treatment-naïve GBMs, suggesting that dose escalation to $>$90 Gy may be beneficial for local control. However, the risk of severe adverse events, particularly radiation necrosis, increases dramatically [26,27]. The first ever trial of PBT versus IMRT in newly diagnosed GBM patients failed to show significant difference in the primary endpoint of time to cognitive failure. However, reported grade $\geq$2 toxicities were lower in the PBT group as compared with IMRT (particularly fatigue and lymphopenia) [28,29]. These clinical results were supported by dosimetric analysis showing that PBT was effective at reducing the minimum, average and maximum dose to essentially all analysed structures outside the treatment field. Nevertheless, the potential long-term cognitive benefits of reducing exposure of normal tissues may simply be masked by the short life expectancy of GBM.

Although there is no direct evidence comparing PBT to XRT in the reirradiation context, early data from retrospective series, as presented in this review, for the treatment of recurrent high- and low-grade gliomas indicate that PBT is an alternative to photons and, by reducing integral and exit radiotherapy dose, may have an advantageous side-effect profile [13–15]. The extrapolation of toxicity data from currently ongoing trials investigating the role of PBT in de-novo glioma patients will probably help in the reirradiation setting as well (e.g. NRG-BN001; NRG-BN005). However, prospective direct-comparison studies will be needed to better understand how PBT compares to XRT and, in general, more randomised data of reirradiation in glioma is needed to guide practice.

In the recurrent meningioma setting, both the retrospective series included in our review [18,19] reported that disease control, and consequently overall survival, are significantly associated with World Health Organization grade and the time from previous radiotherapy. In brain diseases associated with a long life expectancy, such as benign meningiomas, the impact of radiation-induced late adverse events can be significant over the lifespan, including, but not limited, to cognitive impairment, pituitary dysfunction and secondary cancers. The characteristics of the Bragg peak may allow decreased integral dose to be delivered to critical structures within the brain, as shown in two comparative planning studies [17,20]. Substantial clinical evidence as well as modelling studies support the correlation between the dosimetric advantage to critical structures in the brain (e.g. hippocampi, brain parenchyma) and the reduced risk of late radiation-induced adverse events, such as secondary cancers and cognitive impairment [30–32]. Even if, at present, the level of clinical evidence justifying the use of PBT for reirradiation is low, the lack of other salvage options might push the clinician towards considering reirradiation, accepting the higher risk of toxicities. When used, reirradiation should be carried out using highly conformal radiation techniques and, where available, PBT could be considered in selected patients who would probably benefit the most from the integral dose reduction (Figure 2). In a comprehensive review on the role of PBT in intracranial meningiomas, Weber *et al.* [33] suggested that reirradiation of progressing/recurring tumours with PBT should be discussed on a case-by-case basis, and younger patients with benign tumours will probably benefit the most. Other authors have suggested that the GTV also needs to be taken into account, as the larger the meningioma, the higher the theoretical advantage offered by PBT. From evaluating the characteristics of patients who developed late toxicity in the retrospective series of meningiomas reported by Imber *et al.* [18] and included in our review, it seems that age and previous administered dose are also important factors to consider when assessing the possibility of reirradiating recurrent meningioma.

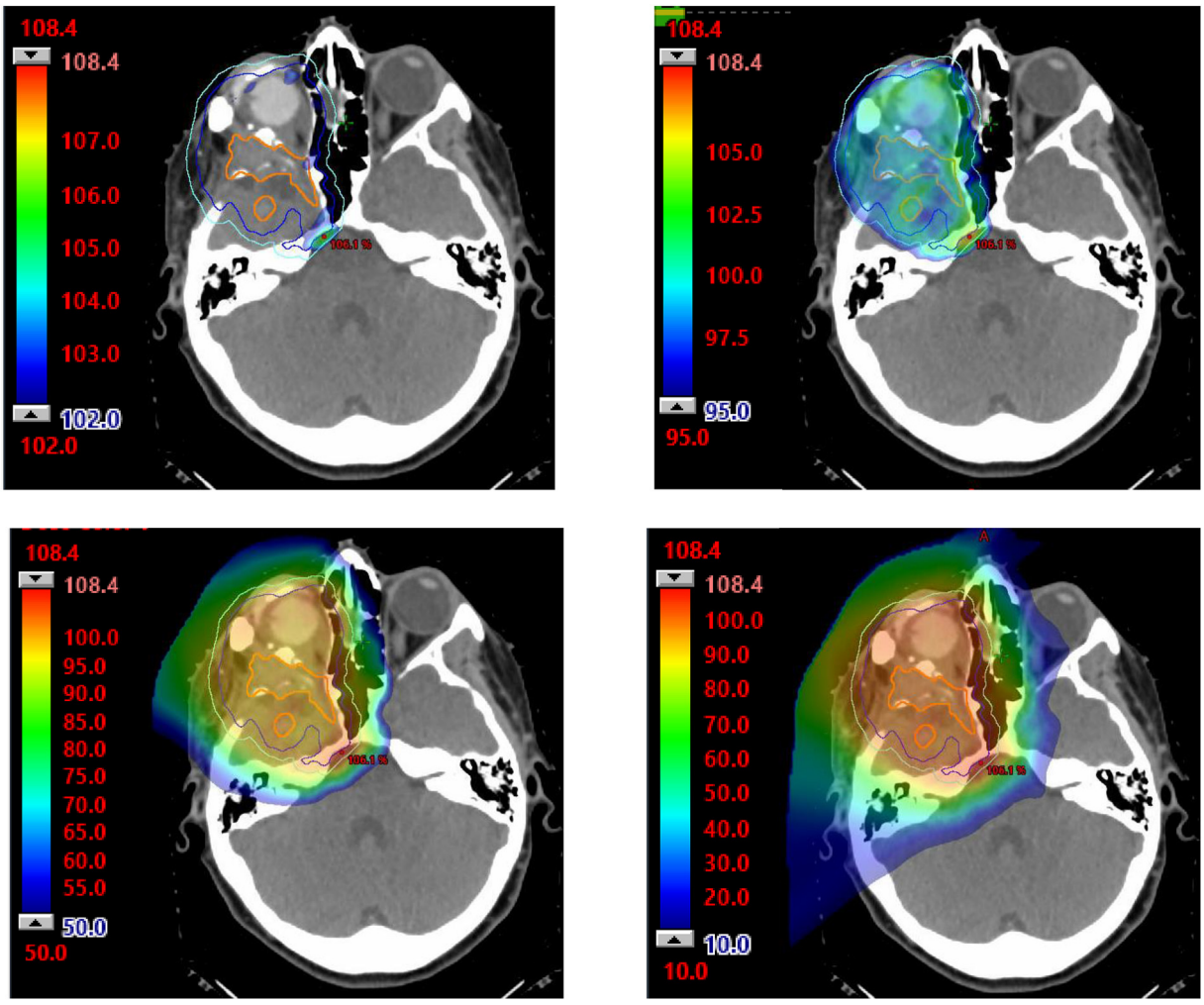


**Fig 2.** Representative two-dimensional dose distributions in a patient reirradiated for a secondary atypical (World Health Organization Grade II) meningioma of the base of skull (prescription dose 54 GyRBE in 30 fractions). The patient had received conventional photon radiotherapy as an infant for the treatment of retinoblastoma of the right eye (40 Gy in 16 fractions).

The only grade 4 toxicities observed in the presented series have been reported by McDonald *et al.* [10] in their cohort of BoS and sacral chordomas. This is probably related to the higher prescription doses and anatomical challenges in both the first-line and reirradiation settings due to the well-known radioresistance of these tumours. However, no lethal events directly attributable to radiation-induced toxicities have been described in the presented articles. This might be related to the median time interval allowed between the first and the second course of radiation, not inferior to 20 months which has allowed some tissue recovery, but a higher incidence of toxicities with longer follow-up times cannot be excluded.

In consideration of the high cumulative doses, the proximity of critical structures as well as young patient age, PBT is expected to minimise the probability of normal tissue complications in the reirradiation setting of paediatric ependymomas, as postulated by modelling studies [32] and described in the retrospective series by Eaton *et al.* [12]. This work reiterates the value of macroscopic surgical resection at the time of disease recurrence prior to reirradiation, to optimise patient survival, in line with literature evidence [34,35]. Due to the small number of toxicity events in this series, the authors could not draw definitive conclusions about recommendations for OAR constraints with PBT reirradiation. This reinforces the need for collecting prospective high-quality toxicity data in PBT, to inform the development of toxicity models, guide patient selection and plan optimisation [36–38].

## Conclusions

This review has shown that reirradiation of brain/BoS tumour recurrences with PBT can provide good local control with generally acceptable toxicity rates. However, reirradiation of tumour recurrences in the brain or BoS setting needs to consider several factors that can increase the risk of toxicities. Therefore, patient selection is crucial. In line with the recently released ASTRO model policies for PBT reirradiation cases have been included in group 1 indications [24]. In such cases, PBT is justified by the necessity

to sculpt the dose around the target volume to avoid exceeding the cumulative tolerance dose of nearby normal tissues. Nevertheless, long-term follow-up within a well-designed and standardised surveillance schedule, including a detailed collection of OAR dose data, is required to better assess clinical outcomes and late toxicity rates and their trend over time. Randomised evidence is needed to select the best radiation modality in this group of patients.

## Author contributions

**SG** and **GW** are the guarantors of integrity of the entire study. **SG** was responsible for study concepts and design and carried out the literature research and the experimental studies/data analysis. **SG**, **NGB**, **MCA** and **GW** prepared the manuscript. **NGB**, **MCA**, **BAJ-F**, **AC**, **DI**, **SP**, **RC**, **RR**, **ES** and **GW** edited the manuscript.

## Conflicts of interest

The authors declare no conflicts of interest.

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### References

[1] Andratschke N, Willmann J, Appelt AL, Alyamani N, Balermpas P, Baumert BG, *et al*. European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus on re-irradiation: definition, reporting, and clinical decision making. *Lancet Oncol* 2022;23:e469–e478. https://doi.org/10.1016/S1470-2045(22)00447-8.

[2] Kim JH, Jenrow KA, Brown SL. Mechanisms of radiation-induced normal tissue toxicity and implications for future clinical trials. *Radiat Oncol J* 2014;32:103–115. https://doi.org/10.3857/roj.2014.32.3.103.

[3] Nieder C. Second re-irradiation: a delicate balance between safety and efficacy. *Phys Med* 2019;58:155–158. https://doi.org/10.1016/j.ejmp.2019.01.004.

[4] Chargari C, Escande A, Dupuis P, Thariat J. Reirradiation: a complex situation. *Cancer/Radiothérapie* 2022;26:911–915. https://doi.org/10.1016/j.canrad.2022.06.016.

[5] McBride WH, Schaue D. Radiation-induced tissue damage and response. *J Pathol* 2020;250:647–655. https://doi.org/10.1002/path.5389.

[6] Lawrence YR, Li XA, el Naqa I, Hahn CA, Marks LB, Merchant TE, *et al*. Radiation dose-volume effects in the brain. *Int J Radiat Oncol Biol Phys* 2010;76:S20–S27. https://doi.org/10.1016/j.ijrobp.2009.02.091.

[7] Byun HK, Han MC, Yang K, Kim JS, Yoo GS, Koom WS, *et al*. Physical and biological characteristics of particle therapy for oncologists. *Cancer Res Treat* 2021;53:611–620. https://doi.org/10.4143/crt.2021.066.

[8] Wilson MC. Evidence-based medicine: how to practice and teach EBM. *ACP J Club* 2001;134. https://doi.org/10.7326/acpjc-2001-134-1-a15.

[9] Ng SP, Wang H, Pollard C, Nguyen T, Bahig H, Fuller CD, *et al*. Patient outcomes after reirradiation of small skull base tumors using stereotactic body radiotherapy, intensity modulated radiotherapy, or proton therapy. *J Neurol Surg B Skull Base* 2020;81:638–644. https://doi.org/10.1055/s-0039-1694052.

[10] McDonald MW, Linton OR, Shah MV. Proton therapy for reirradiation of progressive or recurrent chordoma. *Int J Radiat Oncol Biol Phys* 2013;87:1107–1114. https://doi.org/10.1016/j.ijrobp.2013.09.038.

[11] Nangia S, Gaikwad U, Noufal M, Chilukuri S, Patro K, Nakra V, *et al*. Proton therapy for skull-base adenoid cystic carcinomas: a case series and review of literature. *J Cancer Res Ther* 2022;18:629. https://doi.org/10.4103/jcrt.jcrt_1236_21.

[12] Eaton BR, Chowdhry V, Weaver K, Liu L, Ebb D, MacDonald SM, *et al*. Use of proton therapy for re-irradiation in pediatric intracranial ependymoma. *Radiother Oncol* 2015;116:301–308. https://doi.org/10.1016/j.radonc.2015.07.023.

[13] Saeed AM, Khairnar R, Sharma AM, Larson GL, Tsai HK, Wang CJ, *et al*. Clinical outcomes in patients with recurrent glioblastoma treated with proton beam therapy reirradiation: analysis of the Multi-Institutional Proton Collaborative Group Registry. *Adv Radiat Oncol* 2020;5:978–983. https://doi.org/10.1016/j.adro.2020.03.022.

[14] Scartoni D, Amelio D, Palumbo P, Giacomelli I, Amichetti M. Proton therapy re-irradiation preserves health-related quality of life in large recurrent glioblastoma. *J Cancer Res Clin Oncol* 2020;146:1615–1622. https://doi.org/10.1007/s00432-020-03187-w.

[15] Gulidov I, Gordon K, Semenov A, Gogolin D, Lepilina O, Golovanova O, *et al*. Proton re-irradiation of unresectable recurrent brain gliomas: clinical outcomes and toxicity. *J BUON* 2021;26:970–976.

[16] Mizumoto M, Okumura T, Ishikawa E, Yamamoto T, Takano S, Matsumura A, *et al*. Reirradiation for recurrent malignant brain tumor with radiotherapy or proton beam therapy: technical considerations based on experience at a single institution. *Strahlenther Onkol* 2013;189:656–663. https://doi.org/10.1007/s00066-013-0390-6.

[17] McDonald MW, Wolanski MR, Simmons JW, Buchsbaum JC. Technique for sparing previously irradiated critical normal structures in salvage proton craniospinal irradiation. *Radiat Oncol* 2013;8. https://doi.org/10.1186/1748-717X-8-14.

[18] Imber BS, Neal B, Casey DL, Darwish H, Lin AL, Cahlon O, *et al*. Clinical outcomes of recurrent intracranial meningiomas treated with proton beam reirradiation. *Int J Part Ther* 2019;5:11–22. https://doi.org/10.14338/ijpt-18-00045.1.

[19] El Shafie RA, Czech M, Kessel KA, Habermehl D, Weber D, Rieken S, *et al*. Evaluation of particle radiotherapy for the re-irradiation of recurrent intracranial meningioma. *Radiat Oncol* 2018;13. https://doi.org/10.1186/s13014-018-1026-x.

[20] Poel R, Lobmaier AS, Andratschke N, Unkelbach J, Tanadini-Lang S, Guckenberger M, *et al*. Dosimetric comparison of protons vs photons in re-irradiation of intracranial meningioma. *Br J Radiol* 2019;92. https://doi.org/10.1259/bjr.20190113.

[21] Goff KM, Zheng C, Alonso-Basanta M. Proton radiotherapy for glioma and glioblastoma. *Chin Clin Oncol* 2022;11. https://doi.org/10.21037/cco-22-92.

[22] Farrag A, Voordeckers M, Tournel K, De Coninck P, Storme G. Pattern of failure after helical tomotherapy in head and neck cancer. *Strahlenther Onkol* 2010;186:511–516. https://doi.org/10.1007/s00066-010-2130-5.

[23] Ho JC, Phan J. Reirradiation of skull base tumors with advanced highly conformal techniques. *Curr Oncol Rep* 2017;19:82. https://doi.org/10.1007/s11912-017-0639-9.

[24] https://www.astro.org/uploadedFiles/_MAIN_SITE/Daily_Practice/Reimbursement/Model_Policies/Content_Pieces/ASTROPBTModelPolicy.pdf. ASTRO model policies for PBT n.d.
[25] Tsien CI, Pugh SL, Dicker AP, Raizer JJ, Matuszak MM, Lallana EC, *et al*. NRG Oncology/RTOG1205: A randomized phase II trial of concurrent bevacizumab and reirradiation versus bevacizumab alone as treatment for recurrent glioblastoma. *J Clin Oncol* 2023;41:1285–1295. https://doi.org/10.1200/JCO.22.00164.
[26] Tsien C, Pugh S, Dicker AP, Raizer JJ, Matuszak MM, Lallana E, *et al*. Randomized phase II trial of re-irradiation and concurrent bevacizumab versus bevacizumab alone as treatment for recurrent glioblastoma (NRG Oncology/RTOG 1205): initial outcomes and RT plan quality report. *Int J Radiat Oncol Biol Phys* 2019;105. https://doi.org/10.1016/j.ijrobp.2019.06.539.
[27] Fitzek MM, Thornton AF, Rabinov JD, Lev MH, Pardo FS, Munzenrider JE, *et al*. Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial. *J Neurosurg* 1999;91:251–260. https://doi.org/10.3171/jns.1999.91.2.0251.
[28] Mohan R, Liu AY, Brown PD, Mahajan A, Dinh J, Chung C, *et al*. Proton therapy reduces the likelihood of high-grade radiation-induced lymphopenia in glioblastoma patients: phase II randomized study of protons vs photons. *Neuro Oncol* 2021;23:284–294. https://doi.org/10.1093/neuonc/noaa182.
[29] Brown PD, Chung C, Liu DD, McAvoy S, Grosshans D, Al Feghali K, *et al*. A prospective phase II randomized trial of proton radiotherapy vs intensity-modulated radiotherapy for patients with newly diagnosed glioblastoma. *Neuro Oncol* 2021;23:1337–1347. https://doi.org/10.1093/neuonc/noab040.
[30] Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Clinical Investigation: Late effect incidence of second malignancies among patients treated with proton versus photon radiation radiation oncology. *Int J Radiat Oncol Biol Phys* 2013;87.
[31] Gondi V, Deshmukh S, Brown PD, Wefel JS, Tome WA, Bruner DW, *et al*. Preservation of neurocognitive function (NCF) with conformal avoidance of the hippocampus during whole-brain radiotherapy (HA-WBRT) for brain metastases: preliminary results of phase III Trial NRG Oncology CC001. *Int J Radiat Oncol Biol Phys* 2018;102:1607. https://doi.org/10.1016/j.ijrobp.2018.08.056.
[32] Gaito S, Burnet N, Aznar M, Crellin A, Indelicato DJ, Ingram S, *et al*. Normal tissue complication probability modelling for toxicity prediction and patient selection in proton beam therapy to the central nervous system: a literature review. *Clin Oncol* 2022;34:E225–E237. https://doi.org/10.1016/j.clon.2021.12.015.
[33] Weber DC, Bizzocchi N, Bolsi A, Jenkinson MD. Proton therapy for intracranial meningioma for the treatment of primary/recurrent disease including re-irradiation. *Front Oncol* 2020;10. https://doi.org/10.3389/fonc.2020.558845.
[34] Messahel B, Ashley S, Saran F, Ellison D, Ironside J, Phipps K, *et al*. Relapsed intracranial ependymoma in children in the UK: patterns of relapse, survival and therapeutic outcome. *Eur J Cancer* 2009;45:1815–1823. https://doi.org/10.1016/j.ejca.2009.03.018.
[35] Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. *Lancet Oncol* 2009;10:258–266. https://doi.org/10.1016/S1470-2045(08)70342-5.
[36] Hwang E, Burnet NG, Crellin AM, Ahern V, Thwaites DI, Gaito S, *et al*. A novel model and infrastructure for clinical outcomes data collection and their systematic evaluation for UK patients receiving proton beam therapy. *Clin Oncol* 2022;34:11–18. https://doi.org/10.1016/j.clon.2021.09.010.
[37] Hwang E, Gaito S, France A, Crellin AM, Thwaites DI, Ahern V, *et al*. Outcomes of patients treated in the UK Proton Overseas Programme: non-central nervous system group. *Clin Oncol* 2023;35:292–300. https://doi.org/10.1016/j.clon.2023.02.009.
[38] Gaito S, Hwang EJ, France A, Aznar MC, Burnet N, Crellin A, *et al*. Outcomes of patients treated in the UK Proton Overseas Programme: central nervous system group. *Clin Oncol* 2023;35:283–291. https://doi.org/10.1016/j.clon.2023.01.024.