EJC Paediatric Oncology 4 (2024) 100183

Contents lists available at ScienceDirect

EJC Paediatric Oncology

journal homepage: www.journals.elsevier.com/ejc-paediatric-oncology

Original research

Re-irradiation for progressive Diffuse Intrinsic Pontine Glioma (DIPG): The Spanish experience

Elena Panizo-Morgado [a], Felisa Vazquez-Gómez [b], Marta Perez-Somarriba [c], Miriam Pavon-Mengual [d], Andrés Morales-La Madrid [d], Blanca Lopez-Ibor [e], Palma Solano [f], Blanca Martinez de las Heras [g], Marta Cortés-Hernández [h], Miguel García-Ariza [i], Roberto Carlos Raynero-Mellado [j], Marta Martinez-Merino [k], Ana de Lucio Delgado [l], María Tallón-García [m], Carmen Garrido-Colino [n], Irene Ortiz-Gonzalez [o], Raquel Portugal [p], María Baro-Fernández [q], Carmen Gonzalez San-Segundo [r], Felipe Calvo [s], Alvaro Lassaletta [t,*]

[a] *Department of Paediatrics, Clínica Universidad de Navarra, Madrid, Spain*
[b] *Department of Paediatric Haematology and Oncology, Hospital Universitario Niño Jesús, Madrid, Spain*
[c] *Paediatric Cancer Center Barcelona, Hospital Sant Joan de Déu, Spain*
[d] *Paediatric Cancer Center Barcelona, Hospital Sant Joan de Déu, Barcelona, Spain*
[e] *Paediatric Haematology and Oncology Unit, Hospital Universitario HM Montepríncipe, Boadilla del Monte, Madrid, Spain*
[f] *Division of Oncology, Department of Paediatrics, Hospital Virgen Del Rocio, Sevilla, Spain*
[g] *Paediatric Haematology and Oncology Unit, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[h] *Paediatric Oncology Unit, Hospital Materno Infantil de Málaga, Hospital Regional Universitario de Málaga, Málaga, Spain*
[i] *Paediatric Haematology and Oncology Unit. Instituto Investigación Sanitaria Biobizkaia. Hospital Universitario Cruces, Barakaldo, Bilbao, Spain*
[j] *Paediatric Haematology and Oncology Unit, Hospital Universitario de Toledo, Toledo, Spain*
[k] *Paediatric Hematology and Oncology Unit, Complejo Hospitalario de Navarra, Pamplona, Spain*
[l] *Department of Paediatrics, Hospital Universitario Central de Asturias, Oviedo, Spain*
[m] *Department of Paediatrics, Hospital Álvaro Cunqueiro - Complejo Hospitalario Universitario de Vigo, Pontevedra, Spain*
[n] *Paediatric Oncology and Haematology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[o] *Radiation Oncology Department, Hospital Universitari Son Espases, Palma de Mallorca, Spain*
[p] *Department of Paediatric Oncology, Hospital Universitario de Burgos, Burgos, Spain*
[q] *Department of Paediatrics, Haematology and Oncology Unit, Hospital Universitario Doce de Octubre, Madrid, Spain*
[r] *Radiation Oncology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[s] *Radiation Oncology Department, Clínica Universidad de Navarra, Madrid, Spain*
[t] *Department of Paediatric Haematology and Oncology, Hospital Universitario Niño Jesús, Department of Radiation Oncology, Clínica Universidad de Navarra Madrid, Spain*

ARTICLE INFO

Keywords:
Diffuse intrinsic pontine glioma
Diffuse midline glioma
Re-irradiation
Radiotherapy
Paediatrics

ABSTRACT

Introduction: Diffuse intrinsic pontine glioma (DIPG) is the most common malignant brainstem tumour in children. Despite advances in understanding its biology, current treatments have shown minimal impact on overall survival in this fatal disease. Focal radiotherapy (RT) is the only treatment proven to improve symptoms and extend progression-free survival. Albeit palliative, re-irradiation (rRT) has emerged as the best alternative for progressive disease. This study presents the Spanish experience with re-irradiation in DIPG.

Results: Between April 2015 and December 2023, 44 paediatric patients with progressive DIPG underwent rRT in 16 Spanish institutions. Median time from diagnosis to progression was 9.9 months (range, 4.2–24.3 months). Median dose of rRT was 20 Gy (range, 18–40 Gy) in 2 Gy fractions (range, 1.3–4 Gy). Twenty-two patients (50 %) received other treatments besides RT. Clinical improvement was seen in 77.3 %, and radiological improvement in 60 %. Treatment was well tolerated (1 case toxicity >grade 2 related to rRT). Median overall survival was 15.5 months (range, 8.2–63.2 months), with a median time from rRT to death of 4.2 months (range, 0.6–10.3 months). Longer time between diagnosis and rRT (>10 months) and dose of rRT >20 Gy were statistically significantly correlated with better overall survival. There was no survival benefit in patients receiving additional treatments.

* Correspondence to: Department of Paediatric Oncology, Hospital Niño Jesús, Department of Radiation Oncology, Clínica Universidad de Navarra, Madrid, Spain.
E-mail address: alvaro.lassaletta@salud.madrid.org (A. Lassaletta).

https://doi.org/10.1016/j.ejcped.2024.100183
Received 27 May 2024; Received in revised form 19 July 2024; Accepted 24 July 2024
Available online 30 July 2024

Conclusions: Re-irradiation is safe and effective in progressive DIPG patients, not only improving symptoms but also prolonging survival. However, the ideal candidates for rRT remain undefined, as well as the best irradiation scheme. Prospective studies are needed.

1. Introduction

Diffuse intrinsic pontine glioma (DIPG), according to the current WHO classification called Diffuse Midline Glioma, H3 K27 – altered, represents 10 % of all paediatric brain tumours [1]. It is the commonest tumour that appears in the brainstem and its outcome is very poor, with an overall survival below 10 % at 2 years [2,3]. Despite an improved understanding of its biology and the use of classical and novel approaches, such as conventional radio-sensitising agents (alkylating agents, topoisomerase inhibitors, anti-microtubular agents, platinum agents, anti-metabolic agents), targeted therapies (EGFR inhibitors, VEGF inhibitors, PDGFRA inhibitors, ONC201), epigenetic-targeted therapy (HDACi, H3K27 demethylase inhibitors, EZH2 inhibitors) and immunotherapy (oncolytic viruses, checkpoint inhibitors, CAR-T cells, vaccines), survival rates remain poor [4–11]. In recent years, there have been efforts to bypass the blood-brain barrier using techniques such as convection-enhanced delivery or focused ultrasound (FUS), but these methods are still under investigation [12,13].

To date, radiation therapy is the only treatment that seems to alter the course of this devastating and aggressive tumour. After upfront focal radiotherapy with a dose of 54–60 Gy with conventional fractionation (1.8–2.0 Gy daily, 5 days/week) or hypofractionated schedules over 2.5–3 weeks (e.g. doses of 39–45 Gy in 3 Gy daily fractions), nearly 80 % of patients experience a temporary amelioration in their neurological symptoms, followed by an improvement in their quality of life [14–16]. However, the vast majority of patients progress in a median time of 6 months [2,17]. After progression, there are no standard of care guidelines for treatment. Re-irradiation (rRT), with or without chemotherapy and other drugs, has shown some promising results in prolonging survival [9,17–28].

In the published series, rRT extends the time from progression to death and improves neurological symptoms and quality of life, although it is considered a palliative measure [29]. However, there is currently no standardisation in timing, doses or fractionation of this approach [19,26,29–31].

The aim of this study is to collect the Spanish experience of rRT of children with progressive DIPG.

2. Material and methods

A retrospective multicentre study was conducted across Spain, including patients under 21 years of age with progressive DIPG treated with re-irradiation therapy (rRT). A survey was conducted to collect demographic and clinical data for each patient. It was distributed via e-mail through the Brain Tumour Group of the Spanish Society of Paediatric Haematology Oncology (SEHOP), which includes professionals from 30 different hospitals that collectively treat the majority of Spanish paediatric brain tumor patients.

DIPG diagnosis was based on internationally recognized clinical and radiological criteria. Disease progression was defined as neurological decline confirmed by magnetic resonance imaging (MRI). All prior and subsequent therapies, especially corticosteroids, were documented, and any radiotherapy protocol was acceptable.

The primary aim was to assess the impact of rRT on time from progression to death (measured from MRI-confirmed progression to death) and overall survival (from the date of first diagnosis to the date of death). Secondary goals included outlining patient demographics, documenting radiotherapy doses and methods, evaluating adverse effects, and analysing the clinical effects on neurological symptoms (the clinical improvement was assessed by the responsible physicians based on their professional judgment and in accordance with local medical practices).

Descriptive statistics summarized patient and treatment characteristics. Survival distribution was assessed with the Kaplan-Meier method, and differences between groups were analysed using the Log-rank test. Statistical analysis was performed with SPSS version 20 (SPSS Inc., Chicago, IL).

The study was approved by the Ethics Committee for Research with Medicinal Products of the Hospital Infantil Universitario Niño Jesús (HIUNJ), approval number R-0047/21.

3. Results

Between April 2015 and September 2023, 44 patients, all under 21 years of age, diagnosed with progressive DIPG had received rRT in 16 of the 30 Spanish hospitals contacted (3 hospitals did not have re-irradiated any patient with DIPG, and 11 institutions did not respond the survey, probably because no patients were re-irradiated in those institutions). The median age at first diagnosis was 7.8 years (range, 3.4–18.8 years), with a median time to progression of 10 months (range: 4.2–24.3). Local progression was predominant (95.5 %), with two cases of disseminated progression (4.5 %). Table 1 outlines the most significant characteristics of the patients.

Re-irradiation started within a median of 25 days (range, 3–285) following progression. rRT doses varied across institutions and patient conditions, ranging from 18 to 40 Gy, with a median dose of 20 Gy. Daily fractions ranged from 1.3 Gy to 4 Gy with a median daily dose of 2 Gy. Due to progressive disease-related neurological impairment, two patients did not receive the planned 20 Gy. Additionally, another patient underwent craniospinal irradiation with 21.6 Gy due to neuroaxis dissemination. Two patients received two courses of radiotherapy for successive progressions, in addition to the initial treatment.

Re-irradiation was generally well-tolerated. Only eight patients experienced adverse effects during treatment, with most radiation-related toxicity being mild (asthenia, nausea, and hearing impairment). Only one case had toxicity greater than grade 2, which was hydrocephalus requiring shunt placement. There were two other serious adverse effects unrelated to rRT: bronchial aspiration leading to respiratory failure, one of which was caused by a respiratory infection. Only three patients had to discontinue treatment: two due to bronchial aspiration and one due to disease progression.

At the time of rRT, all patients experienced neurological deterioration. Following rRT, neurological symptoms improved in 34 patients (77.3 %). MRI was conducted in 35 patients (79.5 %) to assess tumour response, showing improvement in 21 patients (60 %). Among those without response, three had radiological stability, while two experienced tumour growth, initially interpreted as pseudo-progression.

Regarding concurrent treatment, corticosteroids were the main medication prescribed. At the start of rRT, 41 patients (93.2 %) were on dexamethasone. Eight patients (19.5 %) were able to stop treatment by the end of rRT, while data for two patients is unavailable.

Twenty-two patients (50 %) underwent treatments other than radiation or corticosteroids. Sixteen patients received additional treatment after the first RT course. Fifteen patients received therapy during or after rRT. Details are provided in Table 1. After a median observation period of 15.5 months post-diagnosis, 40 patients (93 %) passed away, three were alive at the time of data analysis (Fig. 1), and one was lost to follow-up. The median time from rRT to death was 4.2 months (range, 0.6–10.3 months).

We found differences in survival according to the time of progression. Patients who progressed before 10 months from diagnosis had

Table 1
Patient and treatments characteristics.

	Age at diagnosis (years)	Months from diagnosis to relapse	Time from firsRT to rRT (months)	Days from relapse to rRT	rRT total dose (fraction)	MRI improvement	DEX pre & post rRT	Symptoms improvements	Adverse effects	Months from rRT to death	Follow up (OS) (months)	Pre/post rRT treatments	Additional treatment after the first RT course	Treatments during rRT or follow up
1	8.95	13.8	14.10	20	20 (2)	NO	YES/ YES	YES	NO	7.23	21.70	NO/NO		
2	4.35	12.2	14.97	106	20 (1.3)	YES	YES/ NO	YES	NO	6.17	21.87	NO/NO		
3	6.31	9.9	11.03	58	21 (3)	YES	YES/ NO	YES	NO	10.33	22.20	NO/NO		
4	5.04	7.1	7.57	31	18 (1.8)	NA.	YES/ YES	YES	NO	1.10	9.23	YES/YES	Lomustine	Thalidomide, celecoxib, etoposide, cyclophosphamide, vemurafenib
5	6.20	6.8	8.00	70	20 (2)	NA.	YES/ n.a	NO	NO	3.50	12.63	NO/NO		
6	6.94	7.7	6.53	33	19.8 (1.8)	YES	YES/ YES	YES	NO	5.53	14.37	YES/NO	Pomalidomide	
7	3.35	11.7	14.10	110	20 (2)	YES	YES/ YES	YES	NO	6.83	22.20	NO/NO		
8	7.63	19.3	19.23	22	20 (2)	NO	YES/ YES	YES	NO	2.97	23.00	YES/NO	"Angiocomb protocol" (topotecan, thalidomide, etoposide, celecoxib)	
9	9.60	8.4	8.67	43	6 (2)	NO	YES/ YES	NO	NO	2.23	12.07	YES/NO	Oncolytic virus	
10	8.56	11.6	12.17	27	24 (1.6)	YES	YES/ NO	YES	YES	8.53	21.07	NO/NO		
11	5.33	10.3	9.97	27	24 (1.6)	YES	YES/ NO	YES	NO	2.20	13.37	NO/NO		
12	9.17	22.2	21.93	24	24 (1.6)	YES	YES/ NO	YES	NO	6.07	29.10	NO/NO		
13	6.05	6.6	5.87	5	20 (2)	YES	NO/ NO	YES	NO	5.03	11.77	NO/YES		Rapamicyn, irinotecan
14	10.75	11.0	10.70	15	20 (2)	YES	YES/ n.a	YES	NO	6.93	18.43	NO/NO		
15	8.55	12.0	17.37	175	21.6 (1.8)	YES	YES/ NO	YES	NO	6.17	23.97	NO/NO		
16	5.32	8.5	8.50	16	20 (2)	NO	YES/ YES	YES	NO	4.00	13.07	NO/NO		
17	6.16	8.1	8.67	36	20 (2)	NA.	YES/ YES	YES	YES	2.67	11.93	NO/NO		
18	4.16	10.5	10.20	15	20 (2)	YES	NO/ NO	YES	NO	4.20	15.20	NO/NO		
19	13.85	9.4	8.63	7	20 (2)	NA.	YES/ YES	NO	NO	0.63	10.23	NO/NO		
20	12.86	10.0	9.67	3	20 (2)	NA.	YES/ YES	NA.	NO	5.6.	15.73	NO/NO		
21	7.37	9.2	11.03	62	30.6 (1.8)	NO	YES/ YES	YES	NO	7	18.27	NO/NO		
22	9.48	9.6	9.67	21	20 (2)	YES	YES/ YES	YES	NO	3.77	14.07	NO/NO		
23	6.32	10.8	9.83	14	40 (2)	YES	YES/ YES	YES	NO	3.10	14.40	NO/NO		

(*continued on next page*)

Table 1 (*continued*)

	Age at diagnosis (years)	Months from diagnosis to relapse	Time from firsRT to rRT (months)	Days from relapse to rRT	rRT total dose (fraction)	MRI improvement	DEX pre & post rRT	Symptoms improvements	Adverse effects	Months from rRT to death	Follow up (OS) (months)	Pre/post rRT treatments	Additional treatment after the first RT course	Treatments during rRT or follow up
24	14.9	10.7	10.30	14	20 (2)	NO	YES/ YES	NO	YES	3.80	14.93	NO/NO		
25	7.9	6.9	7.00	20	19.8 (1.8)	NA.	YES/ YES	YES	NO	4.17	11.77	NO/NO		
26	4.6	17.4	18.00	34	20 (2)	NO	YES/ YES	NO	NO	8.50	27.03	NO/YES		Oncolytic virus, irinotecan, temozolomide, bevacizumab, pembrolizumab
27	10.7	9.3	9.80	63	20(2)	NO	YES/ YES	YES	NO	4.57	15.93	NO/YES		Clinical trial not specified
28	3.5	13.4	13.33	8	30 (2)	YES	YES/ YES	YES	NO	8.33	22.03	NO/YES		Everolimus
29	8.6	6.3	6.97	25	30(2)	NA	YES/ YES	NO	NO	1.03	8.17	YES/YES	Nivolumab, ipilimumab	Oncolytic virus
30	17.0	18.7	17.40	20	30 (2)	YES	YES/ YES	YES	NO	9.20	28.53	YES/YES	Dasatinib	ONC201
31	11.3	18.1	17.83	13	20(2)	YES	YES/ YES	YES	NO	6.43	24.93	YES/YES	Pomalidomide	Oncolytic virus
32	7.7	7.1	7.07	28	30(2)	YES	YES/ YES	NO	NO	3.80	11.80	YES/YES	Nivolumab	Oncolytic virus
33	7.6	11.07	11.07	70	20.0 (1.9)	NO	YES/ YES	YES	NO	6.83	18.43	YES/NO	ONC201, bevacizumab	
34	11.1	11.73	11.73	8	30.60 (1.8)	YES	YES/ YES	YES	NO	n/a	20.67 (lost)	NO/NO		
35	8.3	8.43	8.43	8	23.40 (1.8)	NO	YES/ YES	YES	NO	5.03	14.60	NO/NO		
36	4.5	12.53	12.53	285	25.20 (1.8)	NO	YES/ YES	NO	YES	1.00	14.70	YES/YES	Nimotuzumab, irinotecan, temozolomide, bevacizumab, etoposide, valproic acid	Dasatinib
37	12.7	8.83	8.83	204	20.00 (2.5)	NA.	YES/ YES	NO	YES	0.70	14.93	YES/NO	Vinorelbine, nimotuzumab, irinotecan, bevacizumab, etoposide, valproic acid	
38	3.8	7.10	7.10	8	25.00 (2.5)	NO	YES/ YES	NO	NO	55.2	63.17 (alive)	YES/YES	Oncolytic virus, bevacizumab, pembrolizumab, irinotecan, temozolomide	Bevacizumab, etoposide, valproic acid
39	12.5	7.43	7.43	19	20.00 (2.5)	NA	YES/ YES	YES	NO	2.77	11.40	NO/YES		Etoposide, valproic acid
40	18.8	24.40	24.40	20	40.00 (4)	YES	YES/ YES	YES	NO	6.30	31.30	NO/YES		Bevacizumab, carboplatin, etoposide
41	11.7	12.03	12.03	26	30.00 (2)	YES	YES/ YES	YES	YES	3.47	16.17	YES/NO	Oncolytic virus, bevacizumab	
42	15.0	9.20	9.20	33	30.00 (2)	NO	YES/ YES	YES	NO	2.63	12.67	YES/YES	Everolimus	Dabrafenib

(*continued on next page*)

Table 1 (*continued*)

	Age at diagnosis (years)	Months from diagnosis to relapse	Time from firsRT to rRT (months)	Days from relapse to rRT	rRT total dose (fraction)	MRI improvement	DEX pre & post rRT	Symptoms improvements	Adverse effects	Months from rRT to death	Follow up (OS) (months)	Pre/post rRT treatments	Additional treatment after the first RT course	Treatments during rRT or follow up
43	7.6	11.27	11.27	22	30.00 (2)	YES	NO/ NO	YES	NO	n/a.	24.93 (alive)	YES/YES	Oncolytic virus	Everolimus
44	15.5	12.13	12.13	26	30.00 (2)	NA	YES/ YES	NO	YES	n/a	13.77 (alive)	YES/NO	Oncolytic virus, bevacizumab	

n/a: not available; rRT: re-irradiation; DEX: dexamethasone; MRI: magnetic resonance imaging

Fig. 1. (A) Overall survival**. (B)** Overall survival in patients who received >20 Gy (green) versus patients who received ≤20 Gy in rRT (blue) (P = 0.017).

shorter survival than those who progressed after 10 months (13.1 months vs. 22 months, p<0.001) (Fig. 2). Similar disparities were observed in the time from rRT to death. The median time from rRT to death was 3.8 months (range, 0.6–10.3 months) for patients who progressed early (less than 10 months) and 6.2 months (range, 2.2–9.2 months) for those who progressed later (p=0.041) (Fig. 2). Furthermore, higher radiotherapy doses during rRT were associated with prolonged survival. Patients who received >20 Gy had a median estimated survival of 21.1 months, in comparison to 14.9 months for those who received ≤20 Gy (p=0.017) (Fig. 1).

However, there was no evidence of a significant difference in overall survival between patients who received concomitant treatment and those who did not.

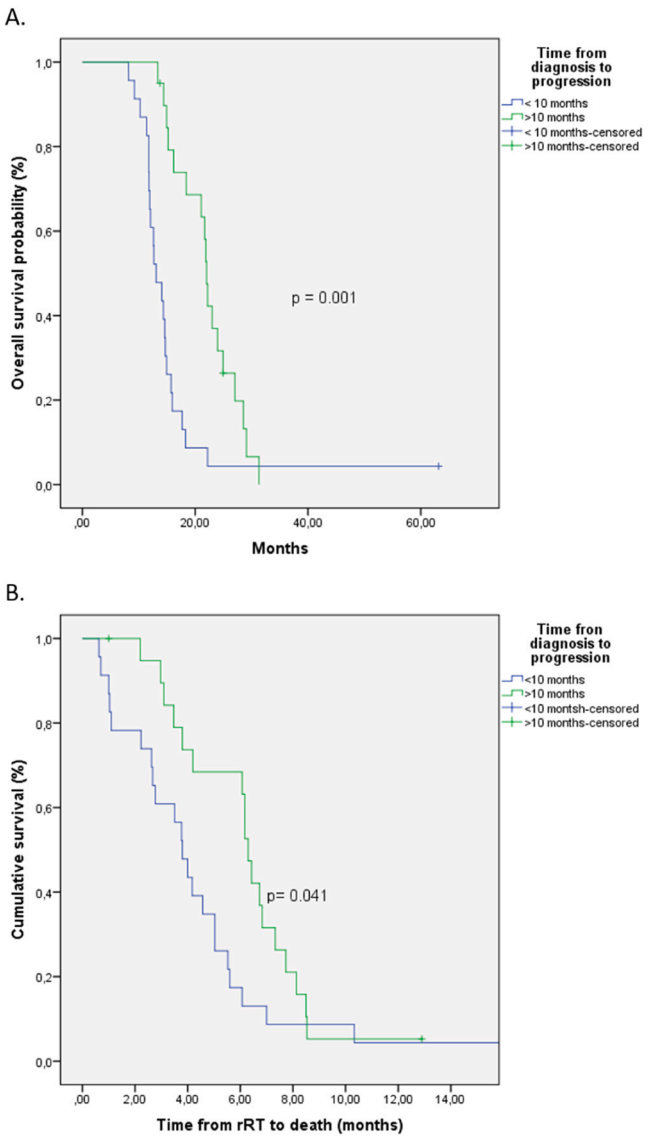

Fig. 2. Outcomes according to time to progression(A) Overall survival in patients who progressed before 10 months (blue) versus patients who progressed after 10 months (green) (P = 0.001). (B) Time from rRT to death in patients who progressed before 10 months (blue) versus patients who progressed after 10 months (green) (P = 0.041).

4. Discussion

In recent years, progress has been made in understanding the biology of DIPG through patient biopsies and autopsies. However, this has not been translated into curative therapies or improved survival rates. Radiotherapy remains the most effective method of disease control, both initially and during progressions.

A limited number of studies have reported the outcomes of rRT for recurrent DIPG. Lu *et al.* analysed some in a meta-analysis [19]. Authors concluded that rRT at progression, when performed safely and appropriately, may offer potential benefits. However, current evidence is scarce. Additionally, the specific subgroup of DIPG patients who would benefit most from re-irradiation remains unidentified. Table 2 provides a summary of the most pertinent literature on rRT in DIPG.

This study presents results from the largest series of a multi-institutional register of rRT in DIPG patients. Consistent with other reports (see Table 2), the median radiotherapy dose is 20 Gy, with no significant toxicities observed. Most patients show clinical and/or radiological improvement and the overall survival rate aligns with expectations for this tumour type (15.5 months). However, our survival results are below average, possibly due to a larger sample size, reduced use of additional therapies, and a shorter duration of response after the first radiotherapy course; the median time from initial RT to rRT in our group is 10.2 months (range, 5.9–24.4 months), while other studies report approximately 12.5 months. This phenomenon can be attributed to two factors: either our patients exhibited a more aggressive disease, or progression was identified faster than other series. Given that patients were treated at different centres, it is likely a combination of both explanations. In any case, consistent with previous findings, we observed that longer intervals between initial radiation and disease progression correlate with extended intervals between re-irradiation and subsequent progression or death [23,26].

Recently in Spain, the SEHOP Brain Tumour Working Group standardized DIPG management with therapeutic guidelines. Diagnosis is based on clinical and radiological findings, with biopsies recommended based on individual risk assessment. First-line treatment involves radiotherapy, either 50–60 Gy over 6 weeks or a hypofractionated 33–40 Gy over 3 weeks. Additional chemotherapies or biologic therapies are at each center's discretion due to lack of proven effectiveness. At progression, re-irradiation (20–30.6 Gy) is recommended for patients with a sustained response for at least 6 months, with further therapies or clinical trials suggested.

A detailed examination of the data reveals notable discrepancies between patients. Twenty patients (45 %) received doses higher than 20 Gy, correlating with better outcomes. Only half of the patients (22) underwent supplementary treatment, and 13 patients (39 %) participated in clinical trials. Although additional treatments did not improve survival rates, they may enhance progression-free survival. The Spanish healthcare system may contribute to the observed differences. With universal and decentralised access, each autonomous community manages healthcare within Health Areas, including one tertiary hospital per 20,000 inhabitants [32]. This structure improves access but can lead to varying levels of specialisation and an unequal distribution of resources for rare conditions like childhood cancer. The SEHOP Brain Tumour Group develops easy-to-follow clinical guidelines and provides expert case assessments. However, management practices are expected to differ among the 30 hospitals surveyed.

In recent years, several clinical trials for diffuse midline tumours have emerged in Spain, including the BIOMEDE TRIAL *(Biological medicines for diffuse intrinsic pontine glioma eradication)* and immunotherapy approaches [8,34–36]. Despite some promising preliminary results, no specific first- or second-line trials are currently open. Until new trials begin, treatments are guided by biopsy findings or access to ONC201 (a selective antagonist of the dopamine receptor DRD2 that can cross the blood-brain barrier), which is available on first and subsequent lines within the expanded use programme [6].

Given the lack of alternative strategies and ethical concerns about relocating palliative patients for early trials abroad, re-irradiation remains the best option at progression. Efforts should focus on improving outcomes. The optimal dose of rRT is still unknown. Chavaz *et al.*, have published their results of better neurological improvement in re-irradiated patients with 20 Gy [29]. Lassaletta *et al.* and Krishnatry *et al.* also reported the safety of doses of 30 Gy [26,33]. Recently, Dassi *et al.* have shared preliminary results using doses above 30 Gy (13 patients with a good clinical status received over 50 Gy), without reporting serious adverse effects. However, more information is needed about the cohort, which opens new horizons [37]. Our data indicate that a dose above 20 Gy confers better overall survival. Therefore, it may be reasonable to reach higher doses in order to maximise the radiation effect without increasing risks, based on these results.

It is also necessary to review the current fractionation regimen. Mankuzhy *et al.* have published excellent results with a hypofractionation programme, which shortens hospital visits and anaesthesia procedures [20]. This is a compelling rationale for considering this

Table 2
Selected published studies of re-irradiation for DIPG.

	Studies	n	Median time from first RT or diagnosis to rRT (months)	Total Dose (Gy)	Fraction (Gy)	Any systemic treatment	Complications possibly related to rRT (grade 3)	Overall survival from diagnosis (months)
1	Fontanilla et al., 2012 [21]	5	13	18–20	2	Yes	No	n/a
2	Massimino et al., 2014 [22]	11	n/a.	19.8	1.8	Yes	No	16
3	Freese et al., 2017 [17]	3	14	20	2	No	No	17.3
4	Janssens et al., 2017 [23]	31	n/a	18–30	1.8–3	Yes	No	13.7
5	Kline et al., 2018 [9]	12	11.8	24 (2: +12 Gy boost)	2–2.4	Yes	No	20.8
6	Lobon-Iglesias et al., 2018 [25]	14	9.4	n/a.	n/a	n/a.	No	19.8
7	Lassaletta et al., 2018 [26]	16	13	21.6 – 36	1.8–3	Yes	1 pontine necrosis	19.3
8	Amsbaugh et al., 2019 [27]	12	12.3	24–30.8	2–2.2	No	1 grade 3 hypoxia and dysphagia	19.5
9	Zamora et al., 2021 [28]	5	10	20–24	2	Yes	No	16.3
10	Krishnatry et al., 2021 [33]	20	8.4	30.6 (WBI) 21.6–30.6 (focal) 39–45 (responders)	1.8	Yes	2 intracranial haemorrhage post-rRT	16.6
11	Mankuzhy et al., 2024 [20]	20	8	20–30 (6 patients) 30–36 (14 patients)	2 3	Yes	No	18
12	**Current study**	44	10.2	20 – 30.6	1.3–2.5	Yes	1 hydrocephalus (shunt required)	15.5

RT: radiotherapy; rRT: re-irradiation; n/a: not available

approach in patients where quality of life is of paramount importance, particularly in patients with a poor performance status.

Research into new radiotherapy (RT) techniques like proton beam therapy and RT-Flash is needed. Currently, proton beam therapy is not recommended for high-grade gliomas, including DIPG, due to poor outcomes and limited survival benefits. However, Muroi *et al.* found that while proton therapy did not improve survival compared to conventional photon radiotherapy, it was well tolerated [38]. The neurocognitive effects of ionising radiation, which can manifest within six months and are age and dose-dependent, make proton therapy a viable option for young children with large tumours due to its better tolerance and growing availability. Furthermore, evidence supports the benefits of re-irradiation with heavy particles like protons, as they allow dose escalation while sparing healthy tissue. In our cohort, one patient received proton therapy during rRT without complications. However, caution is needed to limit brainstem exposure, considering the relative biological effectiveness (RBE) and linear energy transfer (LET) of protons compared to photons [39]. The experimental FLASH radiotherapy technique uses an ultra-high dose rate for less toxicity and more effective tumour control. Preliminary data on its effects on the immune microenvironment of diffuse midline glioma tumours are promising, potentially enabling new synergistic treatment combinations [40].

Nevertheless, while rRT has demonstrated limited efficacy as a standalone treatment, it is imperative to identify the best combination therapy with radiation. Our study did not identify a correlation between any treatment and improved survival. However, due to varying methodologies and the retrospective nature of our study, it is challenging to determine the true benefit of additional treatments.

Our study has limitations. As a retrospective analysis, data reliability depends on the accuracy of clinical histories. While details like radiation dates, doses, and severe toxicities are well-documented, mild side effects and diagnostic nuances (doubts in situations of radio-necrosis and/or progression) may be less clear. We also did not capture certain relevant data, such as initial radiation course details and biopsy availability, due to our focus on re-irradiation. This might mean variations in the initial treatment were missed. Additionally, the study lacks a control group. Despite observing similar survival rates and median survival gains with rRT as reported by other groups (ranging from 13.7 to 19.8 months and 2.7–4.1 months, respectively), the absence of a control group precludes guaranteeing the intervention's benefit [22,23,25,26]. It must also be noted that only 19 of 30 centres provided cases, resulting in potential data gaps. However, major national paediatric oncology reference hospitals are represented. Finally, the lack of molecular data may have limited our ability to interpret outcomes. Correlating survival with patient genomics could have revealed valuable insights into responses to radiotherapy, but this data was not collected.

In conclusion, this series presents the Spanish experience with 44 DIPG patients who underwent re-irradiation. The treatment was feasible and safe, with most patients showing clinical improvements and reduced dexamethasone use. Re-irradiation can extend lifespan by several months and maintain a satisfactory functional status. However, optimizing re-irradiation doses and fractions, and combining it with other therapies, is still necessary.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

CRediT authorship contribution statement

Elena Panizo-Morgado: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marta Martinez-Merino:** Writing – review & editing, Resources, Data curation. **Felisa Vazquez-**

Gomez: Writing – review & editing, Resources, Data curation. **Ana De Lucio-Delgado:** Writing – review & editing, Resources, Data curation. **Maria Tallon-Garcia:** Writing – review & editing, Resources, Data curation. **Marta Perez-Somarriba:** Writing – review & editing, Resources, Data curation. **Carmen Garrido-Colino:** Writing – review & editing, Resources, Data curation. **Miriam Pavon-Mengual:** Writing – review & editing, Resources, Data curation. **Andres Morales-La Madrid:** Writing – review & editing, Resources, Data curation. **Irene Ortiz-Gonzalez:** Writing – review & editing, Resources, Data curation. **Blanca Lopez-Ibor:** Writing – review & editing, Resources, Data curation. **Raquel Portugal:** Writing – review & editing, Resources, Data curation. **Palma Solano:** Writing – review & editing, Resources, Data curation. **Maria Baro-Fernandez:** Writing – review & editing, Resources, Data curation. **Blanca Martinez-De las Heras:** Writing – review & editing, Resources, Data curation. **Carmen Gonzalez-Sansegundo:** Writing – review & editing, Resources, Data curation. **Felipe Calvo:** Writing – review & editing, Resources, Data curation. **Miguel Garcia-Ariza:** Writing – review & editing, Resources, Data curation. **Alvaro Lassaletta:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Roberto Carlos Raynero-Mellado:** Writing – review & editing, Resources, Data curation. **Marta Cortes-Hernandez:** Writing – review & editing, Resources, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

References

[1] D.N. Louis, A. Perry, G. Reifenberger, et al., The 2016 world health organization classification of tumors of the central nervous system: a summary, Acta Neuropathol. 131 (6) (2016) 803–820, https://doi.org/10.1007/s00401-016-1545-1.

[2] N.A. Vitanza, M. Monje, Diffuse intrinsic Pontine glioma: from diagnosis to next-generation clinical trials, Curr. Treat. Options Neurol. 21 (8) (2019) 37, https://doi.org/10.1007/s11940-019-0577-y.

[3] L.M. Hoffman, S.E.M.V. Van Zanten, N. Colditz, et al., Clinical, radiologic, pathologic, and molecular characteristics of long-term survivors of Diffuse intrinsic pontine glioma (DIPG): a collaborative report from the international and European Society for Pediatric Oncology DIPG registries, J. Clin. Oncol. 36 (19) (2018) 1963–1972, https://doi.org/10.1200/JCO.2017.75.9308.

[4] M. Gallitto, S. Lazarev, I. Wasserman, et al., Role of radiation therapy in the management of diffuse intrinsic Pontine glioma: a systematic review, Adv. Radiat. Oncol. 4 (3) (2019) 520–531, https://doi.org/10.1016/j.adro.2019.03.009.

[5] U. Tosi, M. Souweidane, Fifty years of DIPG: looking at the future with hope, Child'S. Nerv. Syst. 39 (10) (2023) 2675–2686, https://doi.org/10.1007/s00381-023-06037-5.

[6] A.S. Chi, R.S. Tarapore, M.D. Hall, et al., Pediatric and adult H3 K27M-mutant diffuse midline glioma treated with the selective DRD2 antagonist ONC201, J. Neurooncol. 145 (2019) 97–105, https://doi.org/10.1007/s11060-019-03271-3.

[7] E. Hayden, H. Holliday, R. Lehmann, et al., Therapeutic targets in diffuse midline gliomas—an emerging landscape, Cancers 13 (24) (2021) 1–41, https://doi.org/10.3390/cancers13246251.

[8] J. Gállego Pérez-Larraya, M. Garcia-Moure, S. Labiano, et al., Oncolytic DNX-2401 virus for pediatric diffuse intrinsic Pontine glioma, N. Engl. J. Med 386 (26) (2022) 2471–2481, https://doi.org/10.1056/nejmoa2202028.

[9] C. Kline, S.John Liu, Sai Duriseti, et al., Reirradiation and PD-1 inhibition with nivolumab for the treatment of recurrent diffuse intrinsic pontine glioma: a single-institution experience, J. Neurooncol. 140 (2018) 629–638, https://doi.org/10.1007/s11060-018-2991-5.

[10] B.C. Thomas, D.E. Staudt, A.M. Douglas, M. Monje, N.A. Vitanza, M.D. Dun, CAR T cell therapies for diffuse midline glioma, Trends Cancer 9 (10) (2023) 791–804, https://doi.org/10.1016/j.trecan.2023.07.007.

[11] Z. Yang, L. Sun, H. Chen, C. Sun, L. Xia, New progress in the treatment of diffuse midline glioma with H3K27M alteration, Heliyon 10 (2) (2024) e24877, https://doi.org/10.1016/j.heliyon.2024.e24877.

[12] U. Tosi, M. Souweidane, Convection enhanced delivery for diffuse intrinsic pontine glioma: review of a single institution experience, Pharmaceutics 12 (7) (2020) 1–15, https://doi.org/10.3390/pharmaceutics12070660.

[13] K. Parekh, S. LeBlang, J. Nazarian, et al., Past, present and future of focused ultrasound as an adjunct or complement to DIPG/DMG therapy: a consensus of the 2021 FUSF DIPG meeting, Neoplasia (U. S.) 37 (October 2022) (2023) 100876, https://doi.org/10.1016/j.neo.2023.100876.

[14] G.O. Janssens, M.H. Jansen, S.J. Lauwers, et al., Hypofractionation vs conventional radiation therapy for newly diagnosed diffuse intrinsic pontine glioma: a matched-cohort analysis, Int. J. Radiat. Oncol. Biol. Phys. 85 (2) (2013) 315–320, https://doi.org/10.1016/j.ijrobp.2012.04.006.

[15] M.S. Zaghloul, A. Nasr, M. Tolba, et al., Hypofractionated radiation therapy for diffuse intrinsic Pontine glioma: a noninferiority randomized study including 253 children, Int. J. Radiat. Oncol. Biol. Phys. 113 (2) (2022) 360–368, https://doi.org/10.1016/j.ijrobp.2022.01.054.

[16] H.J. Kim, C.-O. Suh, Radiotherapy for diffuse intrinsic pontine glioma: insufficient but indispensable, Brain Tumor Res. Treat. 11 (2) (2023) 79, https://doi.org/10.14791/BTRT.2022.0041.

[17] C. Freese, V. Takiar, M. Fouladi, M. DeWire, J. Breneman, L. Pater, Radiation and subsequent reirradiation outcomes in the treatment of diffuse intrinsic pontine glioma and a systematic review of the reirradiation literature, Pract. Radiat. Oncol. 7 (2) (2017) 86–92, https://doi.org/10.1016/J.PRRO.2016.11.005.

[18] R. Krishnatry, J.J. Manjali, G. Chinnaswamy, et al., Clinical approach to re-irradiation for recurrent diffuse intrinsic pontine glioma, Jpn J. Clin. Oncol. (5) (2021) 762–768, https://doi.org/10.1093/jjco/hyab006.

[19] V.M. Lu, J.P. Welby, A. Mahajan, N.N. Laack, D.J. Daniels, Reirradiation for diffuse intrinsic pontine glioma: a systematic review and meta-analysis, Child'S. Nerv. Syst. 35 (5) (2019) 739–746, https://doi.org/10.1007/s00381-019-04118-y.

[20] N.P. Mankuzhy, K.R. Tringale, I.J. Dunkel, et al., Hypofractionated re-irradiation for diffuse intrinsic pontine glioma, Pediatr. Blood Cancer (2024) 1–9, https://doi.org/10.1002/pbc.30929.

[21] H.P. Fontanilla, C.C. Pinnix, L.M. Ketonen, et al., Palliative reirradiation for progressive diffuse intrinsic pontine glioma, Am. J. Clin. Oncol. Cancer Clin. Trials 35 (1) (2012) 51–57, https://doi.org/10.1097/COC.0b013e318201a2b7.

[22] M. Massimino, V. Biassoni, R. Miceli, et al., Results of nimotuzumab and vinorelbine, radiation and re-irradiation for diffuse pontine glioma in childhood, J. Neurooncol. 118 (2) (2014) 305–312, https://doi.org/10.1007/s11060-014-1428-z.

[23] G.O. Janssens, L. Gandola, S. Bolle, et al., Survival benefit for patients with diffuse intrinsic pontine glioma (DIPG) undergoing re-irradiation at first progression: a matched-cohort analysis on behalf of the SIOP-E-HGG/DIPG working group, Eur. J. Cancer 73 (September 2016) (2017) 38–47, https://doi.org/10.1016/j.ejca.2016.12.007.

[24] R. Krishnatry, J.S. Goda, A. Kadam, T. Gupta, G. Chinnaswamy, R. Jalali, V.J. A. Patil, RONC-07. The tale of 100 DIPGs and radiotherapy, Neuro oncol. 20 (Suppl) (2018) 175–176.

[25] M.J. Lobon-Iglesias, G. Giraud, D. Castel, et al., Diffuse intrinsic pontine gliomas (DIPG) at recurrence: is there a window to test new therapies in some patients? J. Neurooncol. 137 (1) (2018) 111–118, https://doi.org/10.1007/s11060-017-2702-7.

[26] A. Lassaletta, D. Strother, N. Laperriere, et al., Reirradiation in patients with diffuse intrinsic pontine gliomas: the Canadian experience, Pediatr. Blood Cancer 65 (6) (2018) 1–5, https://doi.org/10.1002/pbc.26988.

[27] M.J. Amsbaugh, A. Mahajan, P.F. Thall, et al., A phase 1/2 trial of reirradiation for diffuse intrinsic Pontine glioma, Int. J. Radiat. Oncol. Biol. Phys. 104 (1) (2019) 144–148, https://doi.org/10.1016/J.IJROBP.2018.12.043.

[28] P.L. Zamora, S.R. Miller, J.J. Kovoor, Single institution experience in re-irradiation of biopsy-proven diffuse intrinsic pontine gliomas, Child'S. Nerv. Syst. 37 (8) (2021) 2539–2543, https://doi.org/10.1007/s00381-021-05195-8.

[29] L. Chavaz, G.O. Janssens, S. Bolle, et al., Neurological symptom improvement after Re-irradiation in patients with diffuse intrinsic Pontine glioma: a retrospective analysis of the SIOP-E-HGG/DIPG project, Front Oncol. 12 (2022) 1–8, https://doi.org/10.3389/fonc.2022.926196.

[30] M.B. Janjua, V.S. Ban, T.Y. El Ahmadieh, et al., Diffuse intrinsic pontine gliomas: diagnostic approach and treatment strategies, J. Clin. Neurosci. 72 (2020) 15–19, https://doi.org/10.1016/j.jocn.2019.12.001.

[31] C. Cacciotti, K.X. Liu, D.A. Haas-kogan, K.E. Warren, Neuro-oncology practice reirradiation practices for children with diffuse intrinsic pontine glioma, Neuro-oncol. Pract. 8 (October 2020) (2021) 68–74, https://doi.org/10.1093/nop/npaa063.

[32] T. Armenteros-Ruiz, A. Ballesteros-Ron, M. Rodriguez-Mañero, F. Reyes-Santías, Evaluating the decentralisation of the Spanish healthcare system: a data envelopment analysis approach, BMJ Open 14 (3) (2024) e076853, https://doi.org/10.1136/bmjopen-2023-076853.

[33] R. Krishnatry, J.J. Manjali, G. Chinnaswamy, et al., Clinical approach to re-irradiation for recurrent diffuse intrinsic pontine glioma, Jpn J. Clin. Oncol. 51 (5) (2021) 762–768, https://doi.org/10.1093/jjco/hyab006.

[34] J. Grill, G. Le Teuff, P. Varlet, et al., Biological medicines for diffuse intrinsic pontine glioma (DIPG) eradication (BIOMEDE): final results of an international randomized phase II platform trial comparing 3 targeted therapies in combination with radiotherapy from ITCC, 10003, SIOPE-Brain Anzchog 41 (16_suppl) (2023) 10003, https://doi.org/10.1200/JCO.2023.41.16_SUPPL.10003.

[35] D. Ruano, J.A. López-Martín, L. Moreno, et al., First-in-human, first-in-child trial of autologous MSCs carrying the oncolytic virus Icovir-5 in patients with advanced tumors, Mol. Ther. 28 (4) (2020) 1033–1042, https://doi.org/10.1016/j.ymthe.2020.01.019.

[36] D. Benitez-Ribas, R. Cabezón, G. Flórez-Grau, et al., Immune response generated with the administration of autologous dendritic cells pulsed with an allogenic tumoral cell-lines lysate in patients with newly diagnosed diffuse intrinsic pontine glioma, Front. Oncol. 8 (APR)) (2018) 127, https://doi.org/10.3389/fonc.2018.00127.

[37] N. Dassi, A.C.S. Torquato, M. Chen, et al., DIPG-31. is Re-irradiation a potential survival benefit for patients with diffuse intrinsic pontine glioma? Neuro Oncol. 26 (Supplement_4) (2024) 0, https://doi.org/10.1093/neuonc/noae064.084.
[38] A. Muroi, M. Mizumoto, E. Ishikawa, et al., Proton therapy for newly diagnosed pediatric diffuse intrinsic pontine glioma, Child'S. Nerv. Syst. 36 (3) (2020) 507–512, https://doi.org/10.1007/s00381-019-04420-9.
[39] K. Seidensaal, Proton therapy special feature: review article irradiation with protons or heavy ions with focus on head and neck, Skull Base Brain Malig. (2019) (2020).
[40] O. Padilla, H.E. Minns, H.-J. Wei, et al., Immune response following FLASH and conventional radiation in diffuse midline glioma, Int. J. Radiat. Oncol. Biol. Phys. 119 (4) (2024) 1248–1260, https://doi.org/10.1016/j.ijrobp.2024.01.219.