Pediatric Blood & Cancer

WILEY

Pediatric Blood & Cancer | SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY | aspho The American Society of Pediatric Hematology/Oncology

RESEARCH ARTICLE OPEN ACCESS

Feasibility and Safety of High-Dose Proton Re-Irradiation in Recurrent Pediatric Central Nervous System Tumors: A Single-Institution Retrospective Study

Jin-Ho Song[1,2] | Jonathan Baron[2] | Carlos Chavez Perez[3] | Sidharth Ramesh[2] | Jane Minturn[4] | Kavita A. Desai[4] | Amish C. Shah[4] | Jean M. Belasco[4] | Kristina A. Cole[4] | Michael J. Fisher[4] | Phillip B. Storm[5] | Peter M. Madsen[5] | Goldie Kurtz[2] | Robert A. Lustig[2] | Christine Hill-Kayser[2] | Michael J. LaRiviere[2]

[1]Department of Radiation Oncology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea | [2]Department of Radiation Oncology, University of Pennsylvania, Philadelphia, Pennsylvania, USA | [3]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA | [4]Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA | [5]Division of Neurosurgery, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

Correspondence: Michael J. LaRiviere (michael.lariviere@pennmedicine.upenn.edu)

Received: 16 December 2025 | **Revised:** 19 March 2026 | **Accepted:** 16 April 2026

Keywords: neuro-oncology | pediatric CNS tumors | proton therapy | radiation oncology | re-irradiation

ABSTRACT

Purpose: Pediatric central nervous system (CNS) tumors often recur despite multimodality therapy. Although re-irradiation (re-RT) has historically been limited by concerns for severe late toxicities, modern techniques have renewed interest in this approach. Proton therapy provides dosimetric advantages that may enable curative re-treatment with reduced normal tissue exposure.

Methods: We retrospectively reviewed 54 pediatric patients who underwent proton re-RT for recurrent CNS tumors at our institution (2010–2024). Eligible patients had received prior CNS-directed RT at ≤20 years of age. Toxicities were graded per Common Terminology Criteria for Adverse Events (CTCAE) v5.0 as acute (<3 months) or late (≥3 months). Cumulative dosimetry was assessed by registering RT1 and RT2 plans and converting doses to EQD2 ($\alpha/\beta = 2$ Gy). Overall survival (OS) and progression-free survival (PFS) were estimated using Kaplan–Meier methods.

Results: Median age at re-RT was 11 years, with a median interval of 28.5 months between RT courses. The median prescribed re-RT dose was 54 Gy (range, 25–60), yielding a cumulative EQD2 of 102.6 Gy (range, 46.8–112.9). Median OS and PFS were 46.0 and 16.5 months, respectively. Among 16 ependymoma patients, all received full-dose proton re-RT (54–59.4 Gy), yielding a 1-year OS of 91.7% and PFS of 50.0%. Glioma patients had inferior outcomes (1-year OS 55.4%, PFS 41.6%) with a median re-RT EQD2 of 48.1 Gy. An RT interval of ≥12 months was associated with improved OS and PFS. Composite dosimetry in 21 patients showed a median cumulative brain $D_{0.1cc}$ of 109.0 Gy; only one patient developed Grade 3 radiation necrosis (RN). High-grade acute toxicity occurred in 13.0% of patients, all manageable with supportive care.

Conclusion: Proton re-RT for pediatric CNS tumors is feasible and associated with encouraging survival and low rates of serious late toxicity.

Abbreviations: CNS, central nervous system; CTV, clinical target volume; GTV, gross tumor volume; Gy, gray; OS, overall survival; PBT, proton beam therapy; PFS, progression-free survival; PTV, planning target volume; RT, radiation therapy.

Jin-Ho Song and Jonathan Baron contributed equally to this work.

This work was selected as an abstract winner at the Children's Oncology Group Young Investigator Research Competition, held on September 18, 2025 and was presented at the 11th Annual PTCOG-NA Conference on November 7, 2025.

1 | Introduction

Pediatric central nervous system (CNS) tumors are the most frequent solid neoplasms of childhood and are still the leading cause of cancer-related death in children [1]. To achieve better cure rates with acceptable long-term secondary effects, treatment usually consists of a multimodal approach with a combination of surgery, radiotherapy (RT), and chemotherapy. This multimodal approach has led to increased survival rates for many pediatric brain tumors [2].

Despite aggressive initial treatment, a large proportion of pediatric CNS tumors still recur, generally in the CNS. Controlling such recurrences is difficult: the diffuse microscopically invasive nature impedes complete surgical resection, and systemic chemotherapy alone seldom brings about durable CNS control (often due to lack of drug penetration to the brain because of the blood–brain barrier).

In the past, clinicians were reluctant to pursue re-irradiation (re-RT) in children because of concerns about severe late toxicities. In a previously irradiated brain, both repeat surgery and RT carry elevated risks of treatment-related morbidity [3]. Late complications such as radiation necrosis (RN), which can be life threatening, and neurocognitive decline are well-known consequences of high cumulative CNS dose [4, 5]. These risks prompted clinicians to attempt salvage therapy with surgery or chemotherapy rather than to compound risk by accepting the possible catastrophic effects of further radiation.

Advances in RT techniques over the past decade have begun to change this risk–benefit calculus. Modern image-guided and conformal RT methods (including intensity-modulated and stereotactic approaches) now allow more precise dose delivery, sparing critical normal tissues. Proton beam therapy (PBT) provides a dosimetric advantage in comparison to conventional photon RT due to the Bragg peak, which allows for as high tumor dose as possible and a lower exit to normal brain. This lower integral dose is anticipated to result in reduced rates of late complications. In fact, when compared to photon-based techniques, PBT appears to more effectively save cognitive performance, endocrine status, and hearing in children with brain tumors [6–10].

Early clinical experience in the setting of recurrent pediatric CNS tumors has been promising, with appropriately selected patients receiving re-RT with protons, resulting in durable disease control and acceptable toxicity [11–13]. Due to these advantages, PBT is being increasingly favored in situations where re-RT is required for a recurrent pediatric CNS tumor.

Here, we performed a retrospective analysis of the experience of our institution with proton re-RT in children with recurrent CNS tumors. In this study, we present the clinical results and dosimetric data of this cohort to add to the existing knowledge of the safety and efficacy of re-RT in the pediatric CNS tumor population with PBT.

2 | Methods

2.1 | Patient Selection

This study was approved by our institutional review board. We retrospectively reviewed all patients who met the following inclusion criteria: (i) received their first course of RT (RT1) to the CNS at ≤20 years of age; (ii) subsequently underwent a second course of CNS-directed PBT (RT2); and (iii) were treated at our institution between 2010 and 2024. Both Types I and II re-RT, as defined by the ESTRO–EORTC consensus guidelines, were included in the analysis [14].

Re-RT eligibility was determined through multidisciplinary tumor board discussion. Favorable candidates generally included patients who tolerated RT1 well, demonstrated radiographic and/or clinical response to RT1, and had good performance status with a reasonable expectation of clinical benefit from re-RT. All recurrence patterns were considered eligible, including local-only, combined local and distant, and distant-only recurrence. Full-dose re-RT was generally offered for ependymoma and medulloblastoma, whereas hypofractionated regimens were more commonly used for select glioma patients. Patients were generally not excluded from RT2 on the basis of cumulative dose risk alone; exclusion was more commonly considered for a third RT course when triple overlap of high-dose regions was anticipated.

2.2 | Data Collection and Toxicity Assessment

Clinical data, radiotherapy details, treatment-related toxicities, and survival outcomes were collected through a comprehensive review of electronic medical records. PBT doses are reported in gray equivalents (GyE), which assumes relative biological effectiveness (RBE) value of 1.1 when converting between PBT and photon. Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [15]. Toxicities were classified as acute or late based on a 3-month cutoff, and late toxicities were evaluated only in patients with follow-up of at least 3 months.

2.3 | Re-RT Planning

Re-RT planning was individualized on a case-by-case basis through multidisciplinary discussion and was not governed by a strict institutional protocol; however, several general principles guided our approach. For RT2, clinical target volume (CTV) margins were generally no larger than those used for RT1 and were permitted to be smaller (e.g., gross tumor volume [GTV] + 0.5 cm or GTV = CTV) depending on proximity to previously irradiated organs at risk (OAR). Planning target volume (PTV) margins were typically 3 mm for both RT1 and RT2. Cumulative dose constraints were prioritized over target coverage; in most cases, cumulative dose limits included optic structures ≤81 Gy, brainstem ≤110 Gy, and spinal cord ≤75 Gy (EQD2, α/β = 2 Gy). When meeting these constraints required compromise of CTV or PTV coverage, this was permitted after multidisciplinary review.

For focal RT2, the RT1 simulation scan was fused with the RT2 simulation scan during treatment planning. High-dose isodose regions from RT1 were imported into the RT2 planning environment and used to create avoidance structures that informed beam arrangement and optimization. Beyond the formal OAR constraints described above, the planning approach aimed to balance cumulative hot and cold spots, though specific overlap-volume thresholds were not formally defined. In select cases where craniospinal irradiation (CSI) was indicated at RT2, the brainstem-sparing CSI technique described by Hill-Kayser and Kirk [16] was employed.

2.4 | Cumulative Dosimetric Analysis

For retrospective dosimetric analysis, planning computed tomography (CT) datasets from RT1 and RT2 were co-registered using rigid registration, and composite plan sums were generated. Cumulative physical and biological doses were recorded for the constrained OARs described above as well as the whole brain and cochleae. All doses were converted to EQD2 using the linear–quadratic model with an assumed α/β ratio of 2 Gy for late-responding normal tissues.

2.5 | Statistical Analysis

Descriptive statistics were used to summarize clinical and treatment characteristics. Overall survival (OS) and progression-free survival (PFS) were calculated from the end date of the re-RT course to the date of death or disease progression, respectively. Survival outcomes were estimated using the Kaplan–Meier method and compared between groups using the log-rank test. Statistical significance was defined as a two-tailed p value < 0.05. All statistical analyses were performed using SPSS Statistics version 20.0.0 (IBM Corp., Armonk, NY, USA).

3 | Results

3.1 | Patient Characteristics

A total of 54 patients were included in this analysis (Table 1). The median age at RT1 was 7 years (range, 1–19), and 11 years (range, 2–29) at RT2. The cohort consisted of 32 males (59.3%) and 22 females (40.7%). The most common diagnosis was glioma (37.0%), including three diffuse midline glioma (DMG) patients, followed by ependymoma (29.6%), medulloblastoma (14.8%), embryonal/atypical teratoid rhabdoid tumors (13.0%), and others (germ cell tumor and craniopharyngioma). We also included six patients with secondary gliomas, whose initial diagnoses were medulloblastoma (three patients), leukemia (two patients), and ependymoma. The median interval between RT1 and RT2 was 28.5 months (range, 2–285 months).

3.2 | Details of Initial RT Course (RT1)

Details of the RT1 are summarized in Table 2, excluding two patients who received total body irradiation (TBI) and one patient for whom treatment details were unavailable. RT1 was performed with PBT in 27 (52.9%) patients. Median prescription dose was 54 Gy (range, 10.0–60.0 Gy) in 30 fractions. CSI was performed in nine (17.6%) patients with a dose of median 23.4 Gy (range, 18.0–36.0). Surgical resection was performed prior to RT1 in all patients except one, who was diagnosed with a non-germinomatous germ cell tumor and presented with visual symptoms. This patient underwent palliative photon RT to the suprasellar mass with 10 Gy in 4 fractions. Concurrent chemotherapy was administered in 11 patients, including temozolomide in nine patients with glioma and vincristine in two patients with medulloblastoma.

3.3 | Details of Second RT Course (RT2)

RT2 treatment details are shown in Table 3 for all included patients. All patients received PBT. The treatment intent was curative in 39 patients (72.2%). The median prescribed dose was 54 Gy (range, 25–60 Gy), corresponding to a median cumulative EQD2 dose of 102.6 Gy (range, 46.8–112.9). CSI was performed in 20 patients (37.0%); among them, brainstem overlap was excluded in five cases using a previously described technique [16]. Most patients (81.5%) were treated with a standard fractionated (1.8–2.0 Gy per fraction) schedule, whereas 10 patients received hypofractionated regimen, all with palliative intent. Surgical resection prior to RT2 was performed in 61.1% of patients. Concurrent chemotherapy was performed in nine patients (five glioma, two medulloblastoma, and two embryonal tumor patients).

3.4 | Clinical Outcome and Acute Toxicities

The median OS after RT2 was 46 months, with 1-year and 3-year OS rates of 70.3% and 56.0%, respectively (Figure 1A). By histology, patients with ependymoma demonstrated significantly superior OS compared to glioma (log-rank $p = 0.003$; Figure 1B). A longer interval between RT1 and RT2 (≥12 months) was associated with improved OS (log-rank $p = 0.012$; Figure 1C).

The median PFS was 16.5 months (Figure 1D), with 1-year and 3-year PFS rates of 51.3% and 34.2%, respectively. Patients with glioma showed poorer PFS compared to other tumor types (Figure 1E). PFS was significantly improved in patients with a longer interval between RT1 and RT2. The 1-year PFS rate was 62.4% in patients with an interval ≥12 months, compared to 20.8% in those with an interval <12 months (Figure 1F).

Of the 54 patients, 7 (13.0%) experienced Grade ≥3 acute toxicities during or after RT2 (Table S1). The most frequent high-grade events were anorexia (7.4%), weakness (5.6%), and ataxia (3.7%), with isolated cases of otitis media and dysphagia (1.9% each). All events were manageable with supportive measures and did not necessitate treatment discontinuation.

3.5 | Late Toxicities and Composite Plan Analysis

There were 30 patients with at least 3 months of follow-up after RT2. Late toxicities were evaluated only in this subgroup, with a median follow-up of 20 months (range, 3.6–170 months). The diagnosis breakdown was ependymoma (n = 12, 40%), glioma (n = 11, 37%), ATRT/embryonal (n = 3, 10%), medulloblastoma

TABLE 1 | Patient characteristics ($n = 54$).

Variables	*N*	(%)
Age		
Age at RT1	Median 7 years	Range: 1–19 years, (IQR, 3–12)
Age at RT2	Median 11 years	Range: 2–29 years, (IQR, 7–18)
Gender		
Male	32	59.3
Female	22	40.7
Diagnosis		
Ependymoma	16	29.6
Medulloblastoma	8	14.8
Glioma[a]	20	37.0
• DMG	3	
• HGG/GBM	15	
• LGG	2	
Embryonal/ATRT	7	13.0
Germ cell tumor	2	3.7
Craniopharyngioma	1	1.9
RT1-2 interval (months)	Median 28.5 months	Range: 2–285 months (IQR, 12–73)

Abbreviations: DMG, diffuse midline glioma; GBM, glioblastoma multiforme; HGG, high-grade glioma; IQR, interquartile range; LGG, low-grade glioma.
[a]Including six patients with secondary glioma, whose initial diagnoses were medulloblastoma (3 pts), leukemia (2 pts), and ependymoma (1 pt).

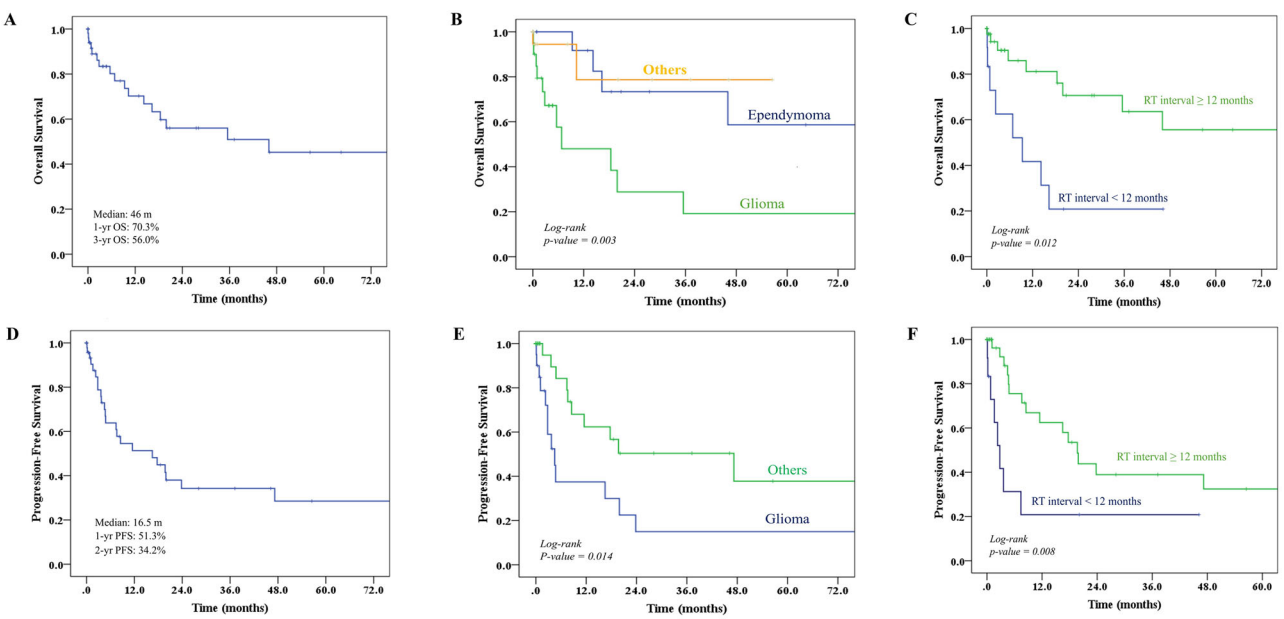

FIGURE 1 | Kaplan–Meier survival curves after proton re-irradiation (RT2). Overall survival (OS): (A) entire cohort, (B) stratified by diagnosis, and (C) stratified by interval between RT1 and RT2. Progression-free survival (PFS): (D) entire cohort, (E) stratified by diagnosis, and (F) stratified by RT interval. Median survival times, 1- and 3-year OS, and 1- and 2-year PFS estimates are shown, with comparisons performed using the log-rank test.

($n = 2$, 7%), and other ($n = 2$, 7%). The median cumulative EQD2 was 105.7 Gy (range, 51.3–112.9), and the median RT interval was 28.0 months (range, 3–215). Twenty-seven of 30 patients (90%) were treated with pencil beam scanning. Late toxicity outcomes were determined from a combination of imaging review and clinical documentation. Three cases of asymptomatic RN were detected only on routine imaging and classified as Grade 1. One patient developed a Grade 3 RN, presenting with headache and vomiting 7 months after completing RT2. This patient had supratentorial ependymoma and received re-RT to the same site

TABLE 2 | RT1 treatment details ($n = 51$).[a]

Variables	*N*	(%)
RT intent		
Curative	50	98.0
Palliative	1	2.0
RT1 technique		
Proton	27	52.9
Photon	24	47.1
RT1 prescribed dose		
CSI dose (in 9 pts)	Median: 23.4 Gy	Range: 18.0–36.0 (IQR, 23.4–23.4)
Total dose	Median 54 Gy	Range: 10.0–60.0 (IQR, 54.0–59.4)
Total dose EQD2	Median 51.3 Gy Average: 51.8 Gy	Range: 11.3–60.0 (IQR, 51.3–56.4)
RT1 fractionations		
1.5 Gy/fraction	1	2.0
1.8–2.0 Gy/fraction	48	94.1
≥2.5 Gy/fraction	2	3.9
RT1 site		
CSI/Supratentorial	1	2.0
No CSI/supratentorial	21	41.2
CSI/Infratentorial	8	15.6
No CSI/infratentorial	20	39.2
Spine only	1	2.0
RT1 location		
Study institution	37	72.5
Outside institution	14	27.5
Surgery before RT1		
GTR/NTR	36	70.5
STR/Bx	14	27.5
No surgery	1	2.0
Chemotherapy		
Before RT1	19	37.3
Concurrent[b]	11	21.6
After RT1	24	47.1

Abbreviations: Bx, biopsy; CSI, craniospinal irradiation; GTR, gross total resection; IQR, interquartile range; NTR, near-total resection; PTS, patients; STR, subtotal resection.

[a]Three patients were excluded. Two patients were treated with total body irradiation, and one patient's detailed information of RT1 was unknown.

[b]Temozolomide (nine patients) or vincristine (two patients).

for local recurrence, with 54 Gy delivered at RT1 and 59.4 Gy at RT2. The interval between the two treatments was 26 months. Symptoms resolved with corticosteroid and bevacizumab therapy. This event was classified as Grade 3 per CTCAE v5.0 because the patient's symptoms necessitated medical intervention.

Composite dosimetric analysis was performed in 21 patients for whom both RT plans were evaluable and both RT courses were delivered using standard fractionation (Table 4). The median interval between RT1 and RT2 was 25.0 months (range, 8.0–168.0), and the median follow-up duration was 35.0 months (range, 1.0–170.0). The cumulative $D_{0.1cc}$ to the brain parenchyma was 109 Gy (range, 61.4–117.2 Gy), with the highest value observed in the Grade 3 RN case. The cumulative $D_{0.1cc}$ to the brainstem and spinal cord was 65.4 Gy (range, 16.4–116.3 Gy) and 52.6 Gy (range, 0.0–70.5 Gy), respectively; no RN or neurologic toxicity was observed in these structures. The cumulative near-maximum dose ($D2\%$) to the brainstem was 64.0 Gy (range, 16.0–115.3 Gy). The $D2\%$ to the optic chiasm was 45.2 Gy (range, 8.1–62.5 Gy). The median cumulative brain V90Gy was 2.6% (range, 0%–12.6%),

TABLE 3 | RT2 treatment details ($n = 54$).

Variables	*N*	(%)
RT2 intent		
Curative	39	72.2
Palliative	15	27.8
RT2 technique		
Proton	54	100.0
• Mixed photon		
RT2 prescribed dose		
CSI dose (in 20 pts)	Median: 36.0 Gy	Range: 23.4–36.0 (IQR, 36.0–36.0)
Total dose	Median 54.0 Gy	Range: 25.0–60.0 (IQR, 42.3–58.0)
Total dose EQD2	Median 51.3 Gy Average: 49.1 Gy	Range: 28.1–60.0 (IQR, 46.8–56.4)
RT2 fractionations		
1.8–2.0 Gy/fraction	44	81.5
≥2.5 Gy/fraction	10	18.5
RT2 site		
CSI/Supratentorial	8	14.8
No CSI/supratentorial	14	25.9
CSI/Infratentorial	12	22.2
No CSI/infratentorial	14	25.9
Spine only	6	11.1
Surgery before RT2		
GTR/NTR	23	42.6
STR/Bx	10	18.5
No surgery	21	38.9
Chemotherapy		
Before RT2	18	33.3
Concurrent	9	16.7
After RT2	16	29.6

Abbreviations: Bx, biopsy; CSI, craniospinal irradiation; GTR, gross total resection; IQR, interquartile range; NTR, near-total resection; RT2, second radiation therapy course; STR, subtotal resection.

confirming that despite high point doses, the volume of brain receiving ≥90 Gy EQD2 remained small. Among the four RN patients, brain V90Gy was numerically higher (median 5.3%, range 0%–11.4%).

3.6 | Subgroup Analysis by Diagnosis

A total of 16 patients received re-RT for recurrent ependymoma. The median age at RT1 was 6 years (range, 1–16), and 9 years (range, 2–18) at RT2. The median RT interval was 24 months (range, 8–76). All patients initially underwent focal RT without CSI, receiving 54–59.4 Gy in 30–33 fractions. RT2 was performed for locoregional progression in 11 patients and for metastatic seeding in 5. All patients with seeding received CSI, whereas 3 of the 11 with locoregional recurrence also received CSI. The RT2 dose to the tumor site was 54–59.4 Gy in all cases, with 36 Gy CSI when indicated. The 1-year OS and PFS rates were 91.7% and 50.0%, respectively. Detailed outcomes according to recurrence pattern and RT2 modality are illustrated in Figure 2. The addition of CSI in patients with locoregional progression did not appear to improve survival, though this interpretation is limited by small sample size.

Re-RT was performed in 14 patients diagnosed with recurrent glioma, including 13 with high-grade glioma and one with low-grade spinal glioma. The median age at RT1 was 10.5 years (range, 2–19) and 13.5 years (range, 7–24) at RT2. The median interval between RT courses was 17 months (range, 2–159). RT2 dosing varied, with a median EQD2 of 48.1 Gy (range, 37.5–56.4 Gy) in a median of 25 fractions (range, 10–33). The 1-year OS and PFS rates were 55.4% and 41.6%, respectively.

There were also six patients with secondary glioma included in this study, of whom five had high-grade and one had low-grade histology. The median age at RT1 was 4.0 years (range, 2–16),

TABLE 4 | Dosimetry of composite plans.

	All patients ($n = 21$)[a]		RN cases ($n = 4$)[b]	
	Median	**Range**	**Median**	**Range**
Clinical characteristics				
RT interval (months)	25.0	8.0–168.0	23.0	8.0–35.0
Follow-up (months)	35.0	1.0–170.0	19.5	4.0–60.0
Cumulative point-dose metrics, $D_{0.1cc}$ (Gy EQD2)				
Brain parenchyma	109.0	61.4–117.2	114.8	98.4–117.2
Brainstem	65.4	16.4–116.3	54.9	16.4–98.9
Spinal cord	52.6	0.0–70.5	47.4	6.1–70.5
Cumulative near-maximum dose, D2% (Gy EQD2)				
Brainstem	64.0	16.0–115.3	52.4	16.0–97.6
Optic chiasm	45.2	8.1–62.5	28.9	13.9–43.8
Optic nerve, left	38.2	0.0–54.3	38.4	9.0–41.7
Optic nerve, right	6.1	0.0–51.3	38.1	6.1–40.0
Cumulative mean dose (Gy EQD2)				
Cochlea, right	34.3	0.0–80.0	32.8	3.3–53.6
Cochlea, left	21.3	0.8–59.6	32.6	7.1–59.2
Pituitary	36.1	4.9–55.1	49.0	8.7–55.1
Cumulative volume receiving ≥90 Gy EQD2				
Brain V90Gy (%)	2.6	0.0–12.6	5.3	0.0–11.4
Cumulative target coverage, PTV2 (Gy EQD2)				
PTV2 D_{max}	108.5	52.0–117.7	115.3	69.8–117.7
PTV2 *D*95%	63.9	35.8–114.8	85.1	55.4–110.6

Note: $D_{0.1cc}$, minimum dose to the hottest 0.1 cm^3; *D*2%, minimum dose to the hottest 2% of the structure volume; EQD2, equivalent dose in 2-Gy fractions ($\alpha/\beta = 2$ Gy); RN, radiation necrosis; V90Gy, percentage of structure volume receiving ≥90 Gy EQD2.

[a]Ependymoma (13 pts), glioma (5 pts), others (3 pts).

[b]RN cases include one patient with Grade 3 symptomatic RN and three patients with Grade 1 asymptomatic imaging changes.

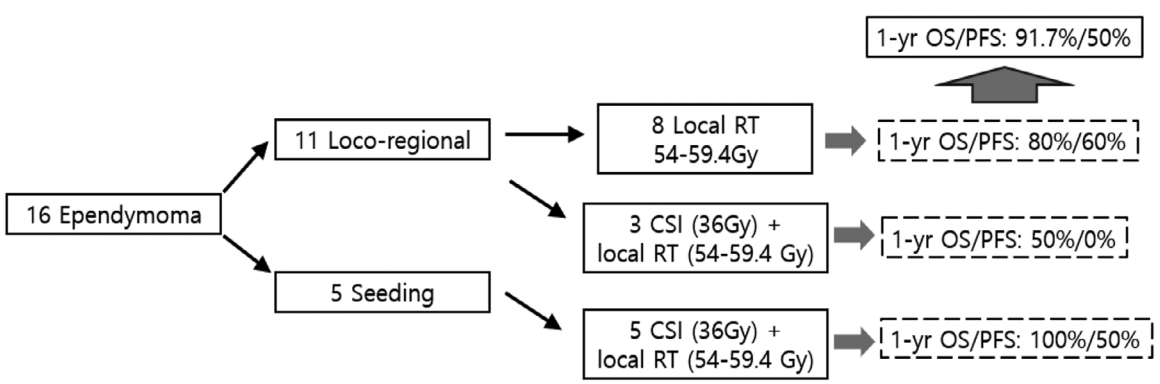

FIGURE 2 | One-year survival outcomes by treatment modality in recurrent ependymoma. Among 16 patients, 11 had locoregional recurrence (8 treated with local RT [54–59.4 Gy], 3 with CSI [36 Gy] plus local RT) and 5 had seeding recurrence (all treated with CSI [36 Gy] plus local RT). One-year overall survival (OS) and progression-free survival (PFS) rates are shown for each subgroup and for the entire cohort. CSI, craniospinal irradiation.

and 20.5 years (range, 14–29) at RT2, with a median interval of 189 months (range, 81–285). The initial diagnoses at RT1 were medulloblastoma ($n = 3$), leukemia ($n = 2$), and ependymoma ($n = 1$). The median RT2 EQD2 was 53.7 Gy (range, 39.3–60.0). All patients with high-grade secondary glioma experienced disease progression or death within 6 months after RT2. In contrast, the patient with low-grade glioma remained progression-free and alive 170 months following re-RT. Due to heterogeneity in

diagnosis and treatment approach, outcomes for other tumor types were not analyzed in detail.

4 | Discussion

The prognosis of recurrent pediatric CNS tumors is relatively poor, and treatment options are very limited. Re-RT might provide an opportunity for disease control or palliation for children with recurrent tumors. However, it has traditionally been limited largely by concerns of severe treatment-related toxicity. PBT offers unique physical characteristics that can be exploited with re-RT, specifically the Bragg peak and lack of exit dose, that enable the implementation of highly conformal dose distributions with steep dose gradients that limit any potential excess irradiation to previously treated normal brain [9]. These dosimetric advantages allow for the administration of definitive radiation doses in a safe way with proton re-RT in the salvage setting.

RN has been the foremost toxicity concern prohibiting broader application of pediatric CNS re-RT, as the occurrence of this late effect in the brain—or worse, the brainstem—can result in debilitating or fatal sequelae. This risk has recently been quantified by the Pediatric Normal Tissue Effects in the Clinic (PENTEC) re-RT task force, which found past a total cumulative dose of ~112 Gy (EQD_2, $\alpha/\beta = 2$) there was roughly a 5%–7% risk of Grade 3–4 brain/brainstem necrosis at a median follow-up of 1.6 years [17]. Our study also suggests that with appropriate patient selection and contemporary proton technology, re-RT with PBT can be accomplished with acceptable toxicity even to relatively high doses.

Although our cohort had higher re-RT doses than most other series, OS outcomes in this series are similar to those reported by others (Table S2). The 1-year OS in our series was ~70%, and there was a median post–re-RT PFS of 16.5 months (mixed histologies). This is in accordance with the proton re-RT series of MD Anderson Cancer Center, which described a 1-year OS of 66.7% following a median re-RT dose of 40 Gy [12]. Equally, a recent multi-institutional review of pediatric CNS re-RT (mixed modalities, median ~45 Gy re-RT dose) reported a median OS of 12.8 months following re-RT [18], equivalent to approximately 50% 1-year survival consistent with our data. Importantly, although we used a higher median re-RT dose (54 vs. 40–50 Gy in these studies), our 1-year disease control rates were at least as good as or better than those previously reported. These similarities indicate that dose-escalated proton re-RT enabled us to manage recurrent tumors in an aggressive manner without any clear survival penalty.

Our subset analysis by diagnosis confirms known prognostic differences in recurrent pediatric CNS tumors. Among the subgroup of patients with ependymoma, the most favorable outcomes were observed after re-RT; in our own series, their 1-year OS was 91.7%, with 1-year PFS ~50%. This discovery is in line with previous studies whose focus was on ependymoma. For instance, a Massachusetts General Hospital cohort of children reirradiated with protons for intracranial ependymoma achieved a 3-year OS of 78.6% [11]. A large St. Jude Children's Research Hospital series (101 recurrent ependymomas) also had a median OS of ~75 months (~6 years) following re-RT [19], which may emphasize that durable remission is feasible in this group. Our 1-year outcomes fall well within this expected range.

In contrast, our patients with malignant gliomas benefited little from re-RT with poor survival outcomes. We refrain from extensive discussion of the glioma subset given the small numbers and heterogenous re-RT doses, but our results align with the consensus that although re-RT may afford temporary disease control or symptom relief in pediatric glioma, it rarely achieves long-term survival in that group [20, 21].

A key finding of this study is the low incidence of serious toxicity despite the relatively high cumulative radiation doses delivered. Only one patient (3.3%) developed Grade 3 RN, which was managed medically without lasting effects. Three additional patients had asymptomatic imaging changes (Grade 1). This safety profile is particularly notable given the median cumulative EQD2 of approximately 102 Gy in our cohort. According to the PENTEC review, the estimated risk of symptomatic RN begins to rise significantly above 112 Gy EQD2 [17]. Compared with prior proton series [11, 12]—including MD Anderson's proton re-RT study (no RN) and MGH's ependymoma cohort (21.4% Grade 2 RN)—our findings reinforce the emerging consensus that PBT can safely enable re-RT in children when appropriately planned. The Swedish national re-RT study also reported a low incidence (6.5%) of Grade ≥3 toxicity despite high brainstem doses, further supporting the tolerability of carefully delivered re-RT [22]. Together, these data indicate that with careful attention to cumulative dose constraints, PBT is a safe and effective approach in the CNS re-RT setting. The favorable toxicity profile observed in this cohort likely reflects a combination of proton-specific dosimetric advantages, individualized overlap-avoidance planning strategies, and careful patient selection, rather than any single factor alone.

Several factors should be considered when interpreting the low observed incidence of RN. The median follow-up for late toxicity was 20 months, which may be insufficient to capture delayed events. Despite high cumulative point doses, the volume of brain receiving ≥90 Gy EQD2 was small (median V90Gy 2.6%), suggesting that individualized overlap-avoidance planning effectively limited high-dose volume. Retrospective toxicity documentation may underestimate the true incidence of Grade 2 events, which can be subclinical or inconsistently documented. Finally, patients selected for re-RT generally had favorable clinical characteristics, and this selection bias should be considered when generalizing these safety findings.

There are additional limitations worth noting. As a retrospective analysis from a single institution, it is subject to diagnostic heterogeneity and the inherent limitations of retrospective data collection. Nonetheless, it represents one of the largest proton-only pediatric re-RT series to date, with uniform treatment delivery and relatively high prescribed doses. Importantly, composite dosimetric analysis was performed in a meaningful subset of patients, enabling direct correlation between dose distribution and observed toxicity. These findings support the feasibility of high-dose proton re-RT in selected pediatric patients, with a favorable safety profile and promising treatment outcomes.

Acknowledgments

The authors have nothing to report.

Funding

The authors have nothing to report.

Ethics Statement

This retrospective study was reviewed and approved by the Institutional Review Board of the University of Pennsylvania and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Given the retrospective nature of the study and the use of de-identified data, a waiver of informed consent was granted by the Institutional Review Board.

Conflicts of Interest

Phillip B. Storm reports serving on the advisory board for Medtronic (paid position) and as a paid consultant for LatusBio. He also serves on the HealthShare Exchange (HSX) Board of Directors. These disclosures are unrelated to the current study. All other authors declare no conflicts of interest.

Data Availability Statement

Research data are stored in an institutional repository and will be shared upon reasonable request to the corresponding author.

References

1. Q. T. Ostrom, M. Price, K. Ryan, et al., "CBTRUS Statistical Report: Pediatric Brain Tumor Foundation Childhood and Adolescent Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014–2018," *Journal of Neuro-Oncology* 24, no. S3 (2022): iii1–iii38, https://doi.org/10.1093/neuonc/noac161.

2. T. Zilli, V. Dolcemascolo, E. Passone, et al., "A Multimodal Approach to the Study of Children Treated for Posterior Fossa Tumor: A Review of the Literature and a Pilot Study," *Clinical Neurology and Neurosurgery* 207 (2021): 106819, https://www.sciencedirect.com/science/article/pii/S0303846721003486.

3. S. Gaito, N. G. Burnet, M. C. Aznar, et al., "Proton Beam Therapy in the Reirradiation Setting of Brain and Base of Skull Tumour Recurrences," *Clinical Oncology Royal College of Radiologists* 35, no. 10 (2023): 673–681, https://doi.org/10.1016/j.clon.2023.07.010.

4. A. Mahajan, P. L. Stavinoha, W. Rongthong, et al., "Neurocognitive Effects and Necrosis in Childhood Cancer Survivors Treated with Radiation Therapy: A PENTEC Comprehensive Review," *International Journal of Radiation Oncology*Biology*Physics* 119, no. 2 (2024): 401–416, https://www.sciencedirect.com/science/article/pii/S0360301621001279.

5. C. Wujanto, B. Vellayappan, E. L. Chang, S. T. Chao, A. Sahgal, and S. S. Lo, "Radiotherapy to the Brain: What Are the Consequences of this Age-Old Treatment?," *Annals of Palliative Medicine* 10, no. 1 (2021): 936–952.

6. T. E. Merchant, H. Cho, H. Shukla, X. Ying, S. Nill, and U. Oelfke, "Proton Versus Photon Radiotherapy for Common Pediatric Brain Tumors: Comparison of Models of Dose Characteristics and Their Relationship to Cognitive Function," *Pediatric Blood & Cancer* 51, no. 1 (2008): 110–117, https://doi.org/10.1002/pbc.21530.

7. M. Mizumoto, Y. Oshiro, T. Yamamoto, H. Kohzuki, and H. Sakurai, "Proton Beam Therapy for Pediatric Brain Tumor," *Neurologia Medico-Chirurgica* 57, no. 7 (2017): 343–355.

8. B. R. Eaton, N. Esiashvili, S. Kim, et al., "Endocrine Outcomes With Proton and Photon Radiotherapy for Standard Risk Medulloblastoma," *Journal of Neuro-Oncology* 18, no. 6 (2016): 881–887, https://doi.org/10.1093/neuonc/nov302.

9. C. B. Simone, J. P. Plastaras, S. K. Jabbour, et al., "Proton Reirradiation: Expert Recommendations for Reducing Toxicities and Offering New Chances of Cure in Patients With Challenging Recurrence Malignancies," *Seminars in Radiation Oncology* 30, no. 3 (2020): 253–261, https://www.sciencedirect.com/science/article/pii/S1053429620300084.

10. J. S. Wilson, C. Main, N. Thorp, et al., "The Effectiveness and Safety of Proton Beam Radiation Therapy in Children and Young Adults With Central Nervous System (CNS) Tumours: A Systematic Review," *Journal of Neuro-Oncology* 167, no. 1 (2024): 1–34, https://doi.org/10.1007/s11060-023-04510-4.

11. B. R. Eaton, V. Chowdhry, K. Weaver, et al., "Use of Proton Therapy for Re-Irradiation in Pediatric Intracranial Ependymoma," *Radiotherapy and Oncology* 116, no. 2 (2015): 301–308, https://doi.org/10.1016/j.radonc.2015.07.023.

12. B. Farnia, N. Philip, R. H. Georges, et al., "Reirradiation of Recurrent Pediatric Brain Tumors After Initial Proton Therapy," *International Journal of Particle Therapy* 3, no. 1 (2016): 1–12, https://www.sciencedirect.com/science/article/pii/S2331518024000271.

13. E. Berlin, R. Eisenberg, C. Hill-Kayser, et al., "Delivery of Re-Irradiation and Complex Palliative Radiotherapy Using Proton Therapy in Pediatric Cancer Patients," *Pediatric Blood & Cancer* 70, no. 12 (2023): e30708, https://doi.org/10.1002/pbc.30708.

14. N. Andratschke, J. Willmann, A. L. Appelt, 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 Oncology* 23, no. 10 (2022): e469–478, https://doi.org/10.1016/S1470-2045(22)00447-8.

15. U.S. Department of Health and Human Services, National Institutes of Health and National Cancer Institute, *Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0* (National Institutes of Health, National Cancer Institute, 2017), https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

16. C. Hill-Kayser and M. Kirk, "Brainstem-Sparing Craniospinal Irradiation Delivered With Pencil Beam Scanning Proton Therapy," *Pediatric Blood & Cancer* 62, no. 4 (2015): 718–720, https://doi.org/10.1002/pbc.25378.

17. T. Ajithkumar, M. Avanzo, E. Yorke, et al., "Brain and Brain Stem Necrosis after Reirradiation for Recurrent Childhood Primary Central Nervous System Tumors: A PENTEC Comprehensive Review," *International Journal of Radiation and Oncology in Biology and Physics* 119, no. 2 (2024): 655–668, https://doi.org/10.1016/j.ijrobp.2023.12.043.

18. A. D. Rao, A. S. Rashid, Q. Chen, et al., "Reirradiation for Recurrent Pediatric Central Nervous System Malignancies: A Multi-Institutional Review," *International Journal of Radiation and Oncology in Biology and Physics* 99, no. 3 (2017): 634–641, https://doi.org/10.1016/j.ijrobp.2017.07.026.

19. D. S. Tsang, E. Burghen, P. Klimo, F. A. Boop, D. W. Ellison, and T. E. Merchant, "Outcomes after Reirradiation for Recurrent Pediatric Intracranial Ependymoma," *International Journal of Radiation Oncology*Biology*Physics* 100, no. 2 (2018): 507–515, https://www.sciencedirect.com/science/article/pii/S0360301617339639.

20. N. Shariff, A. S. Moreno, J. Bennett, et al., "Re-Irradiation for Children With Diffuse Intrinsic Pontine Glioma and Diffuse Midline Glioma," *Radiotherapy and Oncology* 207 (2025): 110865, https://www.sciencedirect.com/science/article/pii/S0167814025001604.

21. T. Perwein, B. Giese, G. Nussbaumer, et al., "How I Treat Recurrent Pediatric High-Grade Glioma (pHGG): A Europe-Wide Survey Study," *Journal of Neuro-Oncology* 161, no. 3 (2023): 525–538, https://doi.org/10.1007/s11060-023-04241-6.

22. A. Asklid, M. P. Nilsson, J. Engellau, et al., "Reirradiation in Paediatric Tumours of the Central Nervous System: Outcome and Side Effects After Implementing National Guidelines," *Clinical Oncology Royal College of Radiologists* 37 (2025): 103667, https://www.sciencedirect.com/science/article/pii/S0936655524004527.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Table S1: Grade 3 or higher acute toxicities during and after re-irradiation (RT2). **Table S2:** Review of previous pediatric CNS re-irradiation studies.