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Original Article

# Re-irradiation for children with diffuse intrinsic pontine glioma and diffuse midline glioma

Nisha Shariff [a,b], Alejandro S. Moreno [a], Julie Bennett [c], Vijay Ramaswamy [c], Anirban Das [c], Anthony P. Liu [c], Annie Huang [c], Uri Tabori [c], Cynthia Hawkins [d], Peter Dirks [e], Eric Bouffet [c], Dana M. Keilty [a], Barbara-Ann Millar [a], David C. Hodgson [a], Derek S. Tsang [a,*]

[a] Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Canada
[b] Department of Clinical Oncology, University Malaya Medical Centre, Malaysia
[c] Division of Haematology/Oncology, Hospital for Sick Children, Canada
[d] Department of Paediatric Laboratory Medicine, Hospital for Sick Children, Canada
[e] Division of Neurosurgery, Hospital for Sick Children, Canada

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ABSTRACT

*Background and purpose:* Diffuse intrinsic pontine glioma (DIPG) and diffuse midline glioma (DMG) are incurable brain malignancies. In this study, we report one of the largest known single-institution cohorts of DIPG/DMG patients undergoing re-irradiation (RT2) to evaluate its effect on survival.
*Materials and methods:* Children aged less than 18 years treated for DIPG/DMG with initial fractionated photon radiotherapy (RT1) and had subsequent recurrence were retrospectively reviewed. Patients treated with or without RT2 were compared. The primary outcomes were overall survival (OS) from time of recurrence after RT1, and from start of RT2 (for the RT2 group).
*Results:* A total of 118 children were included, 39 of whom received RT2. Children treated with RT2 had superior OS, with 6-month OS of 66 % vs 22 % in those who did not undergo RT2 ($p < 0.0001$). Median survivals were 6.9 months for the RT2 group vs 2.7 months for RT1 only. Median time from RT1 to RT2 was 7.7 months; patients with a greater than 1-year latent time between RT1 and RT2 had longer OS from start of RT2 (median 10.9 months vs 5.5 months, $p = 0.023$). 61 % of those treated with RT2 experienced improvement of neurologic symptoms post-RT2. Multivariate analysis identified younger age, adverse imaging findings on the 4-week post-RT1 reassessment MRI (including pseudoprogression), and the absence of RT2 as poor prognostic factors for OS.
*Conclusion:* Re-irradiation was associated with improved survival and neurological recovery in children with recurrent DIPG and DMG. There is a need to identify novel biomarkers to better select patients who respond best to RT2.

## Introduction

Diffuse intrinsic pontine glioma (DIPG) accounts for 80 % of brainstem tumours and 10 % of all pediatric high-grade gliomas. The peak age of incidence is in children between 6 to 8 years of age [1]; individuals with typical radiologic appearances and symptoms have been treated empirically with fractionated radiation, without biopsy. Recently, histone 3 mutations have been found in a majority of patients with DIPG, which has been formally incorporated in the WHO CNS classification of brain tumors in 2016, with subsequent update in 2021 [2,3]. Pathologically, these tumours are termed diffuse midline glioma, H3 K27-altered (DMG). In a recent large meta-analysis, patients with H3 K27 mutations accounted for 63 % of DIPG and 60 % of non-brainstem midline tumours [4]. Regardless of location, median overall survival is 11 months and patients have a 2-year overall survival probability of 5 % with this mutation, making this a devastating diagnosis for children and their families who are diagnosed with DIPG or DMG [4].

Curative surgery is not possible due to the eloquent location. The role of biopsy has been increasing explored over the years to seek targetable mutations, though the need for a biopsy remains debated [1]. Systemic treatment has not clearly shown any substantial survival benefit in clinical trials, possibly due to lack of targetable mutations or insufficient

* Corresponding author at: 610 University Ave, OPG 7-316, Toronto ON M5G 2M9, Canada.
*E-mail address:* derek.tsang@uhn.ca (D.S. Tsang).

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drug delivery across the blood brain barrier. There is increased interest in new agents, novel drug delivery methods and new immunotherapy approaches in this disease [5].

Radiation remains the standard of care in this fatal disease [6] with re-irradiation (RT2) being used increasingly on progression, supported by some retrospective and limited prospective data. Previous studies have reported outcomes of DIPG treated with RT2, but without specifically including diffuse midline gliomas (DMG). Furthermore, comparisons of re-irradiated versus non-re-irradiated cohorts are lacking. The goal of this study was to report and compare outcomes of children with DIPG and DMG treated with one vs. two courses of radiation.

## Methods

### *Study design*

This was a retrospective study of patients aged 18 or less and diagnosed with diffuse intrinsic pontine glioma (DIPG) or diffuse midline glioma (DMG), H3 K27 altered, WHO grade 4. Children diagnosed between January 1998 and August 2024, treated at Princess Margaret Cancer Centre, and received radiation therapy as upfront treatment (RT1) with subsequent clinical or radiologic progression were eligible to be included. For patients with DIPG, diagnosis was made with established clinical criteria, including a short duration of neurologic symptoms and characteristic MR appearance [7]. Patients were offered the option of stereotactic biopsy to establish a diagnosis. Children with histologically confirmed pilocytic astrocytoma on biopsy or supratentorial high grade glioma without H3 K27 alteration were excluded. The study database was locked on September 8, 2024 for analysis. This study was reviewed by the hospital research ethics board (CAPCR 23-5325).

### *Treatments*

After MR imaging with clinical characteristics of DIPG (for non-biopsied patients) or after histologic confirmation of DMG (for biopsied patients), patients underwent radiotherapy with CT simulation and MRI prior to RT1 or RT2. All patients in our cohort were treated with photon radiation. Children were treated with conventional fractionation (1.8 Gy per day) for RT1 to a dose of 54 Gy; two patients with supratentorial primary tumours were treated to 59.4 Gy (Table 1). All patients had a reassessment MRI of the brain with gadolinium at four to six weeks after radiation for radiation response assessment. Thereafter, MRI surveillance was not routinely scheduled, though many patients had MRI upon clinical progression post-RT1.

Target delineation was performed by a radiation oncologist. For both RT1 and RT2, gross tumour volume (GTV) was the area of hyperintensity on FLAIR sequence and any gadolinium enhancement on MRI. Clinical tumour volume (CTV) was a 1 cm expansion from the GTV, editing for anatomical boundaries. A planning target volume (PTV) expansion of 3–5 mm was used. RT2 dose was determined by latent interval from RT1; for patients receiving RT2 less than 6 months from RT1, a dose of 20 Gy in 10 fractions was applied. Children with RT1-to-RT2 latent period of more than 6 months received 30.6 Gy in 17 fractions, while children with a latent period of more than 12 to 18 months received 36 Gy in 20 fractions. Longer latent interval between radiation treatments allows higher retreatment doses, taking into account recovery of normal organs and the brainstem to radiation. Variations were permitted based on treating oncologist discretion. There was no maximum cumulative brainstem dose applied during treatment planning for RT2. However, our institutional RT planning protocol allows for 95 % of the PTV to receive 95 % of the prescribed dose, and RT2 maximum dose to the brainstem was maintained at or below the RT2 prescription.

**Table 1**
Baseline characteristics, stratified by receipt of re-irradiation (RT2).

| Characteristics | Total N = 118 *Number (%)* | RT1-only n = 79 *Number (%)* | RT2 n = 39 *Number (%)* | p |
|---|---|---|---|---|
| Age at start of RT1, years, median (IQR) | 7.7 (5.8–10.7) | 7.7 (6.4–10.5) | 8.3 (5.2–11.8) | 0.85 |
| Female (%) | 61 (51.7) | 40 (50.6) | 21 (53.8) | 0.85 |
| Tumour site (%) | | | | |
| Brainstem | 107 (90.7) | 74 (93.7) | 33 (84.6) | 0.18 |
| Supratentorial* | 11 (9.3) | 5 (6.3) | 6 (15.4) | |
| Biopsy done (%) | 45 (38.1) | 26 (32.9) | 19 (48.7) | 0.11 |
| Grade (biopsied) | | | | |
| High | 39 (88.7) | 21 (26.6) | 18 (46.2) | 0.22 |
| Low | 6 (13.3) | 5 (6.3) | 1 (2.6) | |
| Histology | | | | |
| Astrocytoma grade 2 | 5 (11.1) | 13 (16.5) | 6 (15.4) | 0.02 |
| Astrocytoma grade 3 | 15 (33.3) | 1 (1.3) | 0 | |
| Glioblastoma grade 4 | 10 (22.2) | 8 (10.1) | 2 (5.1) | |
| DMG grade 4 | 14 (31.1) | 4 (5.1) | 10 (25.6) | |
| Ganglioglioma | 1 (2.2) | 0 | 1 (2.6) | |
| Clinical trial enrolment | 34 (28.8) | 24 (30.4) | 10 (25.6) | 0.67 |
| Radiation Technique at | | | | |
| RT1 | 32 (27.1) | 32 (40.5) | 0 (0) | <0.0001 |
| 3DCRT | 86 (72.9) | 47 (59.5) | 39 (100) | |
| IMRT | | | | |
| RT1 dose (Gy)/fractions | | | | |
| 50.4/28 | 1 (0.9)** | 1 (1.3) | 0 (0) | 1.0 |
| 54.0/30 | 113 (95.8) | 75 (94.9) | 38 (97.4) | |
| 55.8/31 | 2 (1.7)** | 2 (2.5) | 0 (0) | |
| 59.4/33 | 2 (1.7)*** | 1 (1.3) | 1 (2.6) | |
| RT2 dose (Gy)/fractions | | | | |
| 19.8/11 | | | 1 (2.6) | |
| 20.0/5 | | | 2 (5.1)**** | |
| 20.0/10 | | | 7 (17.9) | |
| 21.6/12 | | | 1 (2.6) | |
| 23.4/13 | | | 1(2.6) | |
| 24.0/12 | | | 1(2.6) | |
| 30.6/17 | | | 22 (56.4) | |
| 36.0/20 | | | 3 (7.8) | |
| 40.0/15 | | | 1 (2.6)***** | |
| RT2 field | | | | |
| Focal brain | | | 30 (77.0) | |
| Whole brain | | | 2 (5.1) | |
| Craniospinal | | | 5 (12.8) | |
| Spine only | | | 2 (5.1) | |
| Time from RT1 to RT2 | | | | |
| 3 to < 6 months | | | 7 (17.9) | |
| 6 to < 12 months | | | 22 (56.4) | |
| 12 months or more | | | 10 (25.6) | |
| Median time from RT1 to Progression (months) | 6.4 | 5.8 | 7.1 | 0.03 |

* DMG with H3 K27M alteration
** Brainstem tumor.
*** Supratentorial tumor.
**** Patients had 20 Gy in 5 fractions delivered to spinal (out-of-field) recurrence.
***** This patient received 40 Gy in 15 fractions for a distant brain (out-of-field) recurrence.

### *Endpoints*

We performed two primary analyses: a) overall survival (OS) from date of clinical or radiologic progression after RT1, to compare children who did or did not receive RT2; b) OS from start of RT2 to date of death, for children who did receive RT2. Secondary endpoints were clinical (neurological) improvement post-RT1 or post-RT2, dexamethasone use, and toxicities. Adverse imaging findings included any increase in size, bulk, mass effect, or enhancement of the tumor on MR imaging after RT1. Assessment of radiologic progression or response was based on neuroradiologist review. Pseudoprogression was defined as an increase

in tumour bulk, extent, enhancement, or size that stabilized or reduced on subsequent MRI. Disease progression was defined as documentation of new lesions, or persistent increase in tumour bulk, extent, enhancement, or size on MRI.

### *Analyses*

Baseline characteristics were compared with Fisher's exact test (categorical variables) or Wilcoxon signed-rank test (continuous variables). OS was calculated using the Kaplan-Meier method, while individuals alive at last follow-up were censored. A multivariable analysis was done using a Cox regression model, with index time at time of progression after RT1. A subgroup analysis for OS was done for patients who had radiologic confirmation of in-field recurrence post-RT1 with MRI. Results were considered statistically significant with a p-value of less than 0.05. Statistical analyses were done with SAS version 9.4 (Cary, NC).

## Results

### *Clinical characteristics*

One hundred and eighteen children were treated with RT1 for DIPG or DMG. All children had disease progression; the PFS after start of RT1 is reported in Supplementary Fig. 1. Of the 118 children treated with RT1; 39 (33 %) received RT2 upon progression. The median age at diagnosis was 7.7 years for the entire cohort. Baseline characteristics are listed in Table 1. No patient was lost to follow-up.

Biopsy was performed in 45 patients. A total of 24 patients who had H3 K27 testing were all confirmed to have H3 K27M mutation (with a pathologic diagnosis of DMG); clinically validated histone 3 testing was only routinely done for patients diagnosed after 2013. One patient with brainstem ganglioglioma was included in the study; molecular testing showed H3 K27M was present, while BRAF V600E was absent. No patient with histone 3 testing and H3 K27 negative were included in the analysis.

The median time from RT1 to RT2 was 7.7 months for the overall cohort (IQR 6.3–12.0 months) with a median of 11 days from progression after RT1 to the start of RT2. The median time from the start of RT1 to disease progression (median progression-free survival, PFS) was shorter in the RT1-only group than in the RT2 group (5.8 months vs 7.1 months, $p = 0.03$). Seven (18 %) patients in the RT2 group received radiation at an interval of less than 6 months from the start of RT1. Two patients did not complete RT2; one died during treatment, 3 days after starting RT2, due to complications from an extraventricular drain while the other patient declined further treatment after 16 Gy of planned 20 Gy due to neurologic deterioration during RT2. The time between start of RT1 to start of RT2 for these two patients was 12 and 6 months, respectively. Both patients were included in all analyses.

Two patients with distant brain relapse received whole brain RT2 to 30.6 Gy (1.8 Gy per day) while two patients with distant spinal relapse were treated with 20 Gy in five fractions. Both these patients were treated to the entire spine (patient 1: C2 to S2, patient 2: C2 to S3) for diffuse spinal leptomeningeal spread of tumour; CSI was not given due to a short latent interval between RT1 and RT2 (4 and 6 months). In five patients who received craniospinal irradiation (as part of RT2) for distant relapse, CSI was delivered with conventionally fractionated RT to doses of 23.4 Gy ($n = 1$), 30.6 Gy ($n = 2$) and 36 Gy ($n = 2$), followed by focal radiation boosts with doses of 39–54 Gy to the primary site as part of RT2.

### *Response to therapy and toxicities*

Clinical improvement was observed in 95 % of the patients after RT1, with 18 % having a complete clinical response of symptoms. Clinical response to RT1 was not used to guide selection of patients for RT2, with 38 of 39 patients receiving RT2 having had response to RT1, while 74 of 79 patients not re-irradiated had response to RT1 (97 % vs 94 %, $p = 0.66$). Dexamethasone was used in 94 % of the patients during RT1 and 60 % of the patients were able to taper off steroids by the end of treatment. In the overall cohort, 54 % of the patients were treated with systemic, tumour-directed therapy after RT1; of these, nine patients received ONC201 after RT1. A total of 21 patients received bevacizumab; 13 patients received this drug after RT1 (3 of which subsequently received RT2), for presumed tumour/radiation necrosis ($n = 11$) or as a steroid-sparing agent ($n = 2$).

A total of 92 % of the patients were treated with dexamethasone at RT2, and 61 % experienced clinical improvement of neurologic symptoms after RT2. Among the RT2 cohort, 8 patients received bevacizumab after RT2, for presumed tumour/radiation necrosis ($n = 4$), as a steroid-sparing agent ($n = 3$) or for post-RT2 edema ($n = 1$). No patient who finished re-irradiation experienced any other grade 3 or 4 toxicity or neurological deterioration during treatment. One death occurred during RT2 due to complications from a ventricular drain which was deemed not related to radiation treatment, as described previously.

### *Survival*

Patients who received RT2 had a longer median survival after progression from RT1 than those who were not treated with RT2 (6.9 months vs 2.6 months, $p < 0.0001$). The 6-month OS was 66 % (95 % CI 49–79) in the RT2 group vs. 20 % (95 % CI 12–30) in the RT1 group (Fig. 1). In a subgroup analysis of 64 patients who had radiologically confirmed in-field recurrence, those who received RT2 had longer OS, with a median survival of 6.5 months vs 3.3 months ($p < 0.0001$) and 6-month OS of 62 % (95 % CI 40–77) vs 24 % (95 % CI 12–39, Fig. 2). For patients who received RT2, a latent time of more than 1 year between RT1 and RT2 was associated with an improved median survival of 10.9 months when compared to patients with a shorter RT1-to-RT2 latent time (5.5 months, $p = 0.023$, Fig. 3). With an RT1-to-RT2 latent period cut-off point of 6 months, no statistically significant difference in OS was detected ($p = 0.63$, Supplementary Fig. 3). When using initial diagnosis as the index time, OS was significantly longer in the RT2 group (median 16.2 months) as compared to the RT1-only group (median 10.2 months, $p < 0.0001$, Supplementary Fig. 1). As an exploratory analysis, we also evaluated OS from first day of RT2 by known histone 3 mutation and RT2 dose, though RT2 dose was determined by time between RT1 and RT2 (Supplementary Fig. 2 and 4). Finally, PFS after RT2 is reported in Supplementary Fig. 5.

Multivariable analysis identified younger age, adverse imaging findings on the 4-week post-RT1 reassessment MRI (including pseudoprogression), and the absence of RT2 as poor prognostic factors for OS (Table 2). Use of dexamethasone during RT1 ($p = 0.34$), ability to taper dexamethasone after RT1 ($p = 0.67$) or neurological improvement after RT1 ($p = 0.28$) were not prognostic for survival after progression post-RT1. Furthermore, tumor location (brainstem vs. supratentorial, $p = 0.32$), use of biopsy ($p = 0.07$), histologic grade ($p = 0.16$) and use of bevacizumab ($p = 0.20$) were also not associated with survival after progression post-RT1. Finally, known histone 3 mutation (conferring a pathologic diagnosis of diffuse midline glioma) was not prognostic in this cohort of DIPG ($p = 0.9998$, see Supplementary Table 1). Receipt of any tumour-directed systemic therapy trended to an association with survival after progression post-RT1 ($p = 0.051$), but this effect was lost after adjustment for other variables and was not included in the final multivariable model (Table 2).

## Discussion

Our study is the largest known study comparing re-irradiation to no re-irradiation conducted at a single institution. Our results are concordant with those of previous retrospective reports, as summarized in Table 3. The median OS with RT2 was 6.9 months (measured from

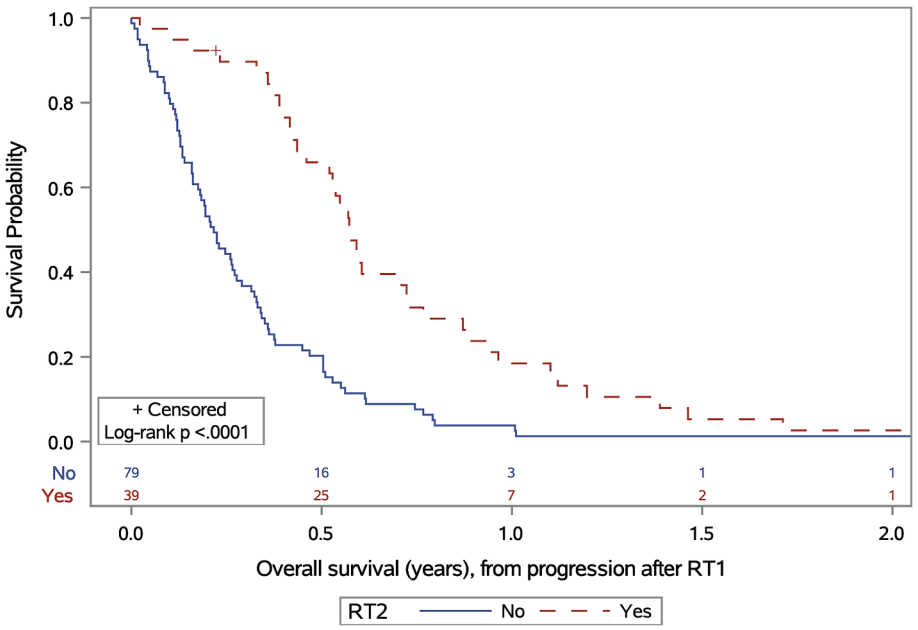


**Fig. 1.** Overall survival, with index time at progression after RT1.

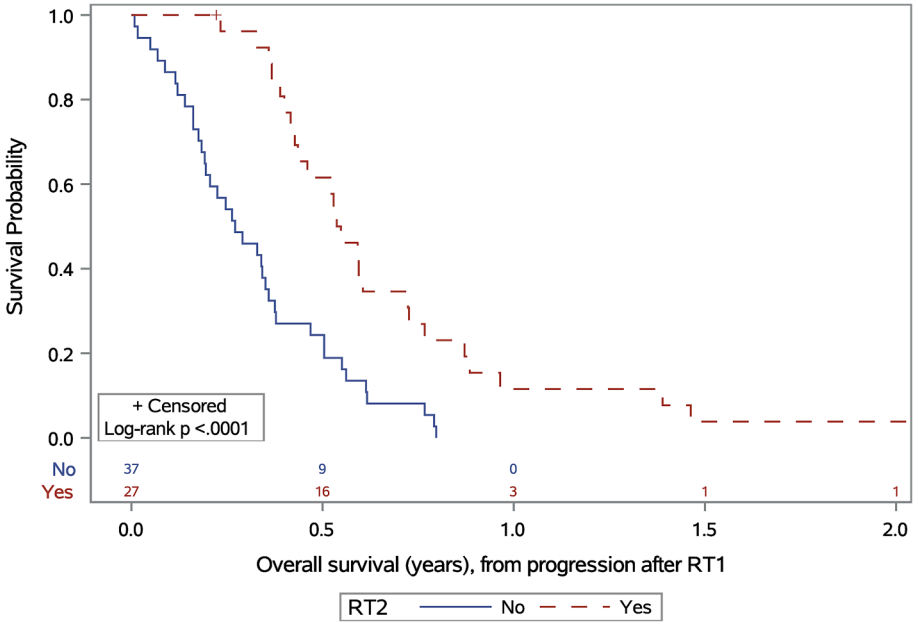


**Fig. 2.** Overall survival, with index time at progression after RT1, in the subgroup of patients who had radiologically confirmed in-field progression after RT1.

progression after RT1) when compared to other studies that reported an overall survival after reirradiation in the range of 2 to 8.2 months. A large pooled analysis of 409 patients from the GPOH HIT-HGG and SIOPE DIPG/DMG Registry reported an improved median survival of 6.6 months with RT2 upon relapse, as compared to 2.2 months for those who did not receive further treatment [8].

A longer interval between RT1 and RT2 was associated with improved survival in patients who received re-irradiation. This has been reported in previous studies [9 10,11,12] and was likely due to more indolent tumour biology in children with longer interval to progression after RT1. However, in the seven patients that were re-irradiated less than 6 months from RT1, all completed RT2 and 4 patients experienced partial clinical improvement. This shows that re-irradiation is feasible with potential for clinical benefit, even when given a short disease-free interval post-RT1.

Clinical improvement after RT1 was reported in 95 % of patients, while 61 % patients had reduced symptoms after RT2. This was comparable with data reported by previous studies where 77–92 % of patients experienced neurological improvement after reirradiation [10,11,13,14]. A successful dexamethasone taper was not shown to be associated with OS in our patient cohort. Two previous studies showed that steroid independence after RT1 was associated with improved progression free and OS when compared to steroid dependence [14,15]. This could be due to differences in the clinical practice of steroid use or the small number of patients who were steroid-dependent after RT1 in our re-irradiated cohort (24 steroid-free vs. 8 steroid-dependent patients).

Our study also included diffuse midline gliomas, which were first defined by the World Health Organization in 2016 [2], and updated in 2021 [3]. We chose to include DMG in our cohort because, as a

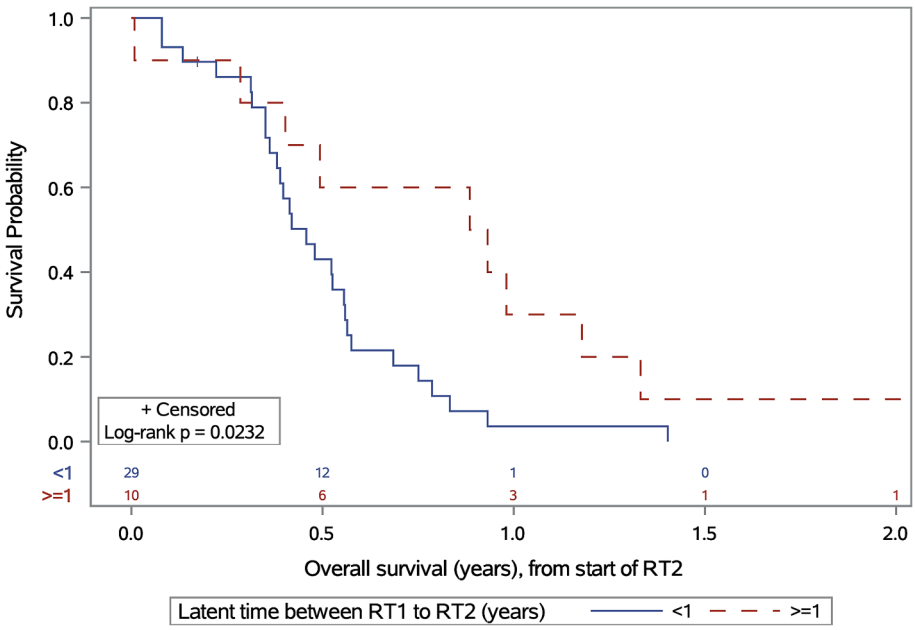


**Fig. 3.** Overall survival in re-irradiated patients only, stratified by latent time between RT1 and RT2.

**Table 2**
Multivariable Cox regression model evaluating factors associated with overall survival for entire cohort (N = 118).

| Variable | Hazard Ratio | 95 % Confidence Interval | p |
|---|---|---|---|
| Age at start of RT1 (per year increase) | 0.92 | 0.87–0.97 | 0.004 |
| Any enlargement of tumor on 1st MRI post-RT1 | 1.45 | 0.97–2.15 | 0.070 |
| RT2 given | 0.36 | 0.24–0.55 | <0.0001 |

molecularly driven disease, the behaviour of DMG is likely similar to DIPG, a majority of which harbour histone 3 mutations. A previous study showed that tumours with H3.1 K27 mutations may have a better survival after RT2 than those with H3.3 K27 mutations [15] (4.9 vs 2.7 months) and future studies should perform comprehensive next-generation sequencing (NGS) to identify as-yet unknown molecular factors associated with responses to RT.

There have been few prior reports of CSI as part of salvage therapy for distant recurrence of DIPG or DMG. Investigators in Spain reported a 10-year-old child treated with 21.6 Gy CSI as RT2, fifteen months after initial focal RT1 of 54 Gy to the brainstem [16]. There is some pre-clinical data suggesting CSI may decrease metastatic disease burden in a mouse model [17]. In our series, five patients received CSI as part of RT2. Further study with larger cohorts is required to determine whether CSI provides a benefit over focal re-irradiation to metastatic sites, and to determine the optimal dose of RT2 with CSI. Mature data from a prospective Italian trial that incorporated 36 Gy CSI for distant relapse is eagerly awaited [18].

In our data, re-irradiation was associated with a survival benefit compared to no re-irradiation. The median time to progression after RT1 in the RT1-only group was shorter than that in the RT2 cohort, which reflects possible selection bias, in that patients whose tumours recurred rapidly after RT1 were less likely to be offered RT2. Consistent with our finding that patients with a longer latent time between RT1 and RT2 derived more absolute survival benefit from RT2, patients whose tumours have better prognostic characteristics and longer expected survival after upfront treatment may be more suited to undergoing re-irradiation [19]. Furthermore, there is a possibility of the RT2 cohort was biased towards longer survival due to immortal time bias, since patients in that cohort could not have died in the time between progression post-RT1 and initiation of RT2. However, we believe the effect of this bias was minimal because the median time from RT1 progression to the start of RT2 was 11 days. Considering the observed difference in median survival of 4.3 months with re-irradiation, this potential source of bias was not clinically significant.

Our study is unable to evaluate specific RT2 doses on survival because dose selection was made based on latent interval between RT1 and RT2. The most common RT2 dose was 30.6 Gy in 17 fractions, which was reserved for patients with more than six months from RT1. There is wide practice variation in RT dose selection globally [20]; a study by Amsbaugh et al suggested 24 Gy in 12 fractions may be most beneficial [13], while other groups have evaluated hypofractionated RT2 [21] to minimize burden of therapy. Furthermore, only a minority of patients in our cohort underwent biopsy and NGS; better clinical and molecular biomarkers are needed to identify patients who will benefit from therapies such as re-irradiation or novel targeted medications. A recently closed prospective phase II trial, ReRAD, will provide more evidence regarding the use of RT2 (NCT03126266). High-quality, prospective data are eagerly awaited to better define the benefits of re-irradiation in DIPG.

## Conclusions

Re-irradiation for children with DIPG or DMG was associated with longer survival after disease progression post-RT1. This study supports other published data and confirms RT2 as a beneficial palliative treatment for this incurable disease. Novel biomarkers and confirmatory prospective data are needed to better select patients most suited to RT2 and identify the ideal re-irradiation dose-fractionation.

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## CRediT authorship contribution statement

**Nisha Shariff:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alejandro S. Moreno:** Writing – review & editing, Project administration, Data curation. **Julie Bennett:** Writing – review & editing, Validation. **Vijay Ramaswamy:** Writing –

**Table 3**
Studies published on reirradiation for DIPG/DMG.

| Paper | RT1, N | RT2, N | RT2 total dose, Gy (Gy per fraction) | Median OS from diagnosis (RT1 group), months | Median OS from diagnosis (RT2 group), months | Median OS after relapse (RT1 group), months | Median OS after relapse (RT2 group), months |
|---|---|---|---|---|---|---|---|
| Present study | N = 79 | N = 39 | 19.8–36 (1.8–2)** | 10.2 | 16.2 | 2.6 | 6.9 |
| Fontanilla et al (2012) [22] | | N = 6 | 18–20 (1.8–2) | | | | 6* |
| Massimino et al (2014) [23] | N = 11 | N = 14 | 19.8 (1.8) | 12 | 16 | | 6* |
| Vanan et al (2015) [24] | | N = 10 | 21.6–36 (1.8) | | | | 9* |
| Freese et al (2017) [25] | N = 24 | N = 3 | 20 (2) | 12 | 18 | | 2* |
| Lassaletta et al (2017) [9] | | N = 16 | 21.6–36 (1.8–3) | 11.3 | 19.3 | | 6.5* |
| Janssens et al (2017) [26] | N = 39 | N = 31 | 18–30 (1.8–3) | 10.3 | 13.7 | | |
| Lobon-Iglesias et al (2017) [15] | N = 100 | N = 14 | | 13 | 19.8 | 4 | 7.5 |
| Kline et al (2018) [27] | N = 19 | N = 12 | 24 (2–2.4) | 8.3 | 20.4 | | 6* |
| Amsbaugh et al (2019) [13] | | N = 12 | 24–30.8 (2–2.2) | | 19.5 | | 5.8* |
| Zamora et al (2021) [12] | | N = 5 | 20–24 (2) | | N/a | | 3.9* |
| Krishnatry et al (2021) [14] | | N = 20 | 21.6–45 (1.8) | | 16.6 | | 5.5* |
| Mankuzhy et al (2024) [17] | | N = 20 | 20–36 (2–3) | | 18 | | 7.5 – 8.2* |
| Panizo-Morgado et al (2024) [10] | | N = 44 | 18–40 (1.3–4) | | 15.5 | | 4.2* |

Blank values = not available or not applicable.
*overall survival from RT2 to death.
**In-field re-treatments only.

review & editing, Validation. **Anirban Das:** Validation. **Anthony P. Liu:** Validation. **Annie Huang:** Validation. **Uri Tabori:** Validation. **Cynthia Hawkins:** Validation. **Peter Dirks:** Validation. **Eric Bouffet:** Writing – review & editing, Validation. **Dana M. Keilty:** Validation. **Barbara-Ann Millar:** Validation. **David C. Hodgson:** Validation. **Derek S. Tsang:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Methodology, Formal analysis, Conceptualization.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: DST is a consultant with Need (https://www.getneed.com/), unrelated to this study.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.110865.

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