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Proton-Based Re-Irradiation of Locally Recurrent Pediatric Brain Tumors in Close Proximity to the Brainstem

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ABSTRACT

Purpose: Local recurrence of aggressive, pediatric brain tumors remains a challenge. We offered full-course re-irradiation with proton therapy (PT) to children with local failures in proximity to the brainstem.

Patients and Methods: Eleven children (7 male, 4 female) underwent fractionated re-irradiation using pencil beam-based PT for local recurrence following maximum prior multidisciplinary treatment for ependymoma ($N = 6$), atypical teratoid rhabdoid tumor ($N = 3$), papillary tumor of the pineal region ($N = 1$) and atypical meningioma ($N = 1$).

Median age at first radiotherapy (RT) was 4.5 years (range: 1.5-14.8); at re-RT was 6.7 years (range: 3.0-18.9); median interval between courses was 21 months (range: 13-160). In 9/11 children Gross Tumor was identifiable.

Primary RT was with photons ($N = 6$) or protons ($N = 5$). Re-RT planning was based on cumulative dose summation. Permissible re-RT OAR doses were individualized. Median prescription dose was 54.0 Gy(RBE) (range 44.0-54.0). All re-treatments were delivered at 1.8-2.2 Gy(RBE) per fraction. A constant RBE value of 1.1 was used.

Results: At median follow-up of 42.5 months (range 7-63), 9 /11 children (82%) achieved local control. Actuarial 2- and 3-year local control and overall survival rates were 89% and 76%, and 82% and 73%, respectively.

Strategies of balancing target dose with OAR considerations resulted in a median cumulative brainstem surface dose ($D_{0.1cc}$) of 81.5 Gy(RBE) (range: 65.8-99.48). No CNS toxicities ≥ Grade 2 were observed, specifically no symptomatic brainstem or brain necrosis.

Conclusion: Selective re-irradiation with pencil beam-based proton radiotherapy, using specifically modified treatment planning approaches, can be effective and safe, even in cases with tumor abutting the brainstem.

Introduction

Local recurrences of aggressive, pediatric brain tumors remain an unfortunate reality even after state-of-the-art multimodality therapy and regardless of whether the radiotherapy modality was photon- or proton-based. The West German Proton Center[1] reported 3-year local control rates in 85 children with ependymoma of 67.3% and of 66.5% in 35 children with atypical teratoid rhabdoid tumor (ATRT) following proton therapy (PT). Corresponding 3-year Overall Survival (OS) rates were 89.2% for ependymoma and 53.2% for ATRT, respectively. The SIOP cooperative group reported 5- and 10-year event-free survival rates of 49.5% and 46.7% and OS of 69.3% and 60.5%,

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; CTV, clinical target volume; CT, computed tomography; $D_{0.1\ cc}$, the dose delivered to 0.1 cubic centimeters; DVH, dose-volume histogram; EQD2, equivalent dose at standard 2 Gy/fraction; EFS, event-free survival; GyRBE, radiation dose in gray with an allowance for RBE, in this case a factor of 1.1; GTV, Gross Tumor Volume; LC, local control; LET, linear energy transfer; MGH, Massachusetts General Hospital; MRI, magnetic resonance imaging; OAR, organ at risk; OS, overall survival; PT, proton beam therapy; PTV, planning target volume; PFS, progression-free survival; RBE, relative biological effectiveness; RT, radiotherapy; TMZ, temozolomide; TYR, tyrosinase; $V_{95\%}$, the volume of tissue receiving 95% of the prescription dose

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respectively.[2] For ATRT the overall prognosis remains poor[3]; US SEER data collected between 2000 and 2015 showed median OS ranging from only 20 to 24 months.[4]

Surgical resection and systemic therapies are the salvage modalities of first choice. However, at some point surgical and systemic salvage therapy options are often exhausted—and the results remain discouraging.[5]

The Collaborative Ependymoma Research Network conducted a prospective phase II clinical trial of dose-dense temozolomide and lapatinib for recurrent low-grade and anaplastic supratentorial, infratentorial, and spinal cord ependymoma.[6] The median progression-free survival (PFS) of 50 enrolled patients was 7.8 months (95% CI: 5.5, 12.2 months); the 6- and 12-month PFS rates were 55% and 38%, respectively.

A recent retrospective study from St. Jude Children's Research Hospital included 64 children with ATRT and confirmed the dismal prognosis of recurrent or treatment-refractory disease.[7] Only five of 64 children (7.8%) were alive at median follow-up of 10.9 years—resulting in 2- and 5-year PFS rates of 3.1% and 1.6%, respectively. Older age at diagnosis, female gender, tyrosinase (TYR) subgroup, and metastatic site of PD were associated with relatively longer survival.

Local recurrences with immediate proximity to the brain stem pose significant challenges for re-irradiation. In case of initial disease close to the brainstem, the first radiation course has typically already delivered brain stem doses considered to be at tolerance levels.

In recent years, the safety of PT even in these dose ranges has been called into question amidst reports of increased risks of brainstem radiation necrosis following treatment of primary posterior fossa tumors with curative intent. The long well-known proton uncertainties of end of range, the increase in relative biologic effectiveness (RBE) beyond 1.1 at the end of range as well as linear energy transfer (LET) changes within the beam path have added to concerns of increased incidence of radiation necrosis of brain parenchyma.[8]

Yet, and in contrast, adult and pediatric patients with mesenchymal skull base tumors (ie, chordomas and chondrosarcomas) are routinely treated to tumor dosages in the range of 68-78 Gy(RBE), and dose constraints routinely permit 60-64 Gy(RBE) to the brainstem surface and/or 53-54 Gy(RBE) to the brainstem center. However, brainstem necrosis remains anecdotal only.[9,10]

We decided to offer re-irradiation with PT in children with first or repeat local failures after their first course of radiation therapy and after reasonable first- or second-line salvage procedures had been exhausted. Whenever feasible, surgical resection preceded re-irradiation.

We selectively applied a full course of fractionated re-irradiation using PT (Internal Review Board reference RB:GS3-EK-1/214-2024).

Patients and methods

Between 10/2018 and 11/2021, eleven consecutive children underwent fractionated re-irradiation using pencil beam scanning-based PT for a local recurrence. Tumor histologies were ependymoma (55%, $N = 6$), followed by ATRT (27%, $N = 3$), papillary tumor of the pineal region, and atypical meningioma ($N = 1$ each). There were 7 male and 4 female patients. Table 1 lists the individual characteristics of the 11 patients, their tumors, and details of the first RT and re-RT and summarizes the key characteristics for the whole group.

The median patient age at first radiotherapy (primary RT) was 4.8 years (range: 1.5-14.8 years). The median age at second radiotherapy (Proton Re-RT) was 7.5 years (range: 3.0-18.9 years). The median time interval between primary RT and Proton Re-RT was 21 months, that is, median 1.75 years, (range: 13-160 months).

The first course of radiation had been applied either with protons (5 patients, 45%) or with photons (6 patients, 55%), delivering radiation doses between 54 and 59.4 Gy/Gy(RBE) with standard fractionation schemas. Treatment plans of the first treatment course were available on all patients as DICOM files and ultimately incorporated to create "cumulative" dose summation plans by combining both treatment plans. The intention of treatment was curative in 10/11 patients. In 10 patients the local recurrence was the only site of recurrence. One patient had been referred for re-irradiation despite evidence of additional intracranial and leptomeningeal spread of disease.

Whenever necessary, treatment was delivered under general anesthesia to ascertain daily reproducibility and to minimize intrafraction patient motion. Overall 8/11 children received treatment under anesthesia either due to young age and/or neurologic impairments (either secondary to disease or to multiple surgical interventions).

Each patient had been discussed extensively at various interdisciplinary tumor boards, and all prior treatment options of either surgery or chemotherapy had been reasonably exhausted. All parents and appropriate patients were informed about potentially fatal brainstem or brain parenchyma necrosis and other potentially high-grade side effects either acute, early-late or late in follow-up. All parents and appropriate patients consented to treatment. The study received ethical approval from the Ethics Commission for Lower Austria (EK-Nummer: GS3-EK-1/214-2024). Outcome data were collected prospectively under this study protocol.

Target volume definition

Re-RT was preceded by surgical resection whenever possible, although in some patients the tumor was deemed unresectable either by location or by other medical considerations, in particular the number of previous surgical resections or attempted resections. Accordingly, in 9/11 children gross tumor volume (GTV) was identifiable on the planning MRI scan. Treatment was prescribed to one Clinical Target Volume (CTV) only. CTV was defined as GTV only in 4/11 children, CTV included the GTV plus postoperative cavity in 5/11 children, and in the remaining 2 children without evidence of gross tumor, the CTV included the postoperative cavity only.

The decision to incorporate a planning target volume (PTV) evolved over time. In the initial 4 patients no specific PTV was added out of concern for added risks of toxicity. These patients received treatment under general anesthesia to minimize any potential motion during treatment. In subsequent patients our general PTV margins of 2 mm for children under anesthesia and 3 mm in older children without anesthesia were adopted. PTV with full geometric CTV expansion was employed in 6/11 children, and in only 1 of these was the PTV intentionally reduced towards the brainstem. However, in this patient no further reduction of the PTV with regard to extension into the brain parenchyma was performed.

Organ at risk dose considerations

Consideration was given on an individual basis as to the permissible re-RT organ at risk (OAR) doses, taking into account "residual" OAR dose tolerance after the first RT course, based on recovery assumptions following several years of time interval between first and second irradiation. For purposes of cumulative dose display, the cumulative doses were left unchanged as nominal values.

The starting point for treatment planning was to limit cumulative brainstem surface doses to < 86 Gy(RBE). However, this was highly individualized depending on evidence of gross tumor at the brain stem surface vs post-op cavity, and also depending on the area of brainstem in immediate contact with the gross local recurrence (Table 1). For brain parenchyma the general strategy was to permit a small volume of ≥ 110 Gy(RBE) cumulative but to avoid any significant volume of ≥ 120 Gy(RBE).

Re-treatment dose schemas

Re-treatments were delivered at standard fractionation doses of 1.8-2.2 Gy(RBE) per fraction (2.2 Gy only in one patient). No

Table 1
Individual patient details, tumor characteristics, treatment details, clinical outcome parameters, and summary statistics.

Case number	Sex	Histology	Age at first RT (years)	First RT dose (Gy or Gy(RBE))	First RT modality	Time from first RT to Re-RT (years)	Re-RT indication (1=in-field, 2=marginal, 3=within RT	Age at Re-RT (years)	Distance from GTV to brainstem (mm)	Percentage of GTV within 2mm brainstem PRV	Re-RT dose (Gy(RBE))	Dose per fx (Gy(RBE))	Follow-up (months)	Alive at last follow-up	Cause of death	Local control at last follow-up	Distant control at last follow-up
1	F	Papillary tumour of pineal region	14.8	55.0	Photon	4.1	1	18.9	0	5.0	54.0	2.0	48	yes		yes	no
2	M	Ependymoma	10.3	54.0	Photon	1.2	1	11.5	0	7.4	54.0	1.8	13	no	tumor	yes	no
3	M	Ependymoma	1.5	54.0	PT	1.8	2	3.3	4	0.0	54.0	1.8	38	yes		no	yes
4	M	ATRT	1.7	54.0	PT	1.9	3	3.6	0	1.4	44.0	2.2	24	no	tumor	yes	no
5	F	Ependymoma	5.1	56.1	Photon	1.6	1	6.7	0	12.0	54.0	1.8	54	yes		yes	no
6	M	ATRT	1.6	54.0	Photon	13.4	2	15.0	5	0.0	53.5	2.14	42	yes		no	no
7	M	Ependymoma	6.0	59.4	Photon	2.3	1	8.3	0	6.8	54.0	1.8	49	yes		yes	yes
8	F	Ependymoma	4.5	54.0	PT	1.9	1	6.4	0 *	29.3 *	54.0	1.8	36	yes		yes	yes
9	M	ATRT	1.7	54.0	PT	1.3	3	3.0	12	0.0	54.0	1.8	7	no	tumor	yes	yes
10	F	Atypical Meningioma	7.7	54.0	Photon	1.7	1	9.4	0	4.9	54.0	1.93	63	no	2° AML	yes	no
11	M	Ependymoma	2.3	59.4	PT	1.1	1	3.4	0 *	30 *	50.4	1.8	48	yes		yes	yes
		Mean	5.2					8.1	2.3	4.2							
		Median	4.5	54.0		1.8		6.7	0.0	4.9	54.0	1.8	42				
		Range	1.5-14.8	54.0-59.4		1.1-13.4		3.0-18.9	0-12	0-30	44.0-54.0	1.8-2.2	7-63				

Summary statistics

Sex		Histology		Modality for first RT	
Male	7 (64%)	Ependymoma	6 (55%)	Photon	6 (55%)
Female	4 (36%)	ATRT	3 (27%)	PT	5 (45%)
		Pineal tumour	1 (9%)		
		Atypical meningioma	1 (9%)		

Location of recurrence after first RT (indication)			Clinical Target Volume (cc)	
In-field (CTV)	(1)	7 (64%)	Median	3.2
Marginal at CTV	(2)	2 (18%)	Range	1.3 - 146.4
Outside CTV, within irradiated volume	(3)	2 (18%)		

Notes: * indicates cases with no postoperative tumor and so no GTV. Here the distances are from CTV to brainstem, and the percentage within the brainstem PRV refers to the CTV.
Note that in 2 cases there was no (post-operative) GTV seen on the planning magnetic resonance imaging (MRI). Note that the prescription dose of 54 Gy(RBE) is appropriate for the tumor types treated, representing almost another full course of treatment. This dose schedule may not be appropriate for more aggressive or more radiation-resistant tumors (eg, chordoma).

hypofractionation schemas were employed. Prescription doses of first RT and Re-RT, total doses, fractionation, and treatment details are summarized in Table 1. In summary, 10/11 patients received Re-RT dose prescriptions ranging between 50.4 and 54.0 Gy(RBE) (median 54.0 Gy(RBE)), while one patient received 44 Gy(RBE).

Treatment planning

All patients underwent planning CT (Big Bore CT, Philips, The Netherlands) and MRI (Ingenia 3.0, Philips, The Netherlands) in the treatment position using MR-compatible immobilization devices and thermoplastic face masks. Images were subsequently fused with non-deformable registration. Plans were optimized using the commercial treatment planning system (RayStation 8B, 11A and 11B SP1 from RaySearch Laboratories AB, Stockholm, Sweden). All patients were treated with pencil beam scanning, and the dose was calculated with a Monte Carlo dose engine with at least 0.5% statistical uncertainty and a dose grid of 2 mm. Case-based robustness was specifically evaluated and optimized. Additional robust optimization was performed if deemed necessary because of anatomic location and potential dose distribution uncertainty. The RBE of protons versus Cobalt 60 Gy was modeled as a constant factor of 1.1. Multiple beams were used to contribute dose to each part of the target, and the maximum dose per single beam was minimized based on multi-field optimization. When superficial targets were present, a Range Shifter was used.

The planning process for re-irradiation is very individualized and includes separate discussion of dose to OARs, based on the assessment of previous irradiation and uncertainty, as an iterative process between the medical physicist and radiation oncologist.

Specific planning aspects of Re-RT using PT

Treatment planning guidelines and parameters were adapted for re-irradiation compared to radiation-naïve patients. The aim was to minimize the risk of side effects due to high accumulated doses or associated biological effects. The planning process for re-irradiation was different in two main ways, namely in the beam angle selection and also in further reducing individual spot weights. Together, these strategies are designed to mitigate the risk of dose deposition from one angle or single highly weighted spots only.

- ➢ The general rule in pediatric PT is to limit the number of treatment fields in order to minimize the volume of brain exposed to any radiation. Treatment fields are preferred that have to traverse through the shortest distance of normal brain parenchyma to reach the target. However, in the specific scenario of re-irradiation, the goal of survival while minimizing risks of necrosis superseded the typical priorities in pediatric neuro-oncology of optimizing neurocognitive outcome and minimizing risks of second malignancy induction. Hence, field entrance angles were preferred that had not been used during the first course (Figure 1). This frequently translated into non-intuitive fields from superior or superior-oblique directions.
- ➢ Beams were selected which did not, or only partly, range out in an OAR, and multiple beams contributed to every part of the target. To a large extent the lateral dose fall-off was used to mitigate a potential increased RBE effect at the end of range (Figure 1).
- ➢ Within our TPS (and others), 2 methods were used to reduce the spot weight and hence uncertainties in the biological end of range, by:

- Decreasing the spot spacing in a layer (Figure 2): The spot spacing defines the distance between the single spots in each energy layer before spots are filtered out during the optimization process. The default value of 1 sets the spots per energy layer (dependent on their spread as a function of energy) such that the distance between the spots equals 1.06 times the average spot size (1σ) (in the patient at the Bragg peak depth).[11] In regular clinical routine, the usual

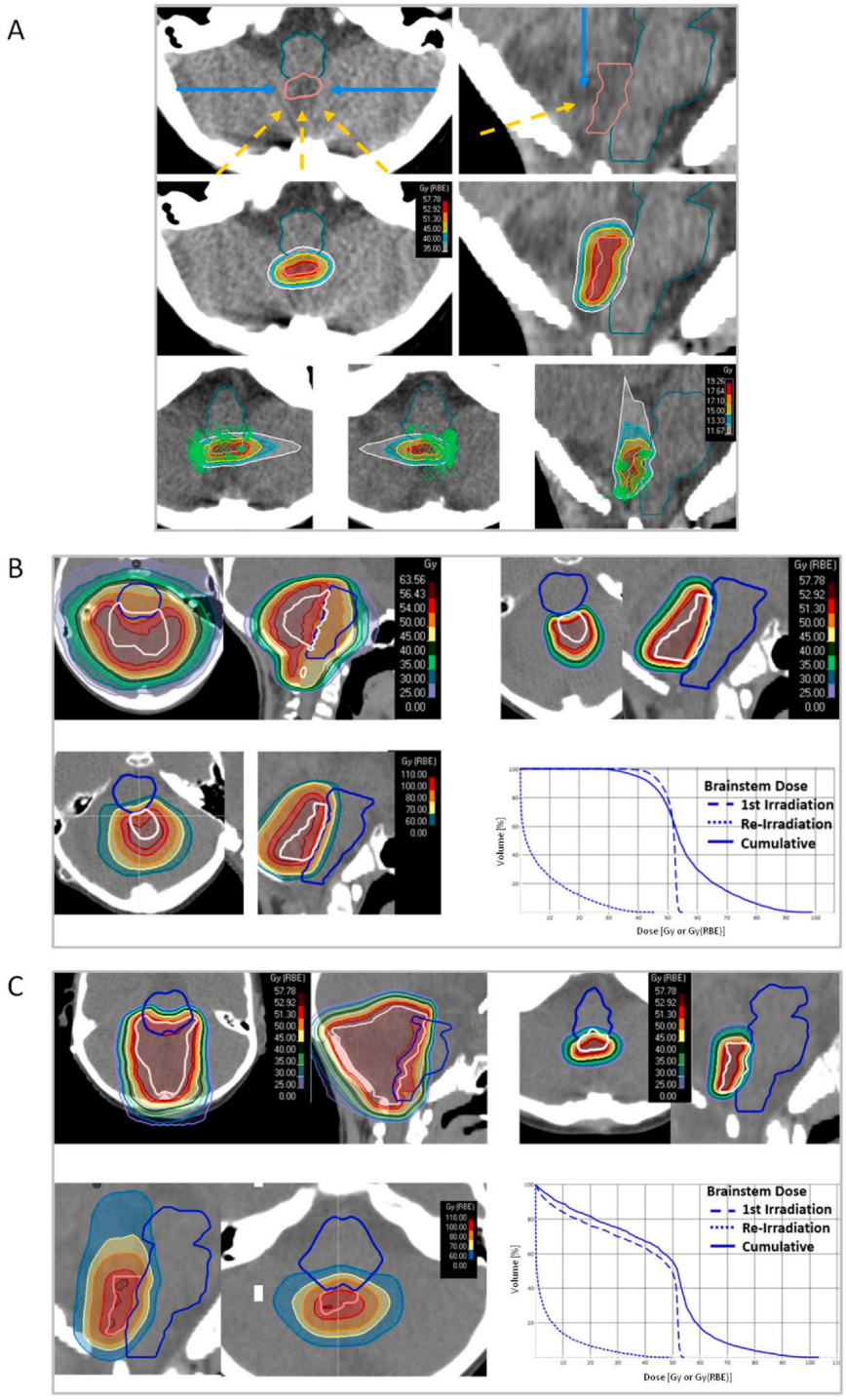

Figure 1. Examples of planning concepts. (A): Representative axial and sagittal planning CT slices showing field arrangements, resulting cumulative dose distribution, and weighted spot distribution for a Proton Re-RT case. Top row: 3 beam directions for re-irradiation (solid blue arrows), that is, 2 lateral opposed beams and 1 non-coplanar beam parallel to the brainstem, chosen in order to avoid overlap with prior fields (dashed yellow arrows); Middle row: resulting cumulative dose distribution; Bottom row: Separate dose contributions from left lateral, right lateral, and non-coplanar beams. Each part of the target receives dose from multiple beams. For each beam, spot positions and their respective weightings are highlighted by a light green cross and a circle (the bigger the circle, the higher the weighting). Note: Higher weighted spots are mainly placed outside the brainstem (OAR). (Pink structure: re-irradiation CTV and dark green structure: Brainstem). (B): Proton Re-RT plan to deliver to 54 Gy(RBE) and associated brainstem DVHs. Diagnosis: Ependymoma, WHO Grade II, treated initially with gross total resection and postoperative photon RT to 59.4 Gy. Proton Re-RT delivered 54 Gy(RBE) at 1.8 Gy(RBE) per fraction. (Light pink structure: Initial and re-irradiation CTV, dark blue structure: Brainstem). (C): Case with CTV coverage modified as a result of brainstem-OAR constraint. Top left: Postoperative photon plan. Top right: Proton Re-RT plan. Bottom left: Cumulative dose plan. Bottom right: Cumulative dose-volume histogram (DVH) of brainstem. (Light pink structure: Initial CTV, mid-pink structure: re-irradiation CTV, Dark blue structure: Brainstem).

parameters result in a spot spacing of approximately 0.4 cm distance. We further decreased the spot spacing to 0.3 cm distance to gain more flexibility. Then, decreasing the spot weight meant that the same dose was delivered with more spots.

- Decreasing the energy layer spacing (Figure 2): The energy layer spacing defines the distance between the Bragg peaks of different energies. By default, the 80% dose levels of the Bragg-peaks are overlapping and is thus energy-dependent.[11] By decreasing the energy layer spacing, the overlap between the single energy layers is increased, leading to more energy layers contributing dose to the target. During the planning process we decreased this value by up to 20%.

➢ Usual values for spot weights for adults are 100 × 10^6 particles and for pediatrics 25 × 10^6 particles. With these 2 methods we reduced further the maximum spot weight to approximately 17 × 10^6. Any residual higher-weighted spots were located primarily outside any OAR (Figure 1).

Results

Local control, patterns of failure, and survival

At median follow-up of 42 months (3.5 years) (range 7-63 months), 9/11 children (82%) remained with local tumor control. Actuarial 2-

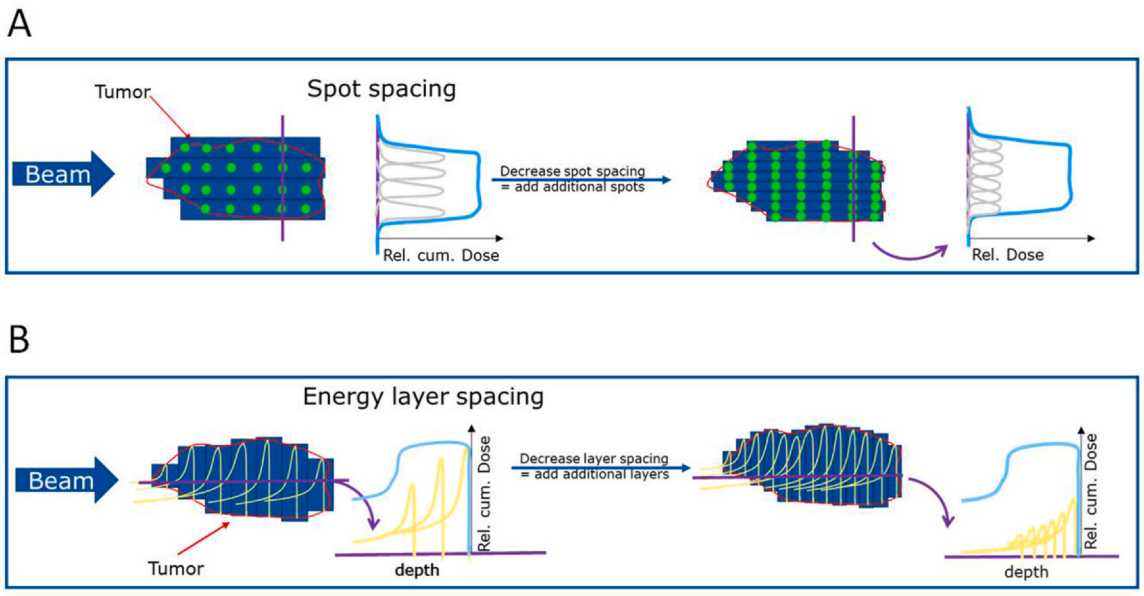

Figure 2. Special measures to reduce spot weight and hence uncertainties in the biological end of range. This increases the number of spots in order to deliver the prescribed dose. (A) The number of spots is increased by decreased spot spacing; (B) The number of spots is increased by decreased layer spacing. See text for further details.

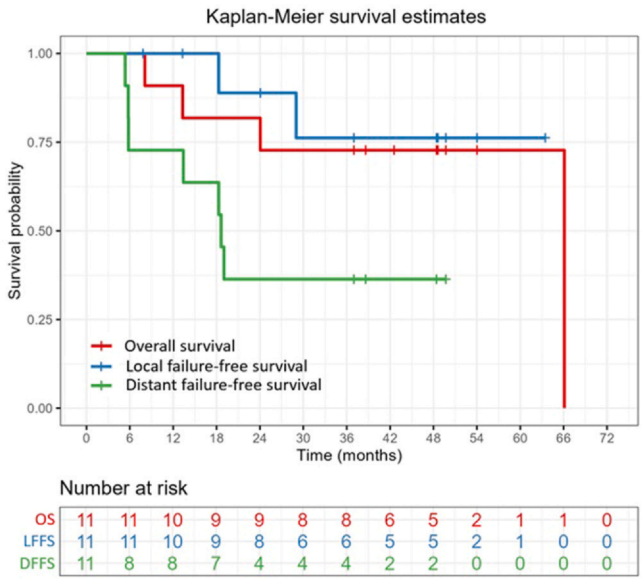

Figure 3. Kaplan-Meier estimates of local control (local failure-free survival), distant failure-free survival, and overall survival of 11 pediatric patients undergoing proton-re-irradiation for recurrent CNS tumors with immediate proximity to the brainstem.

and 3-year local control rates were 89% and 76% (Figure 3, Table 1). As depicted in Figure 3, the rates of distant failure-free-survival were 36% at 2- and 3-years, respectively. Median OS for the entire cohort was 66 months, with 2-year and 3-year OS rates of 82% and 73%.

Two patients experienced local in-field recurrences occurring at 18 and 29 months, respectively, after completion of re-RT (Table 1). One local failure was observed in a patient with ependymoma, who subsequently underwent surgical resection and is alive. The second local failure occurred in a patient with ATRT synchronously with the diagnosis of lepto-meningeal seeding. This patient underwent further systemic therapy and was alive with disease at the time of analysis.

The presumed epicenters of local failures were inside the CTV and fully covered by the prescription dose. There was no marginal failure and no failure thus far in an area under-dosed due to OAR constraints, that is, failures were not related to the area of dose gradient between critical OAR and CTV.

Six additional patients developed intracranial failures distant from the treated side and/or leptomeningeal spread. However, those patients remained locally controlled. In summary, 7 patients developed distant failures, 5 patients without and one with concurrent local failure.

At the time of analysis, 4 patients had died, 3 from progressive disease and 1 from acute myelocytic leukemia, presumably a second malignancy as a result of systemic therapy.

Acute and late side effects

All children tolerated the treatment well, including 8/11 patients requiring general anesthesia. Depending on field arrangements and surface dose, patients developed the expected alopecia over the treatment fields as well as moderate erythema. No ≥ Grade 2 acute toxicities (during and for 90 days after treatment) were observed.

All patients were followed with frequent, sequential routine MR imaging. Only one patient developed transient and asymptomatic contrast enhancement of the brain parenchyma at 8 months after completion of PT (Grade 1 CNS-toxicity). Contrast enhancement resolved spontaneously at 24 months.

During follow-up, 1 patient experienced further deterioration of pre-existing unilateral hearing impairment. No ≥ Grade 2 CNS adverse events/toxicities were observed, notably no symptomatic high-grade brainstem or brain parenchyma necrosis was seen.

Figure 1 depicts a representative re-irradiation plan using protons together with the cumulative dose distribution, delivering 54 Gy(RBE) after a first photon treatment to 59.4 Gy.

Target coverage

The ability to cover the CTV with the intended prescription dose was determined by the proximity of the CTV and related gross disease to the OARs. The median CTV coverage, as determined by the volume receiving 95% of the prescription dose ($V_{95\%}$), was 78% with a range of 31%-100% (Figure 4).

For 2 of 4 patients with coverage less than 50%, 90% of the CTV was still covered by 80% of the prescribed dose. Reduction of the CTV coverage was determined by the OAR constraints of touching organs

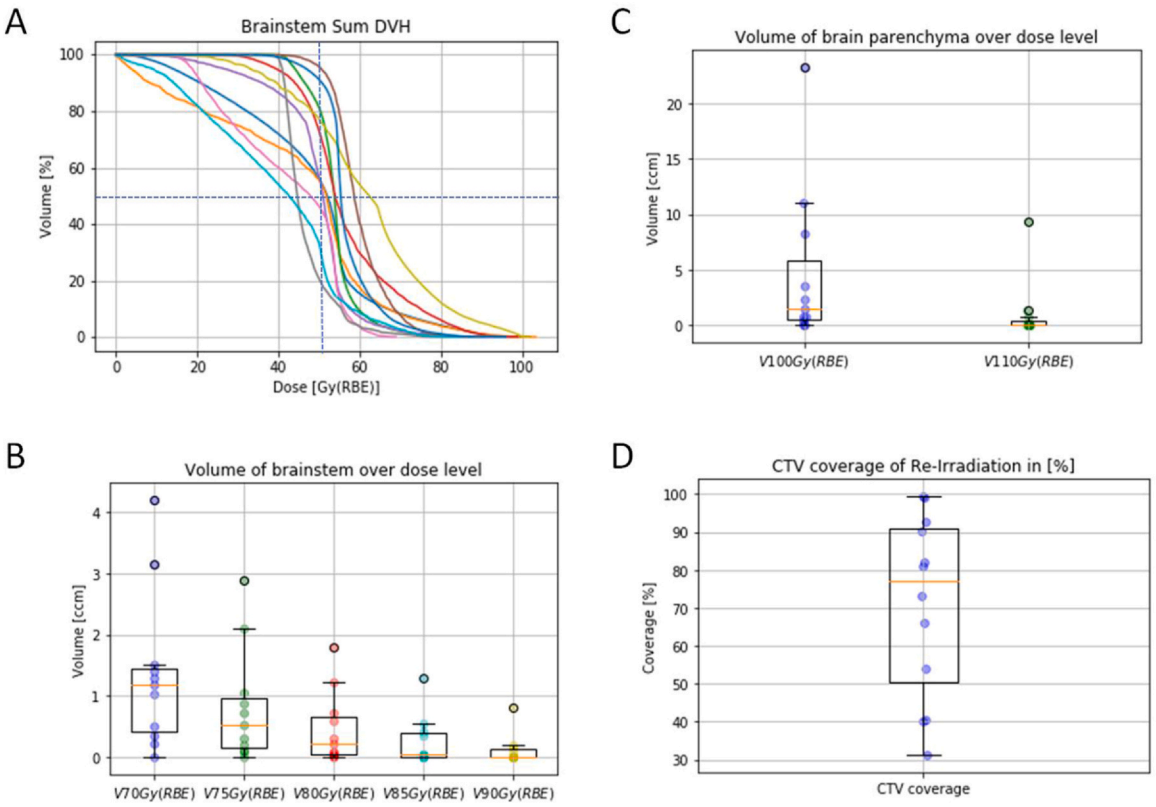

Figure 4. Cumulative dose parameters of 11 patients with PT re-irradiation. (A) Individual, cumulative Brainstem dose-volume-histograms, based on summation plans of 1st RT and Re-RT. (B) Volume of Brainstem receiving cumulative doses of 70-95 Gy(RBE) and above (ie, $V_{70\,Gy}$-$V_{95\,Gy}$). (C) Volume of Brain Parenchyma receiving cumulative doses of 100-110 Gy(RBE) and above (ie, $V_{100\,Gy}$-$V_{110\,Gy}$). (D) Clinical target volume (CTV) coverage in 11 patients. The box indicates the interquartile range, with the median shown as a horizontal red line. The whiskers show the data point closest to 1.5 times the interquartile range, with outliers shown beyond.

that were spared to less than 80% of the prescription dose (Figure 1). The other two patients had OAR constraints of less than 70% of the prescription dose, which still resulted in 90% coverage of the CTV by more than 85% of the target dose.

Brainstem and brain parenchyma Re-RT treatment characteristics

Brainstem and brain parenchyma re-irradiation doses are displayed in Table 2. Strategies of balancing target dose delivery with OAR considerations resulted in a median cumulative dose to the brainstem surface, defined as $D_{0.1cc}$ of 81.5 Gy(RBE) (range: 65.8-99.5 Gy(RBE).

Figure 4 displays the individual cumulative brainstem DVHs in all 11 Patients. The volume of brainstem receiving > 80 Gy(RBE) was limited for most patients to < 1 cc (median 0.22 cc). Cumulative doses to brain parenchyma were limited to 110 Gy(RBE). Doses of 120 Gy (RBE) in normal brain parenchyma were not permissible.

Table 2
Proton-RT and cumulative dose parameters in 11 patients for brainstem and brain parenchyma.

Brainstem		Median (range)
Re-irradiation	$D_{0.1\ cc}$ [Gy (RBE)]	28.8 (18.18-40.58)
	D_{mean} [Gy (RBE)]	3.25 (0.6-9.87)
Cumulative dose	$D_{0.1\ cc}$ [Gy (RBE)]	81.5 (65.8-99.48)
	D_{mean} [Gy (RBE)]	49 (38.93-61.34)
	$V_{80\,Gy\ (RBE)}$ [cc]	0.22 (0.01-1.8)
	$V_{85\,Gy\ (RBE)}$ [cc]	0.05 (0-1.3)
	$V_{90\,Gy\ (RBE)}$ [cc]	0 (0-0.08)
Brain Parenchyma		Median (range)
Cumulative dose	$D_{0.1\ cc}$ [Gy (RBE)]	107.8 (91.6-114.01)
	$V_{100\,Gy}$ (RBE) [cc]	1.4 (0-23.3)
	$V_{110\,Gy}$ (RBE) [cc]	0 (0-9.3)

$D_{0.1\ cc}$ = the dose delivered to 0.1 cm^3.
D_{mean} = the mean dose delivered to a tissue or organ of interest.
$V_{80\ Gy(RBE)}$ = the volume of tissue receiving 80 Gy (with allowance for RBE).
$V_{85\ Gy(RBE)}$ = the volume of tissue receiving 85 Gy (with allowance for RBE).
$V_{90\ Gy(RBE)}$ = the volume of tissue receiving 90 Gy (with allowance for RBE).
$V_{100\ Gy(RBE)}$ = the volume of tissue receiving 100 Gy (with allowance for RBE).
$V_{110\ Gy(RBE)}$ = the volume of tissue receiving 110 Gy (with allowance for RBE).

Discussion

The present small series of patients represents a group of children with mainly recurrent ependymomas or ATRT tumors. They were treated consecutively with a consistent concept of applying a second, full course of radiotherapy at standard dose-fractionation using pencil-beam scanning PT. In our series, no patient has developed symptomatic radiation-induced CNS-necrosis, despite the diagnosis of ependymoma and ATRT in the majority of patients (N = 9/11).

Both histological subtypes have been reported to be associated with a higher risk of radiation-induced brainstem necrosis: 11.6% for ATRT versus 2.4% non-ATRT (P = .008) in the MD Anderson PT Center series of 468 pediatric patients treated with primary proton radiotherapy.[12] In 171 pediatric patients treated with protons at the Paul Scherrer Institute ependymoma versus non-ependymoma emerged as a negative prognostic factor for radiation necrosis.[13]

The median follow-up of > 3.5 years in our series covers the period of highest frequency of early late/late side effects of radiation-induced CNS necrosis. A recent PENTEC review reported a cumulative median latent period between re-irradiation and the development of brain necrosis of 5.7 months (range, 4.3-24 months).[8]

Our data indicate that selective re-irradiation using specifically modified treatment planning and individualized dose delivery can be

Table 3
Summary of the planning approach for re-RT using protons for the patients presented here.

Preparation
- ➢ Dose cube from the first treatment course must be available for import into the Treatment Planning System, to allow cumulative dose calculation.

Dose calculation
- ➢ Use Monte Carlo dose engine with at least 0.5% uncertainty and dose grid of 2 mm.
- ➢ Use additional robust optimization when appropriate.
- ➢ RBE of protons modeled as a constant factor of 1.1.

Dose and dose limits
- ➢ Brain stem
  - o Aim to limit cumulative brainstem surface doses to < 86 Gy(RBE).
  - o Limit the volume of brainstem receiving > 80 Gy(RBE) < 1 cc.
- ➢ Brain parenchyma
  - o Permit small volume to receive ≥ 110 Gy(RBE) cumulative.
  - o Avoid any significant volume of ≥ 120 Gy(RBE) cumulative.
- ➢ Accept that dose coverage of the CTV is reduced by the proximity of OARs.
  - o Median CTV coverage ($V_{95\%}$) may be only 78%.
- ➢ Dose-median 54.0 Gy(RBE) (range 44-54.0 Gy(RBE)).
- ➢ Use standard fractionation of 1.8-2.2 Gy(RBE) per fraction.

Beam direction choices
- ➢ Choose field entrance angles not used during the first RT course (Figure 1). These may be "non-intuitive," eg, from superior or superior-oblique directions.
- ➢ Choose beams which do not, or only partly, range out in an OAR.
- ➢ Ensure that multiple beams contribute to every part of the target.
- ➢ Use Range Shifter for superficial targets.

Specific planning aspects of Re-RT using PT
- ➢ Reduce individual spot weights (by ~ 1.5 times), and thence biological uncertainties, by:
  - o Decrease spot spacing to 0.3 cm (from more usual 0.4 cm), then decrease the spot weight (more spots needed for same dose) (Figure 2).
  - o Decrease energy layer spacing by up to 20%, to increase overlap between layers (requires more energy layers for same dose) (Figure 2).
- ➢ Use multi-field optimization (MFO) so that multiple beams contribute dose to the target and maximum dose per single beam is minimized.
- ➢ Ensure residual higher weighted spots are delivered outside any OAR.
- ➢ Final plan produced through an iterative process between planner and oncologist.

The main aim was to have the best estimate on the cumulative dose, to minimize end of range RBE increase to OARs by different beam directions compared to first treatment and by decreased spot and energy layer spacing.

considered effective and safe. However, exactly what dose can be safely delivered, while still achieving local control, remains an important area for further study, and is part of our ongoing program. We did not use hypofractionation in this first phase since our primary concern was to establish safety. The 2 local failures inside the full prescription dose volume might indicate the need for a more aggressive—possibly hypofractionated-approach in selected situations.

Our planning approach involves careful cumulative dose summation to combine the first course of RT with the Proton Re-RT. Acceptable cumulative brainstem surface doses were individualized, and included allowance for recovery of tolerance with time since the previous course. Beam portals were chosen that had not been used in the previous course and were designed to avoid ranging out in OARs. Spot weights were specifically reduced to minimize uncertainties in dose deposition (see summary in Table 3). Taken together, these measures are designed to make the plan more robust in minimizing the risk of end of range RBE increase due to highly weighted spots being delivered within any OAR. The final plan was produced through an iterative process between planner and oncologist.

Our approach provides clinical evidence to determine a potentially tolerable dose to the brainstem surface in the circumstance of re-irradiation. By using standard fractionation, we avoided the inherent uncertainty of formulae to convert hypofractionated doses into equivalent standard fractionation doses (EQD2).

This issue of brainstem necrosis and thus brainstem tolerance after PT in pediatric brain tumors has received significant attention in recent years and the discussion on whether a specific radiation modality (ie, photons vs protons) carries a higher risk of radiation-induced CNS necrosis has not reached a conclusion.

Devine et al[14] reported on a multi-institutional study of 107 children with posterior fossa tumors treated with photon therapy to a median prescribed dose 55.8 Gy. There was no incidence of Grade ≥ 2 brainstem necrosis, and only 1.9% developed grade 1 changes.[14]

Several analyses of the results following PT have focused on brainstem necrosis after primary radiotherapy (in contrast to re-irradiation): Upadhyay[12] reported on 468 patients < 21 years of age treated with PT at MD Anderson PT Center. Symptomatic (Grade 2-5) necrosis was observed in 15 patients (3.2%) with a cumulative incidence of 3.66% at 2 years. The majority of children (79%) were treated with a passive scattering technique and only the minority with pencil-beam scanning technology. The rate of asymptomatic brainstem imaging changes was 10.9%.

Indelicato[15] for the U Florida Proton Center analyzed 313 pediatric patients who received > 50.4 Gy to the brainstem. The 2-year cumulative toxicity incidence was 3.8% and specifically the Grade ≥ 3 toxicity 2.1%.[15] A study of 178 children with medulloblastoma treated with PT at Massachusetts General Hospital reported a 10-year incidence of brain stem injury of 2.1%.[16] In 2017 the same institution published a 5-year incidence of 2% in 216 children with posterior fossa tumors treated to a median dose of 54 Gy with PT.[17]

Based on the unresolved concern, the Children's Oncology Group Protocol ACNS0831 for newly diagnosed ependymoma differentiated between photon and PT to determine brainstem OAR constraints and de facto lowered it for PT: Maximum permissible constraints using photon therapy were specified as $D_{50\%} < 62$ Gy and $D_{10\%} < 64$ Gy and for PT as $D_{50\%} < 54$ CGE and $D_{0.1cc} < 58$ CGE.

The PENTEC consortium provides an excellent, informative review on re-irradiation of pediatric CNS tumors.[8] It notes one of the inherent challenges to gaining information on the brainstem tolerance, namely that the majority of publications state only the target prescription dose rather than the received dose in the second course or the cumulative dose.

Stating the prescription dose and cumulative doses to targets provides some information on brain parenchyma toxicity and tolerance, yet little information on brainstem tolerance. In re-irradiation, OAR considerations are different between brain parenchyma and brainstem. Brain parenchyma is, by and large, considered a soft OAR where relatively high cumulative doses, close to target prescription, to smaller areas of brain parenchyma are routinely permissible as a prerequisite to deliver adequate radiation doses to the target. In clinical practice, brain

parenchyma cumulative doses of 100-110 Gy and potentially even small areas of 120 Gy (EQD2) are delivered, thereby accepting some risk of ≥ Grade 3 toxicity. In contrast, brainstem OAR constraints have higher planning priority, since radiation-induced necrosis of the brainstem can result in Grade 4 or even Grade 5 toxicity, that is, paresis or death of the patient. Considering the fear of potentially fatal brainstem necrosis, the approach to permitting significantly high doses at the brainstem surface or inside the brainstem continues to be very cautious.

With longer follow-up and additional patient accrual, our series has the potential to provide guidelines as to a permissible surface dose to the brain stem and maximum permissible dosages to small volumes of brainstem.

There remains a difference, as yet unexplained, between the incidence of brainstem injury after protons for pediatric intra-parenchymal CNS tumors and the comparably low incidence after treatment of pediatric skull base chordomas and chondrosarcomas. The majority of pediatric CNS tumors in the posterior fossa are ependymomas, medulloblastomas and ATRT tumors. The standard CNS tumor dose is relatively uniform ranging between 50.4 Gy to maximally 59.4 Gy (RBE) (at standard fractionation) with a typical dose constraint of 54-58 Gy(RBE) to the brainstem. In contrast, it is well established, that the treatment of radio-resistant skull base chordomas requires high radiation doses > 70Gy(RBE). In view of the frequent occurrence of tumor abutting or compressing the brainstem, relatively high OAR constraints to brainstem have been used historically and currently; yet, symptomatic brainstem injury remains anecdotal. The group at Massachusetts General Hospital (MGH) reported on the largest cohort of 204 pediatric patients with skull base chordoma and the longest follow-up period. The actuarial rates of PFS were 64% and 64% at both 10 and 20 years. Typical OAR constraints for brainstem were 67 Gy (RBE) maximum dose to the brainstem surface and 55 Gy(RBE) maximum dose to the brainstem center. Long-term follow up revealed radiographic and symptomatic brainstem injury in only 4 patients (=2%) overall.[10]

Other single-institution series confirm the low rate of brainstem injury in the treatment of pediatric skull base chordomas. Indelicato did not report any cases of brainstem injury in 29 pediatric chordoma patients with a median follow up of 4.3 years treated to a tumor dose of 73.8 Gy(RBE).[9]

Many have attributed the need for more conservative brainstem constraints with PT to the uncertainty of the true radiobiologic equivalent (RBE) dose considering the immediate proximity of the brainstem to most pediatric tumors in the posterior fossa. Differences in pencil beam scanning-based delivery versus passively scattered PT are discussed.[18,19] Recently, Baliga for the MGH group underscored the persistent paucity of fundamental understanding of RBE and LET near the distal portion of the spread-out Bragg peak, emphasizing the importance of biological proton dosimetry.[16] Nevertheless, brainstem injury in the MGH cohort of 178 patients with medulloblastoma was low (2.1%) and comparable to their prior studies from photon-treated brain tumor patients. The authors underline “the importance of careful radiation dosimetry planning, including limiting hot-spots in the brainstem and judicious selection of beam angles in order to keep the incidence of brainstem injury below 2%.”

Proton treatment planning incorporating biological parameters can address either LET-based or RBE-based optimization. Regions of higher LET or RBE in the brainstem or any other OAR can be identified after a plan has met the physical dose specification. Then, higher LET regions can be shifted outside the OAR or avoided altogether. LET-based optimization is already routinely applied in our clinic in the treatment of patients with Carbon Ions.[20]

The positive impact of our measures to increase spot numbers, simultaneously decreasing spot size and layer spacing, on resulting LET distribution and potential RBE changes is presently being investigated further.

Conclusion

In summary, our data indicate that pencil beam-based proton radiotherapy can be safely applied to re-irradiate recurrent pediatric CNS tumors, even in cases with tumors abutting the brainstem, which has been part of the irradiated volume of first-course RT. PT as a tool of re-irradiation can result in long-term tumor control in recurrent pediatric CNS tumors no longer amenable to gross total resection.

Patients are highly selected, and the decision for re-irradiation should be based on detailed interdisciplinary discussions of options for surgery and systemic therapies. CNS toxicities, specifically brainstem necrosis, remain of significant concern. We have developed a specific approach to mitigate and reduce the issues of range uncertainty, end of range variation in RBE and LET deposition in critical OAR’s. This is an area of active research. Considering the complexity of this highly individualized approach, it should only be performed at proton centers with a dedicated pediatric program.

Ethics

The study received ethical approval from the Ethics Commission for Lower Austria (Ethikkommission für das Bundesland Niederösterreich) EK-Nummer: GS3-EK-1/214-2024.

CRediT authorship contribution statement

E.B. Hug: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing - original draft, Writing - review and editing. L. Brodbek: Data curation, Formal Analysis, Methodology, Software, Validation, Writing - original draft, Writing - review and editing. M.S. Stock: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing - original draft, Writing - review and editing. J. Gojo: Conceptualization, Formal Analysis, Investigation, Validation, Writing - review and editing. U. Mock Doz: Conceptualization, Formal Analysis, Investigation, Methodology, Validation, Writing - review and editing. C. Lütgendorf-Caucig: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing - original draft, Writing - review and editing.

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Declaration of Conflicts of Interest

The authors have no conflicts to disclose.

References

1. Peters S, Frisch S, Stock A, et al. Proton beam therapy for pediatric tumors of the central nervous system-experiences of clinical outcome and feasibility from the KiProReg study. *Cancers.* 2022;14(23):5863. https://doi.org/10.3390/cancers14235863
2. Ritzmann TA, Chapman RJ, Kilday JP, et al. SIOP Ependymoma I: final results, long-term follow-up, and molecular analysis of the trial cohort-A BIOMECA Consortium Study. *Neuro Oncol.* 2022;24(6):936–948. https://doi.org/10.1093/neuonc/noac012
3. Buscariollo DL, Park HS, Roberts KB, Yu JB. Survival outcomes in atypical teratoid rhabdoid tumor for patients undergoing radiotherapy in a surveillance, epidemiology, and end results analysis. *Cancer.* 2012;118(17):4212–4219. https://doi.org/10.1002/cncr.27373
4. Quinn TJ, Almahariq MF, Siddiqui ZA, et al. Trimodality therapy for atypical teratoid/rhabdoid tumor is associated with improved overall survival: a surveillance, epidemiology, and end results analysis. *Pediatr Blood Cancer.* 2019;66(12):e27969. https://doi.org/10.1002/pbc.27969

5. Frisch S, Libuschewski H, Peters S, et al. Radiation therapy plays an important role in the treatment of atypical teratoid/rhabdoid tumors: analysis of the EU-RHAB cohorts and their precursors. *Int J Radiat Oncol Biol Phys.* 2024;119(4):1147–1157. https://doi.org/10.1016/j.ijrobp.2024.01.200
6. Gilbert MR, Yuan Y, Wu J, et al. A phase II study of dose-dense temozolomide and lapatinib for recurrent low-grade and anaplastic supratentorial, infratentorial, and spinal cord ependymoma. *Neuro Oncol.* 2021;23(3):468–477. https://doi.org/10.1093/neuonc/noaa240
7. Carey SS, Huang J, Myers JR, et al. Outcomes for children with recurrent/refractory atypical teratoid rhabdoid tumor: a single-institution study with molecular correlation. *Pediatr Blood Cancer.* 2024;71(10):e31208. https://doi.org/10.1002/pbc.31208
8. Ajithkumar T, Avanzo M, Yorke E, et al. Brain and brain stem necrosis after re-irradiation for recurrent childhood primary central nervous system tumors: a PENTEC comprehensive review. *Int J Radiat Oncol Biol Phys.* 2024;119(2):655–668. https://doi.org/10.1016/j.ijrobp.2023.12.043
9. Indelicato DJ, Rotondo RL, Mailhot Vega RB, et al. Local control after proton therapy for pediatric chordoma. *Int J Radiat Oncol Biol Phys.* 2021;109(5):1406–1413. https://doi.org/10.1016/j.ijrobp.2020.11.051
10. Ioakeim-Ioannidou M, Niemierko A, Kim DW. Surgery and proton radiation therapy for pediatric base of skull chordomas: long-term clinical outcomes for 204 patients. *Neuro Oncol.* 2023;25(9):1686–1697. https://doi.org/10.1093/neuonc/noad068
11. Janson M, Glimelius L, Fredriksson A, Traneus E, Engwall E. Treatment planning of scanned proton beams in RayStation. *Med Dosim.* 2024;49(1):2–12. https://doi.org/10.1016/j.meddos.2023.10.009
12. Upadhyay R, Liao K, Grosshans DR, et al. Quantifying the risk and dosimetric variables of symptomatic brainstem injury after proton beam radiation in pediatric brain tumors. *Neuro Oncol.* 2022;24(9):1571–1581. https://doi.org/10.1093/neuonc/noac044
13. Bojaxhiu B, Ahlhelm F, Walser M, et al. Radiation necrosis and white matter lesions in pediatric patients with brain tumors treated with pencil beam scanning proton therapy. *Int J Radiat Oncol Biol Phys.* 2018;100(4):987–996. https://doi.org/10.1016/j.ijrobp.2017.11.037
14. Devine CA, Liu KX, Ioakeim-Ioannidou M, et al. Brainstem injury in pediatric patients receiving posterior fossa photon radiation. *Int J Radiat Oncol Biol Phys.* 2019;105(5):1034–1042. https://doi.org/10.1016/j.ijrobp.2019.08.039
15. Indelicato DJ, Flampouri S, Rotondo RL, et al. Incidence and dosimetric parameters of pediatric brainstem toxicity following proton therapy. *Acta Oncol.* 2014;53(10):1298–1304. https://doi.org/10.3109/0284186X.2014.957414
16. Baliga S, Gallotto S, Bajaj B, et al. Decade-long disease, secondary malignancy, and brainstem injury outcomes in pediatric and young adult medulloblastoma patients treated with proton radiotherapy. *Neuro Oncol.* 2022;24(6):1010–1019. https://doi.org/10.1093/neuonc/noab257
17. Gentile MS, Yeap BY, Paganetti H, et al. Brainstem injury in pediatric patients with posterior fossa tumors treated with proton beam therapy and associated dosimetric factors. *Int J Radiat Oncol Biol Phys.* 2018;100(3):719–729. https://doi.org/10.1016/j.ijrobp.2017.11.026
18. Yock TI, Constine LS, Mahajan A. Protons, the brainstem, and toxicity: ingredients for an emerging dialectic. *Acta Oncol.* 2014;53(10):1279–1282.
19. Giantsoudi D, Adams J, MacDonald S, Paganetti H. Can differences in linear energy transfer and thus relative biological effectiveness compromise the dosimetric advantage of intensity-modulated proton therapy as compared to passively scattered proton therapy? *Acta Oncol.* 2018;57(9):1259–1264.
20. Schafasand M, Resch AF, Nachankar A, et al. Dose averaged linear energy transfer optimization for large sacral chordomas in carbon ion therapy. *Med Phys.* 2024;51(6):3950–3960. https://doi.org/10.1002/mp.17102