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Three and Four Courses of Radiation for Children with Recurrent Diffuse Intrinsic Pontine Glioma

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ABSTRACT

Purpose: Re-irradiation (RT2) for children with diffuse intrinsic pontine glioma (DIPG) is increasingly used upon recurrence; however, limited data are available for evaluating additional courses of radiotherapy (RT) for DIPG. The purpose of this case series was to report our institutional experience in treating patients with recurrent DIPG with three (RT3) or four (RT4) courses of RT.

Material and Methods: A retrospective study of all children with DIPG treated with RT3 or RT4 at a single institution was performed. Medical records were reviewed, and composite dosimetry across all delivered courses of RT was reconstructed. All patients received conventionally fractionated photon RT at 1.8–2 Gy per day, with RT3 or RT4 dose prescriptions ranging 18–21.6 Gy in 10–12 fractions to the brainstem.

Results: Five patients were identified; four received three courses of RT while one received four to the brainstem. Median survival from the last course of radiation to death was 4 months; median survival from the first course of RT was 26 months. The median cumulative brainstem D0.03cc for all courses of radiation was 104 Gy (interquartile range: 102–112 Gy). The median time from RT2 to RT3 was 8 months, with partial neurologic recovery (80%) or stable symptoms (20%) after RT3. Radiological appearance of tumor or brainstem necrosis was reported in two patients after RT3 (40%).

Conclusions: A third course of RT may be carefully considered as a treatment option for selected children with recurrent DIPG to provide palliation of neurologic symptoms.

1 | Introduction

Diffuse intrinsic pontine glioma (DIPG) is a fatal disease with no curative treatment. Diagnosis is commonly radiological, with biopsy being used more frequently in recent years to identify targetable molecular alterations and to better understand the biology and prognosis of these patients [1]. However, the role of biopsy remains debatable given the risk of the procedure, sampling bias, and diagnostic yield of these biopsies [1]. If a biopsy is done, the majority of DIPG harbors a characteristic mutation in histone 3 and are pathologically termed diffuse midline gliomas, H3 K27-altered [2, 3].

Abbreviations: CSI, craniospinal irradiation; CTV, clinical target volume; D0.03cc, dose received by 0.03 cm^3; DIPG, diffuse intrinsic pontine glioma; FLAIR, fluid-attenuated inversion recovery; GTV, gross tumor volume; IQR, interquartile range; ONC201, dordaviprone; PTV, planning target volume; RT, radiation therapy; RT1, upfront radiation treatment; RT2, re-irradiation; RT3, three courses of radiation; RT4, four courses of radiation.

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Curative surgery is not an option in DIPG due to the anatomic location as well as the diffuse nature of these tumors [4, 5]. No effective systemic options have been identified [6], leaving radiation therapy (RT) as the mainstay of treatment for these patients. Dexamethasone serves as a bridge prior to definitive treatment and is usually weaned off to minimize the adverse effects of corticosteroids [5]. Despite steroids and radiation, most patients progress within 6–8 months after radiation, and median survival is 12 months even with radiation [1, 6, 7]. Re-irradiation (RT2) is an effective but temporary strategy that has been shown to prolong survival in retrospective studies [8, 9]. However, the role of second and third re-irradiation is unclear and limited to case reports or small case series [10–12]. The purpose of this study is to add to this limited body of literature by reporting on patients with DIPG who received three (RT3) or four courses of RT (RT4) and their outcomes.

2 | Methods

This is a retrospective case series of patients treated with three or four courses of radiation for recurrent DIPG between January 1998 and August 2024 at a single institution. Medical records and digital radiotherapy plans were reviewed. This study was reviewed and approved by the hospital research ethics board.

After magnetic resonance imaging (MRI) and symptoms characteristic of DIPG [5] or confirmatory biopsy demonstrating diffuse midline glioma with H3 K27 alteration, patients underwent upfront fractionated radiotherapy (RT1). All courses of RT were delivered with a daily dose of 1.8–2 Gy per fraction. Treatment planning was with intensity-modulated radiotherapy or volumetric modulated arc therapy, except for Patient 5 who was treated with 3D conformal radiotherapy for RT3 (due to clinical urgency of treatment start). All patients were treated with photon radiation for all courses of RT. Routine contrast-enhanced MRI was obtained for children 4–6 weeks after each course of RT and at the time of any symptomatic change. Patients were clinically evaluated every 2–4 months until death. Re-irradiation was offered to patients with clinical, symptomatic progression and was confirmed with MRI findings of disease progression. RT2 dose was determined by latent interval from RT1; patients with RT1-to-RT2 latent period of more than 6 months received 30.6 Gy in 17 fractions. At the oncologist's discretion, institutional policy permitted a prescription of 36 Gy in 20 fractions for children with a latent period of greater than 12 months; no child received RT2 of greater than 30.6 Gy in this report. The treatment dose for RT3 was 18–21.6 Gy in 10–12 fractions for all patients.

Target volumes were contoured with the aid of a contrast-enhanced MRI study. For all courses of RT, the gross tumor volume (GTV) included the area of hyperintensity on fluid-attenuated inversion recovery (FLAIR) sequence and gadolinium enhancement on MRI (if present). Clinical target volume (CTV) was a 1 cm expansion from the GTV, edited for anatomical barriers to spread (i.e., tentorium). A planning target volume (PTV) of 3 mm was used for all courses of RT. There were no maximum cumulative brainstem dose constraints applied during radiation planning; however, (a) institutional RT planning protocol allows coverage of 95% of the PTV to receive 95% of the prescribed dose; (b) maximum dose to the brainstem (voxel max) was maintained at or below prescription dose. Therefore, for a patient prescribed 20 Gy re-irradiation, at least 95% of the PTV volume would be covered by the 19 Gy isodose line, with a brainstem D_{max} or dose received by 0.03 cm^3 (D0.03cc) at or below 20 Gy. Where stated, equivalent doses in 2 Gy fractions (EQD2) and biologically effective doses (BED) were calculated [13], assuming $\alpha/\beta = 2$.

To calculate cumulative doses received by the brainstem, archival plans from both Pinnacle (v9.8) and RayStation (v6, v8, and v10B, RayStation Laboratories, Stockholm, Sweden) treatment planning systems were anonymized and imported into a single treatment course for each patient within RayStation. Planning CT scans for all radiation courses were rigidly registered, and the cumulative brainstem dose was summed for all plans based on these rigid registrations. The PTV for each radiation plan (in cm^3) was recorded alongside the volume of intersection of the PTV for each radiation course for a given patient.

In a secondary, post hoc analysis, we compared children with DIPG treated at our institution with RT2 only and those treated with RT3. Overall survival was calculated using the Kaplan–Meier method, and groups were compared using the log-rank test. The index time was the date of disease progression after RT2. Statistical analysis was done using SAS version 9.4 (Cary, NC).

3 | Results

A total of five eligible patients were identified: four children received three and one child received four courses of radiation to the brainstem. One patient (Patient 4) received radiation to spinal metastases after three courses of radiation to the brainstem; this out-of-field course of RT was not considered re-irradiation for the purpose of this study. Patient characteristics and clinical course are detailed in Tables 1 and 2, respectively. Patients received a median maximum cumulative brainstem dose (D0.03cc) of 104 Gy (interquartile range [IQR]: 102–112 Gy); the distribution of brainstem doses is shown in Figure 1. Radiation planning indices are reported in Table 3. PTV over time, across each course of RT, is shown in Figure 2. Cumulative prescription doses, reported as equivalent doses in 2 Gy fractions (EQD2) and biologically effective dose (BED), are shown in Table S1; median total EQD2 and BED were 100.4 Gy and 200.7 Gy_2, respectively. Four patients in our series progressed with disseminated disease, three intracranial, and one spinal; the median survival after diagnosis of metastases was 7.5 months (IQR: 3.5–14).

All patients had clinical benefits from radiation, with stabilization of symptoms or partial neurological recovery. Median survival from the last radiation to the brainstem was 4 months (IQR: 3–6), while median survival after the initial course of radiation was 26 months (IQR: 16–33). When comparing children treated with RT3 versus those treated with RT2 only, children selected for RT3 had longer median survival from the time of disease progression after RT2: 5.4 months (RT3 group), as compared with 2.1 months (RT2 only, $p = 0.001$; Figure S1). All patients in the RT3 group were deceased at the time of analysis. Herein, we provide a short narrative description of each patient.

TABLE 1 | Baseline characteristics and courses of radiation for all patients.

Patient	Sex	Age at diagnosis	Histology	RT1 Dose (Gy/fractions)	RT2 Interval RT1–RT2 (months)	RT2 Dose (Gy/fractions)	RT3 Interval RT2–RT3 (months)	RT3 Dose (Gy/fractions)	RT4 Interval RT3–RT4 (months)	RT4 Dose (Gy/fractions)	Survival after RT1 (months)	Survival after last course of RT to brainstem (months)
1	M	10	None	54/30	6	30.6/17	9	18/10			14	3
2	F	3	None	54/30	15	30.6/17	4	20/10			26	4
3	M	6	None	54/30	10	30.6/17	10	20/10	5	18/10	38	8
4	F	14	High-grade astrocytoma H3 K27M	54/30	12	30.6/17	8	20/10	3	8/1 *(cervical spine)*	28	6
5	F	6	None	54/30	9	30.6/17	5	21.6/12			19	3

Note: All courses of RT were directed at the brainstem unless specified otherwise.
Abbreviations: RT1, first course of radiation; RT2, second course of radiation; RT3, third course of radiation; RT4, fourth course of radiation.

3.1 | Patient 1

Patient 1 presented with a history of dysphagia, ophthalmoplegia, and blurring of vision. He was treated with radiation for a radiological diagnosis of DIPG with 54 Gy in 30 fractions. He had a partial clinical response and was able to attend school and play soccer after RT1. He was on dexamethasone during treatment and was weaned off by the end of radiation. He had clinical and radiological progression 5 months after initial radiation with right-sided leg weakness and limping. He completed RT2 to a dose of 30.6 Gy in 17 fractions and experienced neurological improvement with his ataxia. During RT2, he experienced vertigo, uncontrolled serum glucose, and weight gain while on dexamethasone treatment. He started on dordaviprone (ONC201 [14]) following RT2 and received treatment for 2 months. Three months after completion of RT2, he developed neurological deterioration with supratentorial extension of the pontine tumor and obstructive hydrocephalus. The family was offered surgical cerebrospinal fluid (CSF) diversion [15], but they declined; he was re-treated with RT3 of 18 Gy in 10 fractions. During treatment, he clinically improved with a decrease in the severity of hydrocephalus but remained non-ambulatory. He was treated with acetazolamide during RT3 and started on bevacizumab after completion of RT3 as a steroid-sparing strategy. He weaned off steroids 4 weeks after completion of RT3. He died 3 months after completion of RT3 in the hospital due to neurologic decline, aspiration, and respiratory failure.

3.2 | Patient 2

Patient 2 presented with symptoms of ataxia and emesis. She started radiation based on a radiological diagnosis of DIPG and completed 54 Gy in 30 fractions to the brainstem. She was started on dexamethasone during radiation for worsening ataxia and was weaned off prior to the end of RT1. She had a complete neurological recovery and was able to attend school. Fifteen months after RT1, she had clinical progression with worsening gait. MRI showed local tumor progression and new lesions in the left thalamus and lateral geniculate body, with no spinal or leptomeningeal metastases. She was re-treated with RT2 of 30.6 Gy in 17 fractions including all sites of dissemination and had partial neurological improvement with residual ophthalmoplegia. She presented with seizures 4 months after RT2, and disease progression was confirmed on MRI. She underwent a third ventriculostomy for symptomatic hydrocephalus and later underwent RT3 at 20 Gy in 10 fractions. One month after completion of RT3, she was started on bevacizumab for radiological evidence of tumor necrosis with some clinical improvement but remained mostly non-ambulatory. She died 4 months after RT3 at home.

3.3 | Patient 3

Patient 3 presented with ataxia, dysarthria, and vomiting and was diagnosed with DIPG based on MRI findings with mild hydrocephalus. He was treated with radiation 54 Gy in 30 fractions and concurrent dexamethasone. He experienced partial clinical improvement after radiation with mild residual dysmetria and hemiparesis. He was fully active and was able to attend school. He had neurological and radiologic progression 10 months

TABLE 2 | Clinical response to radiation and toxicities.

	RT1		RT2		RT3		RT4		Radiation/Tumor necrosis	
Patient	**Response**	**Dexamethasone taper**	**Response**	**Dexamethasone taper**	**Response**	**Dexamethasone taper**	**Response**	**Dexamethasone taper**	**Imaging findings**	**Bevacizumab**
1	Partial, ambulatory	End	Partial, ambulatory	After	Partial, non-ambulatory	After			No	Yes (after RT3)
2	Complete, ambulatory	End	Partial, ambulatory	End	Partial, ambulatory	After			Yes (after RT3)	Yes (after RT3)
3	Partial, ambulatory	After	Partial, ambulatory	After	Partial, ambulatory	After	Partial, ambulatory with walking aid	After	Yes (after RT3)	No
4	Complete, ambulatory	After	Partial, ambulatory	After	Stable, ambulatory	After	*Partial pain relief, non-ambulatory (Cervical spine)*	*After*	Yes (after RT1)	No
5	Complete, ambulatory	End	Complete, ambulatory	After	Partial, non-ambulatory	After			No	No

Note: Dexamethasone taper describes whether patients were able to taper off dexamethasone at the end of the course of radiation ("End"), or continued with dexamethasone taper after completion of the course of RT ("After"). Radiation or tumor necrosis describes imaging findings of T1 ring-enhancing lesion(s) within the irradiated brainstem tumor.

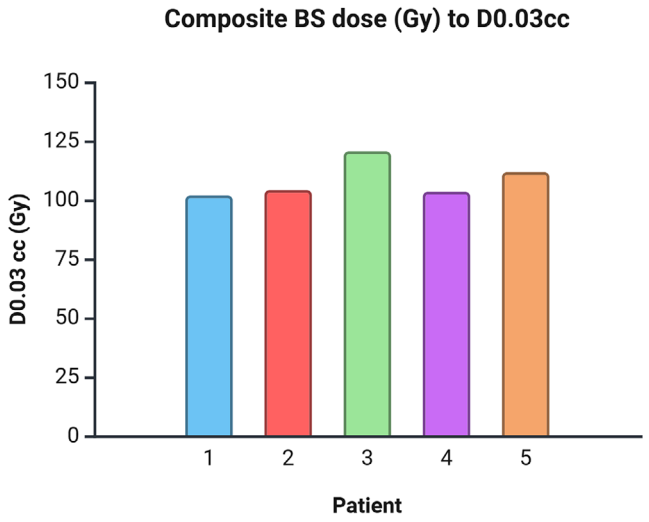

FIGURE 1 | Cumulative brainstem (BS) doses (dose to 0.03cc, D0.03cc) received by each patient. The highest cumulative BS dose is for Patient 3, who received four courses of radiation to the brainstem.

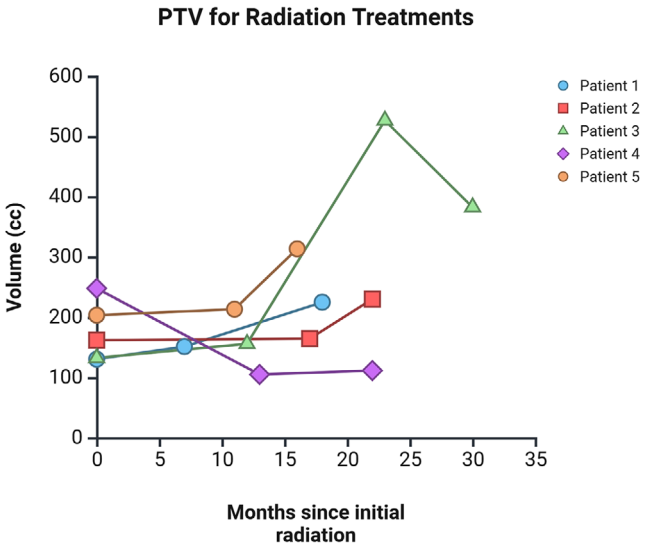

FIGURE 2 | Planning target volume (PTV) for each patient over time. A marker denotes the PTV at the time of planning for each course of RT. Most patients had larger PTV with each subsequent progression event.

after RT1 and had re-irradiation with 30.6 Gy in 17 fractions. He tolerated RT2 well with almost complete recovery of his symptoms. Despite this, he progressed 8 months after RT2 with moderate hydrocephalus and required a ventriculoperitoneal (VP) shunt insertion. His MRI showed in-field tumor progression with mild cerebellar herniation as well as supratentorial dissemination with cerebellar folia involvement suggestive of leptomeningeal disease. He completed RT3 to the primary tumor and all sites of dissemination to a dose of 20 Gy in 10 fractions. He experienced neurological improvement initially; however, he had disease progression at 5 months post RT3 with worsening ataxia and nystagmus. MRI showed intratumoral hemorrhage, necrosis, and overall disease progression. He received RT4 18 Gy in 10 fractions. All courses of RT are presented in Figure 3. MRI after RT4 reported a marginal reduction in tumor size. He died 8 months after completion of RT4 at home.

3.4 | Patient 4

Patient 4 presented with headache, emesis, left-sided hemiparesis, and urinary retention. She underwent a stereotactic biopsy of the brainstem tumor and external ventricular drain placement for hydrocephalus. No VP shunt was placed. Histology reported diffuse midline glioma, H3.1 H27 M mutation, and PTPN11p.R351 SNV was detected via TruSight RNA sequencing. She started on radiation 54 Gy in 30 fractions and required a slow steroid taper past completion of RT1 due to headaches. She had a complete neurological recovery and was able to attend school. She had disease progression 11 months after radiation and presented with diplopia and disease progression was confirmed on MRI with a necrotic component. She was re-irradiated with 30.6 Gy in 17 fractions and was tapered off steroids after completion of RT2. Her symptoms improved and she was able to complete radiation without complications. One month after RT2, she received eight cycles of trametinib and remained fully active despite mild right hemiparesis. Seven months after RT2, she was re-treated with RT3 with 20 Gy in 10 fractions for in-field primary disease progression. Her dysphagia improved, with residual ataxia and ophthalmoplegia; she was able to attend Grade 12. After RT3, she was started on dordaviprone for 3 months after which she had local progression as well as out-of-field C5–C7 cervical cord

TABLE 3 | Radiotherapy planning and dosimetric parameters of patients.

	Planning target volume (cm^3)					Cumulative brainstem dose (Gy)		
Patient	RT1	RT2	RT3	RT4	PTV overlap (all courses of RT)	D0.03cc	D0.1cc	D1cc
1	130.5	151.5	225.8		115.7	102.01	101.91	101.53
2	162.3	164.5	230.2		142.5	104.28	104.06	103.51
3	132.6	156.1	526.6	382.6	120.0	120.67	120.51	120.22
4	247.9	105.2	111.6	Cervical spine	92.9	103.58	103.48	103.01
5	203.6	213.5	313.5		156.7	111.87	111.35	109.96

Abbreviations: D0.03cc, dose received by 0.03 cm^3; D0.1cc, dose received by 0.1 cm^3; D1cc, dose received by 1 cm^3; PTV, planning target volume.

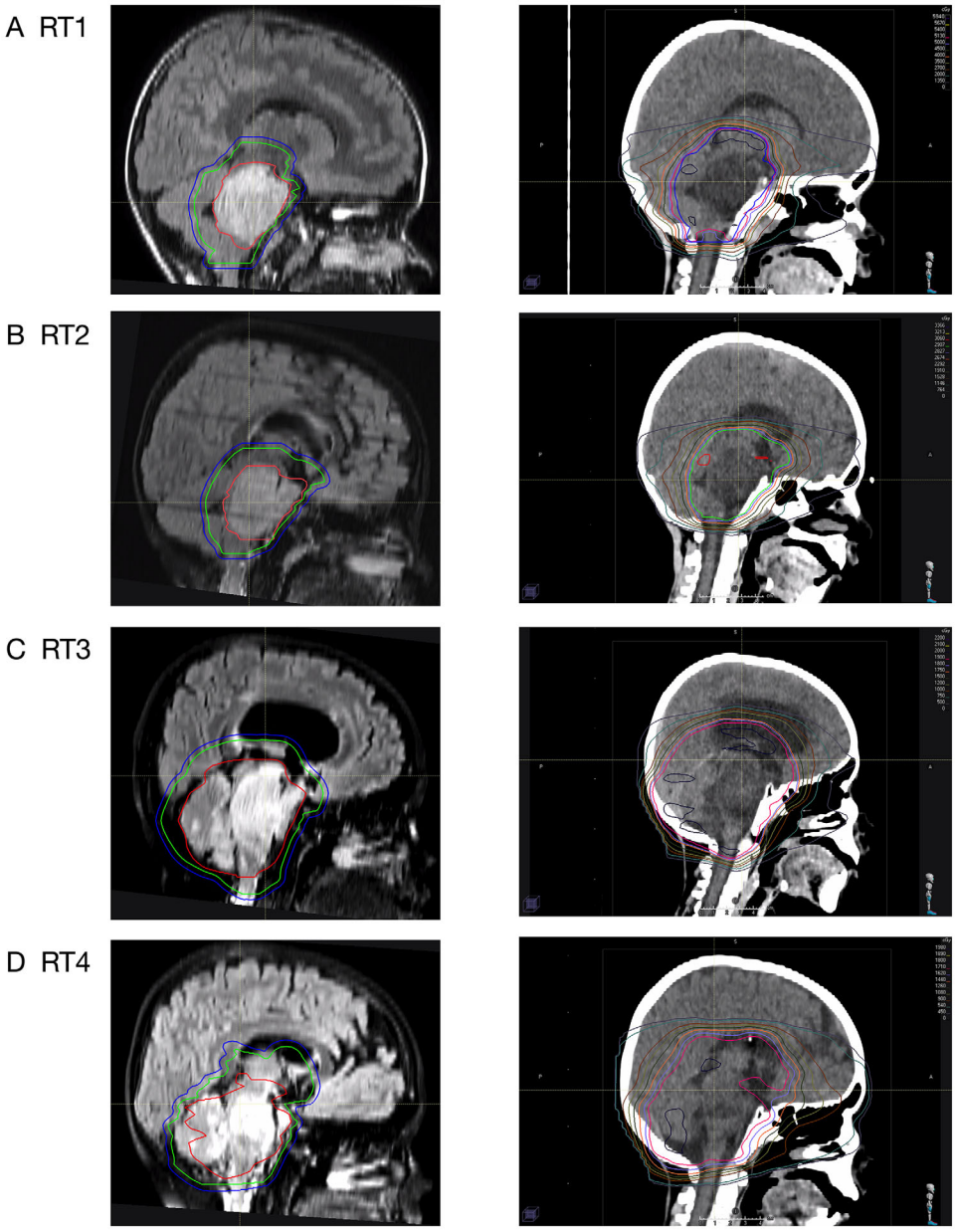

FIGURE 3 | Planning target volume (PTV) of Patient 3 who was treated with four courses of radiation to the brainstem. (A) RT1 January 2018; (B) RT2 February 2019; (C) RT3 January 2020; (D) RT4 July 2020. Images in the left column show sagittal reconstructions of the FLAIR magnetic resonance imaging (MRI) at the time of RT planning; the gross tumor volume (GTV) is delineated in red, the clinical target volume (CTV) in green, PTV in blue. Images in the right column show radiation dose distributions; the isodose line color legend is shown in the top right corner of each panel.

metastases with no other sites of dissemination or leptomeningeal disease. She was treated with palliative radiation 8 Gy in one fraction to her spine for pain control and required an epidural steroid injection. RT4 to the primary was not given due to a short interval of 4 months after RT3 and poor performance status. She died 3 months after spinal radiation due to respiratory failure secondary to progressive DIPG and remained on dordaviprone until her demise.

3.5 | Patient 5

Patient 5 presented with headaches with no neurological deficits and was radiologically diagnosed with DIPG on MRI. Radiation was deferred at the request of their parents, and she was treated 3 months after diagnosis when she progressed with hydrocephalus, which was managed conservatively. She completed radiation 54 Gy in 30 fractions with concurrent dexamethasone that was weaned off by the end of treatment. Post-treatment MRI showed a radiological response with a decreased tumor size and improved hydrocephalus. Nine months after RT1, she presented with dysphagia and headaches. Tumor progression was confirmed on MRI with cerebellar tonsillar herniation and stable hydrocephalus. She was treated with 30.6 Gy in 17 fractions with complete recovery of symptoms. Unfortunately, 4 months later she developed ataxia, dysphagia, and radiological hydrocephalus. MRI reported disease progression with basal ganglia and cerebellar dissemination. She was offered RT3 and treated

with 21.6 Gy in 12 fractions to the primary including involved sites of dissemination with partial neurological recovery. However, she remained confined to a wheelchair and died 3 months after RT3.

4 | Discussion

This study reports on five patients who underwent RT3 and one patient who underwent RT4 for progressive DIPG, which adds to the previously published case series. A previous report of two cases that received RT3 only was published; one of the patients in that series is also reported in the present case series [10]. Zaghloul et al. reported six patients who received RT3, four of which got RT3 to the brainstem; one other died prior to completion of RT3; and one had RT3 to a distant recurrence [16]. Median survival after progression post-RT2 was 4.1 months, consistent with our data. The median total BED was 189.5 Gy_2, while in the present series, the median total BED was 200.7 Gy_2. Asklid et al. also reported four patients with DIPG undergoing RT3; however, characteristics and dosimetry were not separately reported for those four children, but were combined with other histologies [12]. In our study, all patients experienced symptom stability or clinical improvement after RT3 or RT4 and had effective—albeit temporary—palliation of symptoms, with a median survival of 4 months after the last irradiation treatment to the brainstem. One patient survived 8 months after RT4.

It should be emphasized that third or fourth courses of radiation for DIPG are not curative. This treatment entails patients attending the hospital for up to 2 weeks of additional therapy, and it requires time and commitment from the patient and family for additional medical appointments, which may affect quality of life. However, in carefully selected patients who have a response to RT1 and RT2, low-dose RT3 may be considered as a suitable and temporarily effective palliative treatment. Although we found a statistically significant improvement in survival among children treated with RT3 as compared to those treated with RT2 alone, this should be interpreted with caution due to the likely selection bias favoring the RT3 group; those children selected for RT3 may have had better performance status and more indolent disease course. Furthermore, the RT3 group must have survived from the time of progression post-RT2 to the start of the third irradiation; thus, the comparison is subject to immortal time bias favoring the RT3 group. Therefore, the role of RT3 in extending survival should be validated in larger cohorts across different institutions and care settings.

The doses of RT3 used in the present study (18–21.6 Gy, 1.8–2 Gy per day) were selected based on prior experience with the lower end of dose-fractionation schemes used for RT2 [17]. National guidelines from the Swedish Working Group of Pediatric Radiotherapy recommend RT3 to a dose of 20 Gy in 10 fractions at least 3 months after RT2 in patients who experienced clinical benefit from RT2 [18]. These guidelines recommend no GTV to CTV expansion, with only a 5 mm margin from GTV to form the PTV. Our experience using more generous CTV expansions for re-irradiation has not resulted in unexpected toxicity [19]. Because patients in the present case series were all homogeneously treated with RT3 doses within a narrow range, our data do not comment on other possible dose-fractionation schemes. Furthermore, no patient received hypofractionated RT, either as RT1 [20] or RT2 [21]. Future work should explore whether administering RT3 is safe and feasible in the setting of prior hypofractionated courses of RT for DIPG to reduce the additional treatment burden on the patient and their family in this palliative context.

Radiation necrosis can be difficult to differentiate from tumor progression and typically appears as increased heterogenous contrast enhancement with edema within a previously irradiated volume [22]. Advanced MRI techniques such as magnetic resonance spectroscopy and magnetic resonance perfusion studies can help differentiate progression or radiation necrosis [22]. A PENTEC review of central nervous system (CNS) tumors in pediatric and young adults evaluated the risk of brain and brainstem necrosis in patients who received re-irradiation to a median cumulative prescription dose of 103.8 Gy [23]. The risk of brainstem necrosis was 5%–7% with cumulative re-irradiation doses of about 112 Gy in EQD2, with a median time to development of necrosis of 5.7 months from RT2. The median cumulative brainstem dose was 104 Gy in our series, comparable to those reported in the PENTEC data. In our data, Patient 3 received a cumulative dose of 121 Gy after four courses of radiation with radiological evidence of brainstem necrosis. However, tumor necrosis was also noted on MRI after RT1 (54 Gy) in Patient 4, which may be attributable to pseudoprogression. Overall, given the terminal nature of DIPG, the temporary symptom palliation achieved with re-irradiation may outweigh the perceived risks of brainstem necrosis.

Secondary disseminated disease has been reported in pontine gliomas in the range of 13%–50%, with an interval of 7–9 months from diagnosis to dissemination [24]. Overall survival after diagnosis of dissemination for high-grade gliomas was 4–8 months [24]. The use of craniospinal irradiation (CSI) in patients with metastatic disease has been reported in de novo metastatic cases [25, 26] or patients who progress with metastatic disease [27]. Perez et al. report the use of CSI in a patient with intracranial dissemination, who died 12 months after the first radiologic diagnosis of metastases. In our cohort, children who were treated with focal radiation to sites of metastases (Patients 2, 3, 4, and 5) had a median survival of 7.5 months after diagnosis of metastatic disease.

Limitations of this study are that rigid registration was used to sum radiation doses; there were large deformations in some images between radiation treatments due to changes in ventricle size. Nonetheless, we expect cumulative maximum dose estimates to be robust due to the large size of the overlapping targets and the homogeneity of their respective dose distributions. Doses for all radiation treatments were summed directly without accounting for differential radiobiological effects of 1.8 versus 2.0 Gy per fraction. Our study includes a small number of patients and lacks prospective patient-reported outcomes or quality-of-life data. Most patients did not have histologic biopsy or molecular confirmation of diffuse midline glioma. An ongoing study is evaluating health-related quality of life and symptoms in patients and caregivers for children undergoing re-irradiation for DIPG (NCT04670016), though that study is focused on RT2 and not RT3. Other studies for recurrent DIPG are studying the disruption of the blood–brain barrier, novel agents including immune checkpoint inhibitors, and CAR-T-cell therapy, which are ongoing [28–30]. Currently, modeling of the

risk of brainstem radiation necrosis is based on confirmation of brainstem necrosis on radiological imaging [23]. Postmortem histological confirmation of necrosis will supplement our current understanding of radiation necrosis with re-irradiation. The use of bevacizumab in some patients makes the effect of RT3 versus bevacizumab or surgical interventions unclear. In a patient's clinical course, multimodal treatments often occur concurrently, each potentially influencing the overall clinical outcome. Lastly, future radiobiological research is needed to rigorously evaluate the potential for brainstem recovery post-RT1, RT2, and RT3 over time to inform optimal re-irradiation dosing.

5 | Conclusion

A third course of radiotherapy for children with progressive DIPG is a potentially effective treatment option for symptom palliation, with a short additive duration of survival after disease progression. Despite high composite brainstem radiation doses exceeding usual tolerances, radiological brainstem necrosis did not occur in all patients and did not translate to clinical deterioration in function. Comprehensive discussions with carers and clinicians regarding the risks and benefits of RT3 should be emphasized to ensure the best care for these terminal patients. Prospective or multi-institutional data are required to rigorously evaluate the quality of life and survival outcomes in children who receive repeated courses of re-irradiation for DIPG.

Conflicts of Interest

N.S. received salary support from the Princess Margaret Cancer Foundation. D.S.T. is a consultant with Need (https://www.getneed.com/), unrelated to this study.

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Supporting Information

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