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Re-Irradiation in Pediatric Diffuse Midline Glioma: A Multi-Institutional Retrospective Study

Ajay Thomas Alex[1] | Sean P. Hassan[1,2,3] | Helen Benghiat[4] | Liam Herbert[4] | Jennifer Adamski[5] | Shivani Bailey[5] | Claire Esler[6] | Louise Brookes[6] | Molly Bamber[6] | Grace Koudou[6] | Karen Waite[6] | Julie Bennett[7,8] | Anirban Das[7] | Derek S. Tsang[1]

[1]Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada | [2]Arthur J.E. Child Comprehensive Cancer Centre, Calgary, Canada | [3]Department of Oncology, Division of Radiation Oncology, Cumming School of Medicine, University of Calgary, Calgary, Canada | [4]Hall-Edwards Radiotherapy Research Group, Queen Elizabeth Hospital, Birmingham, UK | [5]Division of Pediatric Neuro-Oncology, Birmingham Children Hospital, Birmingham, UK | [6]Nottingham City Hospital, Nottingham University Hospitals NHS Trust, Nottingham, UK | [7]Division of Hematology/Oncology, Hospital for Sick Children, Toronto, Canada | [8]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, Canada

Correspondence: Derek S. Tsang (derek.tsang@uhn.ca)

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ABSTRACT

Background: Children with recurrent diffuse midline gliomas (DMGs) have limited therapeutic options at recurrence. Re-irradiation (RT2) may be used at progression, but with uncertainty about the benefit.

Methods: We conducted a multi-institutional retrospective study of children aged < 18 with DMG treated at three centers (Toronto, Canada; Birmingham, UK; Nottingham, UK). Patients with radiologic progression after the first radiation (RT1) were included. Overall survival (OS) was calculated from the date of progression after RT1. Survival was analyzed using the Kaplan–Meier method. Multivariable Cox regression identified independent predictors of OS.

Results: A total of 167 patients were included with a median age of 7.9 years; 54 (32%) received RT2. Children selected for RT2 had a longer interval from RT1 to progression (0.79 vs. 0.52 years, $p < 0.0001$). Median OS from progression was longer in the RT2 group (0.59 years) compared to the no RT2 cohort (0.21 years; $p < 0.0001$). Six-month OS was 68% versus 16%, and 1-year OS was 19% versus 3%, respectively. Patients needing RT2 ≥ 1 year after RT1 had superior survival compared with earlier RT2 (0.81 vs. 0.42 years; $p = 0.0041$). Higher RT2 dose (≥30.6 Gy) showed a non-significant trend towards longer OS ($p = 0.086$). In multivariable analysis, use of RT2 was the strongest independent predictor of survival (HR 0.29, 95% CI 0.20–0.42; $p<0.0001$).

Conclusion: In this large, multi-institutional international cohort, children with DMG treated with re-irradiation at progression showed a survival benefit, supporting re-irradiation as a key component of salvage therapy.

1 | Introduction

Diffuse midline glioma (DMG) is a highly aggressive and infiltrative pediatric brain tumor arising in midline structures, most commonly the brainstem, where it is frequently referred to as diffuse intrinsic pontine glioma (DIPG). These tumors are characterized by H3K27 alterations and are associated with poor outcomes. DMG accounts for 80% of brainstem tumors and 10%

Abbreviations: 3DCRT, three-dimensional conformal radiation therapy; DIPG, diffuse intrinsic pontine glioma; DMG, diffuse midline glioma; IMRT, intensity-modulated radiation therapy; MRI, magnetic resonance imaging; OS, overall survival; QoL, quality of life.; RT1, First radiation therapy; RT2, Re-irradiation.

of pediatric high-grade gliomas. It has a median overall survival (OS) of 8–13 months and a 2-year survival rate of less than 10% [1, 2].

Given the eloquent location of these midline tumors, surgical resection is not feasible in most patients, and biopsy is possible but a higher-risk procedure. Radiation therapy remains a key component of definitive management. However, disease progression is almost universal. Systemic treatment approaches, including targeted therapies and immunotherapeutic strategies, have yet to show a clinically meaningful improvement in survival in either newly diagnosed or recurrent disease [3, 4]. During disease progression, treatment options are limited, and treatment is ultimately palliative. Re-irradiation has increasingly been used as a salvage approach, supported by small retrospective series and limited prospective studies [5–8]. However, there remain concerns by many care teams about the benefit of re-irradiation in this terminal disease, as well as a lack of clarity about optimal timing of radiation, dose, and fractionation [8].

Given the variability in clinical practice across jurisdictions, further real-world evidence is needed to define the role of re-irradiation in children with recurrent brainstem DMG. The objective of this multi-institutional retrospective study was to evaluate and compare survival in pediatric patients with recurrent brainstem DMG treated with re-irradiation versus those managed without re-irradiation [8].

2 | Methods

2.1 | Study Design

This was an international, multi-institutional, retrospective cohort study conducted at Princess Margaret Cancer Centre Toronto, Canada; Hall-Edwards Radiotherapy Research Group, Queen Elizabeth Hospital, Birmingham, UK; and Nottingham City Hospital, Nottingham, UK. Patients were eligible if they were less than 18 years old, diagnosed with DMG (biopsy-proven or radiographically defined), completed initial radiotherapy (RT1), and subsequently developed radiologic progression. Children who were treated with RT1 between 2010 and 2024 were included. Research ethics board approval was obtained.

2.2 | Data Collection

Clinical and treatment data were obtained from electronic medical records at each site. Variables collected included demographic characteristics, tumor site, biopsy status, histopathology, H3K27M status when available, enrollment in a therapeutic clinical trial, steroid exposure, RT1 and RT2 treatment parameters (dose/fractionation), early post-RT1 MRI findings, dates of radiologic progression, and survival outcomes. RT1 was defined as the first course of radiotherapy, which consisted of conventionally fractionated photon external beam radiotherapy, delivered predominantly to 54 Gy in 30 fractions. RT2 was defined as any second course of radiotherapy given after disease progression. RT2 parameters (dose, treatment volume) were determined by treating oncologist's discretion.

2.3 | Statistical Analysis

Baseline characteristics were compared between RT1-only and RT2 groups using the χ^2 test or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The primary endpoint was OS, calculated from the date of radiologic progression after RT1, and was compared between patients who received re-irradiation (RT2) and those who did not. Survival distributions were estimated using the Kaplan–Meier method and compared using the log-rank test. Statistical significance was defined as $p < 0.05$.

A multivariable Cox proportional hazards model was made to identify independent predictors of OS from the date of progression after RT1. Covariates included use of RT2, age, sex, biopsy status, histology, tumor grade, H3K27M status (if available), clinical trial enrollment, early post-RT1 MRI enlargement, steroid use, RT1 technique, and time from RT1 to progression. The analyses were performed in SAS version 9.4 (Cary, NC, USA).

3 | Results

A total of 167 patients who received RT1 for brainstem or DMG (H3K27-altered) and later had radiologic progression were included. The median age at RT1 was 7.9 years (IQR 5.8–11.0). The cohort had a balanced sex distribution (84 females, 50.3%; 83 males, 49.7%) and included patients treated at Princess Margaret Hospital, Toronto (118, 70.6%), Queen Elizabeth Hospital, Birmingham (28, 16.8%), and Nottingham City Hospital, Nottingham (21, 12.6%). Baseline characteristics are listed in Table 1 and were generally balanced between patients who received RT2 (54, 32.3%) and those who did not (113, 67.7%). All brainstem-located tumors considered DIPG. Of the total cohort, 150 patients had brainstem tumors (DIPGs) and 17 had non-brainstem DMGs. RT1 technique was the only strongly differential variable, with IMRT used more frequently in RT2 recipients (52/54, 96.3%) than in non-recipients (66/113, 58.4%; $p < 0.0001$). Other baseline factors, including age, sex, treatment site, biopsy status, pathology subtype, grade, H3K27M status, and RT1 dose/fractionation, did not significantly differ between groups. Molecular data were limited: BRAF status was available for 23 patients, with 1 BRAF-positive case who received RT2. FGFR/PDGFRA status was available for eight patients; one patient was FGFR-positive and did not receive RT2, while three patients had PDGFRA mutations, of whom one received RT2, and two did not. Biopsy was performed in 29/54 (53.7%) of RT2 patients versus 43/113 (38.1%) of patients treated without RT2 ($p = 0.056$). Four children received dordaviprone at any point during their disease course.

RT1 consisted predominantly of 54 Gy in 30 fractions (144/167, 86.2%), while the remaining patients received 39–40 Gy (12, 7.2%), 50.4 Gy (1, 0.6%), 55.8 Gy (2, 1.2%), or 59.4 Gy (2, 1.2%). Early MRI performed at around 6 weeks post-RT1 demonstrated radiologic enlargement in 60 patients (35.9%)—associated with post-radiotherapy inflammation or pseudo-progression—who were less likely to undergo RT2 (10/60, 16.7%) than those without early enlargement (44/107, 41.1%). Median progression-free survival after RT1 was 0.49 years (95% CI 0.44–0.56) for the full cohort. The median time from RT1 to progression was longer among patients who eventually underwent RT2 (0.79 years) than

TABLE 1 | Baseline characteristics, stratified by receipt of re-irradiation (RT2).

Characteristics		All patients ($n = 167$)	RT1-only ($n = 113$)	RT2 ($n = 54$)	p value
Age at start of RT1, years	Median (IQR)	7.9 (5.8–11.0)	7.8 (6.2–10.0)	8.8 (5.2–13.2)	0.38
Female sex		83 (49.7%)	58 (51.3%)	25 (46.3%)	0.54
Tumor site	Brainstem	150 (89.8%)	104 (92.0%)	46 (85.2%)	0.17
	Non-brainstem	17 (10.2%)	9 (8.0%)	8 (14.8%)	
Biopsy performed	Yes	72 (43.1%)	43 (38.1%)	29 (53.7%)	0.06
Tumor grade (biopsied, $n = 72$)	High grade	66 (91.7%)	38/43 (88.4%)	28/29 (96.6%)	0.39
	Low grade	6 (8.3%)	5/43 (11.6%)	1/29 (3.4%)	
H3K27M status (tested, $n = 51$)	H3K27M positive	51/51 (100%)	25/25 (100%)	26/26 (100%)	
Clinical trial enrolment	Yes	41 (24.6%)	30 (26.5%)	11 (20.4%)	0.39
RT1 technique	3DCRT	41 (24.6%)	40 (35.4%)	1 (1.9%)	< 0.0001
	IMRT	118 (70.7%)	66 (58.4%)	52 (96.3%)	
	Stereotactic	2 (1.2%)	2 (1.8%)	0 (0%)	
	Other/unknown	6 (3.6%)	5 (4.4%)	1 (1.9%)	
RT1 dose/fractionation	39 Gy/13 fractions	16 (9.6%)	11 (9.7%)	5 (9.3%)	0.84
	54 Gy/30 fractions	144 (86.2%)	96 (85.0%)	48 (88.9%)	
	Other regimens[a]	7 (4.2%)	6 (5.3%)	1 (1.9%)	
Steroid use during RT1[b]	Yes	142/158 (89.9%)	98/106 (92.5%)	44/52 (84.6%)	0.13
Steroid taper pattern[b]	Tapered after RT1	65/142 (45.8%)	51/97 (52.6%)	14/45 (31.1%)	0.054
	Completed at end of RT1	71/142 (50.0%)	42/97 (43.3%)	29/45 (64.4%)	
	Other/unknown	6/142 (4.2%)	4/97 (4.1%)	2/45 (4.4%)	

[a]Other RT1 regimens included 20 Gy/5 fractions, 40 Gy/15 fractions, 50.4 Gy/28 fractions, 55.8 Gy/31 fractions, and 59.4 Gy/33 fractions, each used in ≤2 patients.
[b]Steroid variables are reported among patients with available data (any dexamethasone use $n = 158$; timing of dexamethasone taper $n = 142$).

among those who did not (0.52 years) ($p < 0.0001$), suggesting its role as a treatment selection factor. Overall, 54 patients (32.3%) underwent re-irradiation (RT2). Characteristics of this sub-group undergoing RT2 are reported in Table 2.

OS from the time of progression was significantly longer in patients who received RT2 (0.59 years) than in those who did not (0.21 years; $p < 0.0001$) (Figure 1). Six-month and one-year OS estimates were 68% and 19%, respectively, among RT2 recipients versus 16% and 3%, respectively, among those not treated with RT2.

Subgroup analyses showed that 16 patients receiving RT2 ≥1 year after RT1 had longer survival (median 0.81 years) compared with the 38 patients treated earlier (median 0.42 years; $p = 0.0041$) (Figure 2). RT2 patients who received higher dose (≥30.6 Gy, $n = 29$) trended to improved OS, though not statistically significant (Figure 3), as compared to 20 children treated with RT2 doses <30.6 Gy. Age (<9 vs. ≥9 years), early MRI enlargement, and dexamethasone taper were not associated with OS after RT2 (not shown). When considering time from initial DMG diagnosis, OS was also longer in the RT2 group (1.38 years) than in the no-RT2 group (0.72 years; $p < 0.0001$) (Figure S1). We also did a subgroup analysis including only patients who had more than 6 months of disease-free interval after RT1. In this secondary survival analysis comparing children treated with or without re-irradiation, use of RT2 continued to be associated with a statistically significant lengthening of survival time ($p < 0.001$; Figure 4).

In multivariable Cox regression (Table 3), RT2 remained the strongest independent predictor of survival, associated with a 71% reduction in the hazard of death (HR 0.29; 95% CI 0.20–0.42; $p < 0.0001$). Older age at RT1 was also associated with improved survival, as well as participation in a clinical trial. Sex, pathology, grade, biopsy, H3K27M status, early MRI enlargement, steroid exposure, and time from RT1 to progression were also evaluated, but did not correlate with survival, and were not included in the final model. All covariates met proportional hazards assumptions except RT2, which showed a time-varying effect consistent with a prominent early benefit.

4 | Discussion

This is one of the largest known multi-institutional retrospective data evaluating re-irradiation in pediatric DMGs. Our analysis of 167 patients across the three tertiary centers showed a clinically meaningful benefit of re-irradiation toward OS. Median survival after progression was almost threefold longer in patients receiving re-irradiation as compared to those who did not (0.59 vs. 0.21 years). Re-irradiation was the strongest factor associated with survival in multivariable analysis. However, like all currently available treatments for this incurable tumor, re-irradiation remains a palliative treatment.

The survival outcome reported in our cohort is consistent with previously reported outcomes from smaller, single-institution

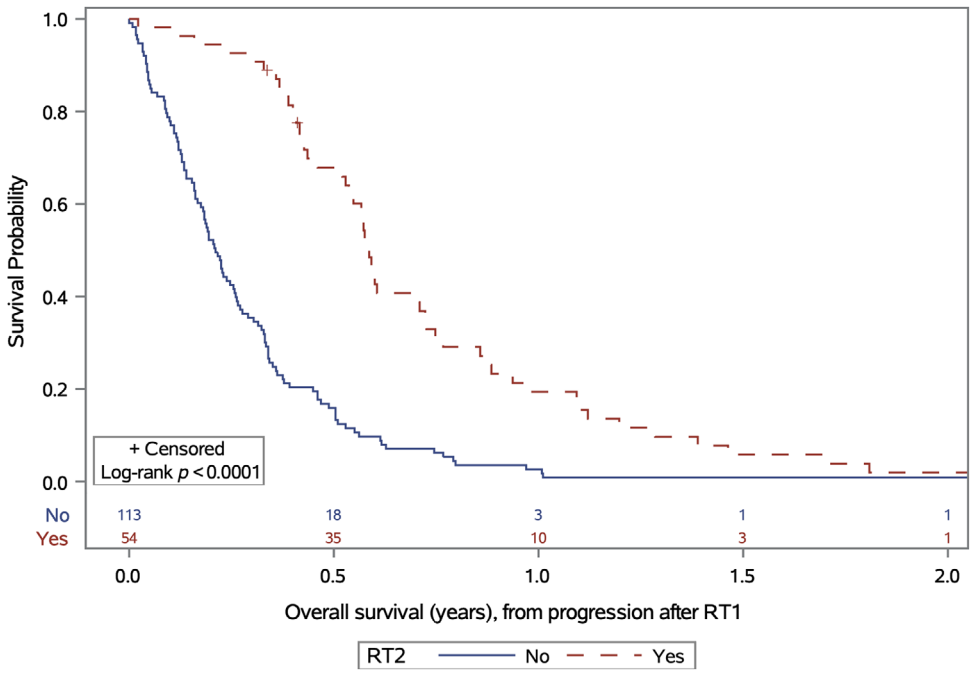

FIGURE 1 | Overall survival (years) from progression after RT1, comparing children undergoing RT2 versus no RT2.

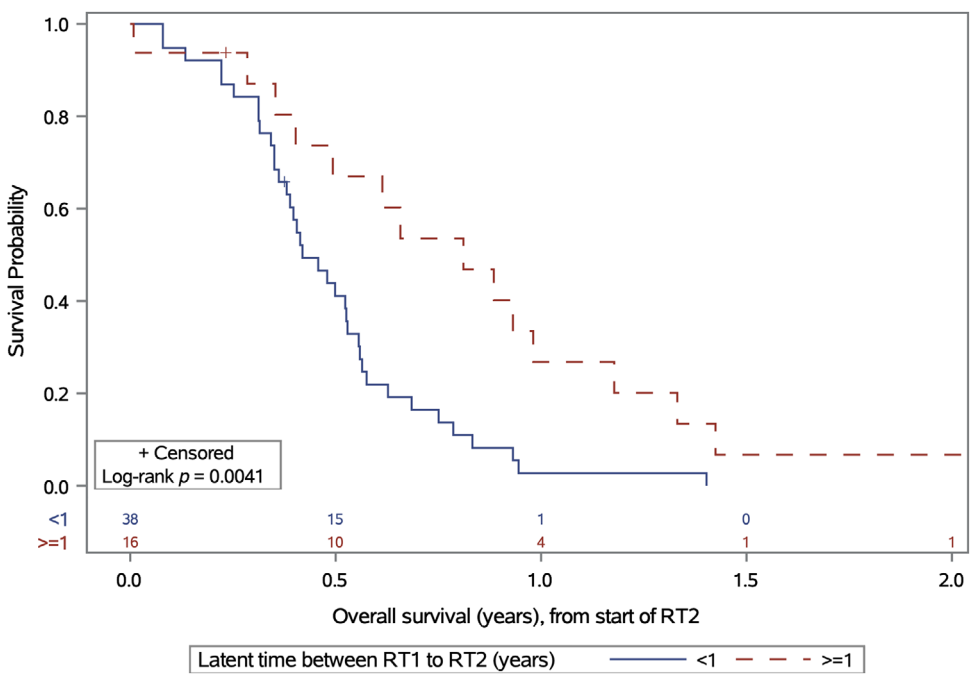

FIGURE 2 | Time between RT1 and RT2 in years, comparing survival after start of RT2.

retrospective studies. However, prior studies are limited by small sample size and heterogeneity. By incorporating the data from the three international centers, our study strengthens the evidence supporting a survival benefit for re-irradiation. The impact of re-irradiation timing is a significant finding of our analysis. Compared to patients treated earlier, those who received RT2 at least a year after their initial radiation therapy had noticeably better survival. In line with earlier results that identified time to progression as an indicator for tumor aggressiveness, this probably indicates a more favorable underlying disease biology in individuals with longer progression-free intervals. This observation reiterates the importance of patient selection and suggests that patients who have a long period of stability post-RT1 are most suitable for RT2; thus, our data help identify patients who are most likely to benefit more from RT2.

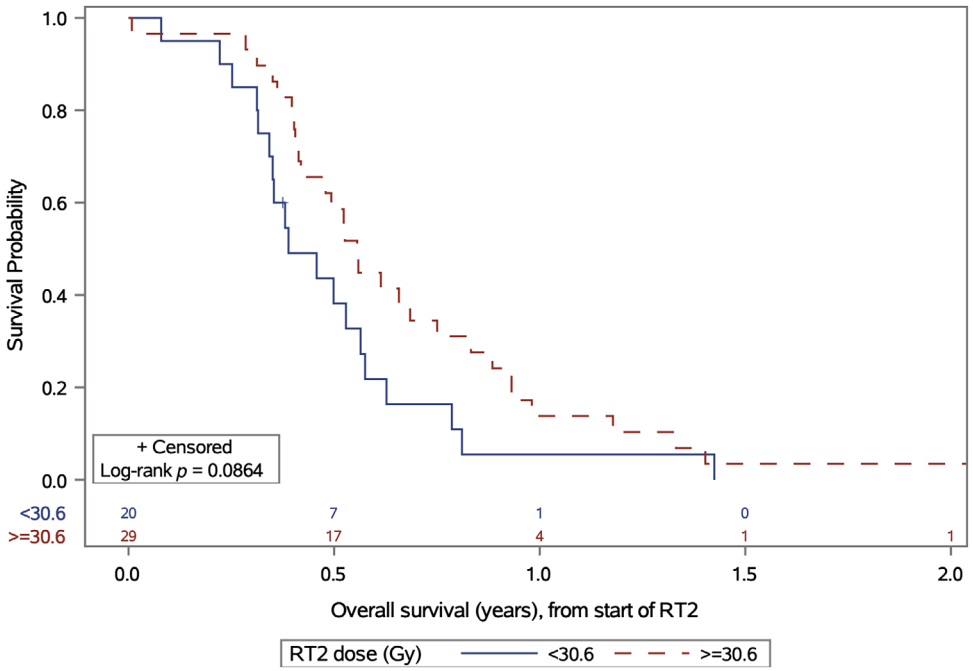

FIGURE 3 | Overall survival (years) from start of RT2, comparing RT2 dose <30.6Gy versus ≥30.6Gy.

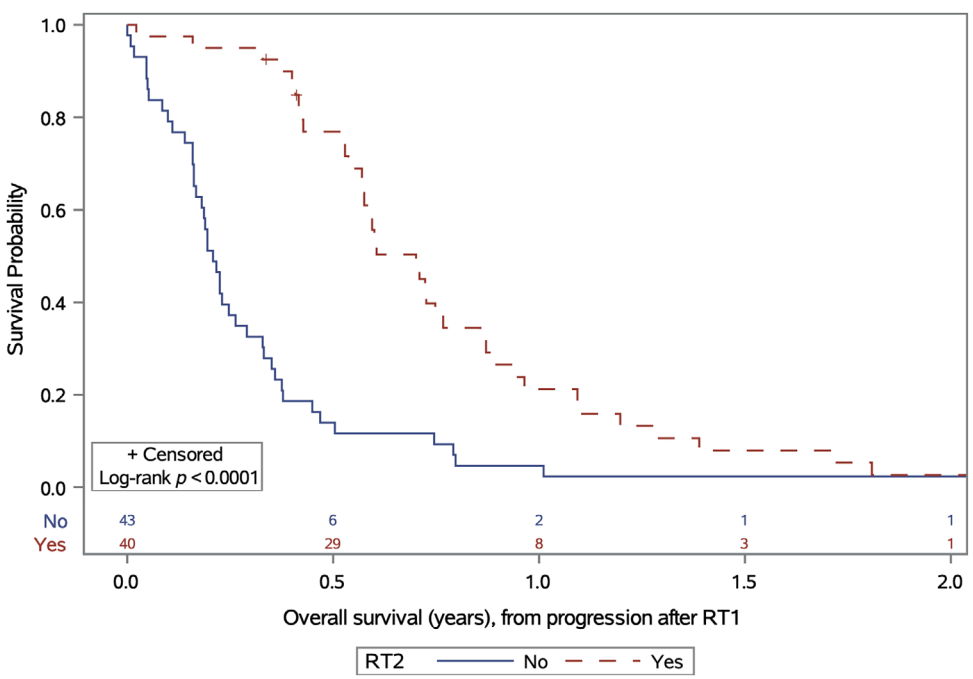

FIGURE 4 | Overall survival (years), comparing RT2 versus no RT2 in the subgroup of patients with a disease-free interval >6 months after RT1 ($p < 0.001$).

Additionally, we noticed a trend toward better survival with greater RT2 doses (≥30.6 Gy); however, this was not statistically significant. This is consistent with ongoing uncertainty over the ideal dose fractionation for re-irradiation in DMG. Even though a higher dose might improve the local control, the benefit must be weighed against the potential cumulative toxicity to brainstem structures. Furthermore, this trend may be confounded by the use of higher RT2 doses in children who have a longer latent period between RT1 and RT2. Overall, the most common re-treatment dose was 30.6 Gy in 17 fractions. Within the literature, a wide range of dose options are reported, ranging from 15 to 54 Gy, with 20, 24, and 30.6 Gy as common options [9]. In addition, there is emerging interest in the use of hypofractionated re-irradiation regimens to minimize time at cancer centers and

TABLE 2 | Radiotherapy planning details for re-irradiation (RT2).

Characteristic	Category	RT2 ($n = 54$)
RT2 technique	3DCRT	7/52 (13.5%)
	IMRT	45/52 (86.5%)
RT2 dose (Gy)	19.8 Gy	5 (9.3%)
	20.0 Gy (5–10 fractions)[a]	15 (27.8%)
	21.6–24.0 Gy	4 (7.4%)
	30.6 Gy	24 (44.4%)
	36.0–40.0 Gy[b]	6 (11.1%)
RT2 fractions	5–11 fractions	20 (37.0%)
	12–15 fractions	6 (11.1%)
	17 fractions	24 (44.4%)
	20 fractions	4 (7.4%)
RT2 field	Focal brain	42 (77.8%)
	Whole brain	5 (9.3%)
	Craniospinal	5 (9.3%)
	Spine only	2 (3.7%)
Latent time from RT1 to RT2, years	Median (IQR)	0.76 (0.55–1.02)

[a]20 Gy in 5 fractions was used in 5 patients, while 20 Gy in 10 fractions was used in 10 patients.

[b]36 Gy in 20 fractions was used in 4 patients, 39 Gy in 13 fractions was used in 1 patient, and 40 Gy in 15 fractions was used in 1 patient.

TABLE 3 | Multivariable analysis of factors associated with survival at the time of disease progression after initial radiation (RT1).

Characteristic	Adjusted hazard ratio	95% CI	*p* value
Use of re-irradiation (RT2)	0.29	0.20–0.42	< 0.001
Age at RT1 (per year increase)	0.93	0.89–0.87	0.0018
Clinical trial enrolment	0.67	0.47–0.97	0.0034
Brainstem tumor location	0.65	0.37–1.12	0.1215

maximize patient time at home [5]. Future studies should focus on identifying optimal dose and fractionation regimens in the setting of re-irradiation.

Since patients who received RT2 had a longer delay between RT1 and progression, indicating more favorable disease biology and clinical condition, selection bias is a potential limitation of our study. We used multivariable analysis to account for this, but residual confounding cannot be ruled out. Other factors that could have affected patient selection for RT2 include patient response to RT1, the child's performance status at recurrence, and family preference. Unfortunately, our study's retrospective design meant there were no data on patient-reported outcomes and quality-of-life (QoL) parameters. Amsbaugh et al. evaluated QoL in children in a small prospective study of children treated for DIPG [6]. Further QoL data in larger cohorts of children treated with re-irradiation are eagerly awaited, including data from ongoing studies at other institutions (e.g., ClinicalTrials.gov identifier NCT04670016). Finally, our study did not collect detailed information about the nature of clinical trial interventions among children enrolled in a study. Trial participants are known to have better survival outcomes due to a tendency to enroll individuals with better performance status and due to trial eligibility criteria that exclude poorer-performing patients [10]. It was also not possible to distinguish radiation necrosis from tumor progression; thus, we retained OS as the primary endpoint, rather than a surrogate such as progression-free survival; toxicity data were not available in our multi-institutional cohort due to the palliative course of children after RT2 and a desire not to systematically require children to return to the hospital for regular MR imaging evaluation.

Despite these limitations, our study has important clinical implications for patients with recurrent DMG, especially when there are limited systemic therapy options with meaningful survival benefit. Our results support adopting RT2 as a standard salvage option in children with recurrent DMG and diffuse intrinsic pontine glioma, particularly those with good performance status and longer latent interval from initial radiation.

5 | Conclusion

In this large multi-institutional dataset of children with DMGs, re-irradiation at progression was associated with a significant improvement in OS and emerged as the strongest independent predictor of outcome. Patients with longer intervals from initial radiotherapy showed longer survival benefit after re-irradiation. Most children were treated with 30.6 Gy (1.8 Gy per day), though the ideal dose of re-irradiation remains an area of future investigation.

Ethics Statement

As a minimal risk retrospective study, this project was reviewed and approved by the hospital research ethics board and conducted in accordance with the Declaration of Helsinki (2024 version); CAPCR-ID: 23–5325.

This is a retrospective study; patient consent was not required.

Conflicts of Interest

D.S.T. and J.B. are consultants with Need (need.ai), outside the submitted work. All other authors declare no conflicts of interest.

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Supporting Information

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

Supporting File 1: pbc70498-Supp-0001-SuppMatt.docx