



Efficacy and safety of hypofractionated radiotherapy versus conventional fractionated radiotherapy in diffuse intrinsic pontine glioma: A systematic review and meta-analysis

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ABSTRACT

Background: Diffuse intrinsic pontine glioma (DIPG) stands as the predominant type of brainstem glioma. It is characterized by a notably brief median survival period, with the majority of patients experiencing disease progression within six months following radiation therapy. This systematic review and meta-analysis aims to assess the efficacy and safety of hypofractionated radiotherapy (HFRT) compared to conventionally fractionated radiotherapy (CFRT) in DIPG treatment.

Materials and methods: A systematic literature search was conducted in four databases, and relevant studies comparing HFRT and CFRT in DIPG were included. Data were extracted and analyzed for overall survival (OS), progression-free survival (PFS), and treatment-related toxicities. Statistical analysis was performed using random-effects models with heterogeneity assessment.

Results: Five studies met the inclusion criteria, comprising 518 patients. No significant difference in one-year OS was observed between HFRT and CFRT (29% vs. 22%, $p = 0.94$). The median OS was similar in both treatment groups (9.7 vs. 9.3 months, $p = 0.324$). Similarly, no significant difference in one-year PFS was found between HFRT and CFRT (19.8% vs. 16.6%, $p = 0.82$), with comparable median PFS (9.3 vs. 9.4 months, $p = 0.20$). In meta-regression analysis, there was no association of chemotherapy ($p > 0.05$) or radiation biologically effective dose (BED) ($p > 0.05$) regarding OS or PFS outcomes. There were no significant differences in treatment-related toxicities.

Conclusions: HFRT yields one-year OS and PFS rates similar to CFRT in DIPG, with no significant differences in treatment-related toxicities. Chemotherapy and BED did not affect OS or PFS.

Key words: diffuse intrinsic pontine glioma; hypofractionated radiotherapy, overall survival, progression-free survival, treatment-related toxicities

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Introduction

Diffuse intrinsic pontine gliomas (DIPG) are malignant brainstem tumors that contribute significantly to brain tumor-related deaths in pediatric patients¹⁻². With a median overall survival (OS) of less than 12 months and limited treatment options, DIPG presents a substantial challenge in pediatric oncology [1, 2]. Gross total resection is generally unattainable due to the tumor's location and infiltrative growth pattern. In such cases, radiotherapy has emerged as the established standard of care for DIPG. Radiotherapy not only provides relief from symptoms but also diminishes the necessity for corticosteroid use and neurological symptoms. Additionally, chemotherapy has shown limited efficacy in treating DIPG, further underscoring the importance of radiotherapy as the primary therapeutic approach [1–5].

Conventionally fractionated radiotherapy (CFRT) is typically employed for DIPG treatment, consisting of a six-week treatment course [1–5]. However, given the dismal prognosis and the importance of preserving patients' quality of life, alternative radiotherapy approaches, such as hypofractionated radiotherapy (HFRT), have gained interest⁶. HFRT offers a shorter treatment duration, fewer hospital visits, and reduced utilization of treatment resources, potentially alleviating the treatment-related burden on patients and their families [6].

While previous studies have attempted to compare the outcomes of HFRT and CFRT, it is challenging to arrive at definitive conclusions due to the limitations posed by small sample sizes and the significant variability in irradiation protocols employed [6]. Consequently, a comprehensive understanding of these different RT modalities' effectiveness and tolerability needs further analysis.

Given the considerable challenges posed by the management of diffuse intrinsic pontine glioma (DIPG), we set out to undertake a comprehensive systematic review and meta-analysis. Our objective was to ascertain whether there exists a disparity in survival outcomes and treatment-related toxicities between two common radiation therapy approaches: hyperfractionated radiotherapy (HFRT) and conventional fractionated radiotherapy (CFRT) in patients diagnosed with DIPG. By synthesizing and analyzing the existing body of

evidence, our aim is to offer valuable insights into the comparative effectiveness of these two radiation therapy strategies for treating this devastating pediatric brainstem tumor. We hope that the findings of this study will not only inform clinical decision-making but also contribute significantly to the ongoing efforts directed toward enhancing patient outcomes in this challenging clinical scenario.

Materials and methods

The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7, 8].

Search strategy

A comprehensive literature search was performed in the following electronic databases: PubMed, EMBASE, Cochrane Library, and Web of Science. The search was conducted from the inception of each database until January 2023. The search strategy used the following keywords and their respective synonyms: “diffuse pontine glioma”, “hypofractionated radiotherapy”, and “conventional fractionation”. Additionally, the reference lists of the included studies and relevant review articles were manually screened to identify further eligible studies.

Inclusion and exclusion criteria

The following criteria were used to decide which studies to include: (1) studies that compared HFRT to CFRT in treating DIPG; (2) studies that included children only; (3) studies where information about the clinical outcomes of interest was available; (4) studies with at least ten patients per treatment arm; and (5) studies written in English. Case reports, conference abstracts, and studies without a control group were excluded.

Data extraction

Two independent reviewers (GAV and AGG) screened the titles and abstracts of the identified studies, and full-text articles were obtained for potentially eligible studies. The resolution of disagreements involved discussion and consensus-building or, if necessary, the assistance of a third reviewer (FYM). The following data were extracted from the included studies: first author, year of publication, study design, sample size, patient characteris-

tics, treatment protocol, and outcomes of interest. The median biologically effective dose (BED) in each trial was also obtained to compare the different radiation doses and fractionations employed in the studies.

Outcomes

The primary outcome of this meta-analysis was overall survival (OS). Secondary outcomes included progression-free survival (PFS) and treatment-related toxicities. Toxicity was divided into grades 1 and 2 or grade 3 or higher (according to the scale reported by the study). The following toxicities were analyzed: dysphagia and skin toxicity (erythema, and dry skin). To estimate the burden of grade 1 and 2 toxicity, we pooled any grade 1 and 2 reported.

Statistical analysis

Data were pooled using the random-effects model to account for potential heterogeneity among the included studies. Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were calculated for OS and PFS, while odds ratios (ORs) and their 95% CIs were calculated for LC and treatment-related toxicities. The heterogeneity among studies was assessed using the I^2 statistic, with $I^2 > 50\%$ indicating substantial heterogeneity. Publication bias was evaluated using funnel plots and Egger's test. All analyses were performed using Review Manager 5.4 and open meta-analysis, with statistical significance set at $p < 0.05$ (two-tailed).

Risk of bias in the included studies

The risk of bias in the included studies was evaluated using the updated Cochrane Risk of Bias tools for randomized trials⁹. RoB 2.0 poses a series of questions (Yes/Possibly Yes/No/No/Possibly No/No) to assess the risk of bias in five domains: bias due to the randomization process, bias from deviations from the intended interventions, bias resulting from missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reporting. Following the instructions and algorithm in RoB 2.0, the overall risk of bias (low risk, some concerns, high risk) for each intervention was determined, with the highest risk of bias in any of the assessed domains determining the overall risk of bias. Considering the Cochrane Handbook recommendation, the funnel plot was

not used because there were less than ten studies in our meta-analysis [10].

Results

Five studies fulfilled the criteria of this meta-analysis (Supplementary File — Fig. S1) [11–15]. Table 1 summarizes the characteristics of the included studies. The selection comprised three randomized controlled trials and two retrospective studies, with one of these being a matched cohort analysis. One of the randomized clinical trials was a three-arm study with two arms using HFRT [15]. Thus, the CFRT arm was counted twice to compare each HFRT arm. These studies were published from 2013 to 2022, evaluating a total of 518 patients, of whom 257 underwent HFRT (39 Gy in 13 fractions or 44.8 Gy in 16 fractions), and 261 underwent CFRT (total dose: 50.4–60 Gy). In the HFRT arm, the median biologically effective dose (BED) was 80 Gy₃ (range 78–90 Gy₃). In the CFRT arm, the median BED was 86 Gy₃ (range, 86–120 Gy₃). In one trial, temozolomide was routinely used concurrently with HFRT [14], while in another study, chemotherapy use was allowed [13]. All patients were treated with three-dimensional conformal radiotherapy (3D-RT).

Overall survival

Five studies evaluated OS as an outcome. Comparing HFRT versus CFRT, no significant difference at 1-year OS was observed (HFRT = 29% vs. CFRT = 22%, RR = 1.32 95% CI: 0.98–1.77, $p = 0.94$, $I^2 = 0\%$) (Fig. 1A). The median OS in the HFRT was 9.3 months (95% CI: 7.8–12 months) compared with 9.7 months (95% CI: 9.4–11 months) in the CFRT group, translating into a mean difference of -0.1 (95% CI: -0.9 – 0.7) with no significant difference between the arms. In the meta-regression analysis, no significant relationship was observed between BED, chemotherapy combination, and median OS (Tab. 2 and Fig. 1B).

Progression free survival

Five studies evaluated PFS as an outcome. Comparing HFRT versus CFRT, no significant difference at 1-year PFS was observed (HFRT = 19.8% vs. CRT = 16.6%, RR = 1.22; 95% CI: 0.84–1.77, $p = 0.82$, $I^2 = 0\%$) (Fig. 2A). The median PFS in the HFRT was 7.0 months (95% CI: 5–8 months)

Table 1. Characteristics of patients, and treatment of studies included in the meta-analysis

Variables/Study	Janssens et al. 2012	Zaghloul et al. 2014	Izzuddeen et al. 2019	Hayashi et al. 2020	Zaghloul. 2022
RT dose	39–44.8 Gy/13–16 fx	54 Gy/30 fx	39 Gy/13 fx	44.8 Gy/16 fx	39 Gy/13 fx
Design	MC	RCT	RCT	R	RCT
Period	2002–2010	2007–2011	2016–2018	2000–2018	2011–2017
N	27	35	18	7	84
Radiotherapy technique	3D	3D	3D	3D	3D
Age (median)	7.5	8.3	9	7.0	7.0
Boys	12	19	7	5	43
Girls	15	16	11	2	42
Definition of GTV (based on MRI)	T2 weighed	T1 with contrast or T2 weighed	T1 with contrast	NR	Fusion with T2 weighed or flair
CTV	GTV + 1.5–2 cm	GTV + 1 cm	T2 flair	NR	GTV + 1 cm
PTV	CTV + 3–5 mm	CTV + 5 mm	CTV + 5 mm	NR	CTV + 5 mm
Chemotherapy	No	No	Yes [#]	Yes [*]	No
			No [#]	Yes [*]	No
					Fusion with T2 weighed or flair
					GTV + 1 cm
					CTV + 5 mm
					No
					No
					54 Gy/30 fx
					RCT
					2011–2017
					84
					3D
					7.1
					36
					48
					Fusion with T2 weighed or flair
					GTV + 1 cm
					CTV + 5 mm
					No
					No

RT — radiotherapy; GTV — gross tumor volume; CTV — clinical tumor volume; PTV — planning tumor volume; RCT — randomized clinical trials; MC — matched cohort; R — retrospective; MC — matched cohort; 3D — three-dimensional conformal; NR — not reported; MRI — magnetic resonance imaging; [#]Ten patients (50%) received chemotherapy in this study; ^{*}Concurrent and adjuvant TMZ was given to patients in the hypofractionated arm

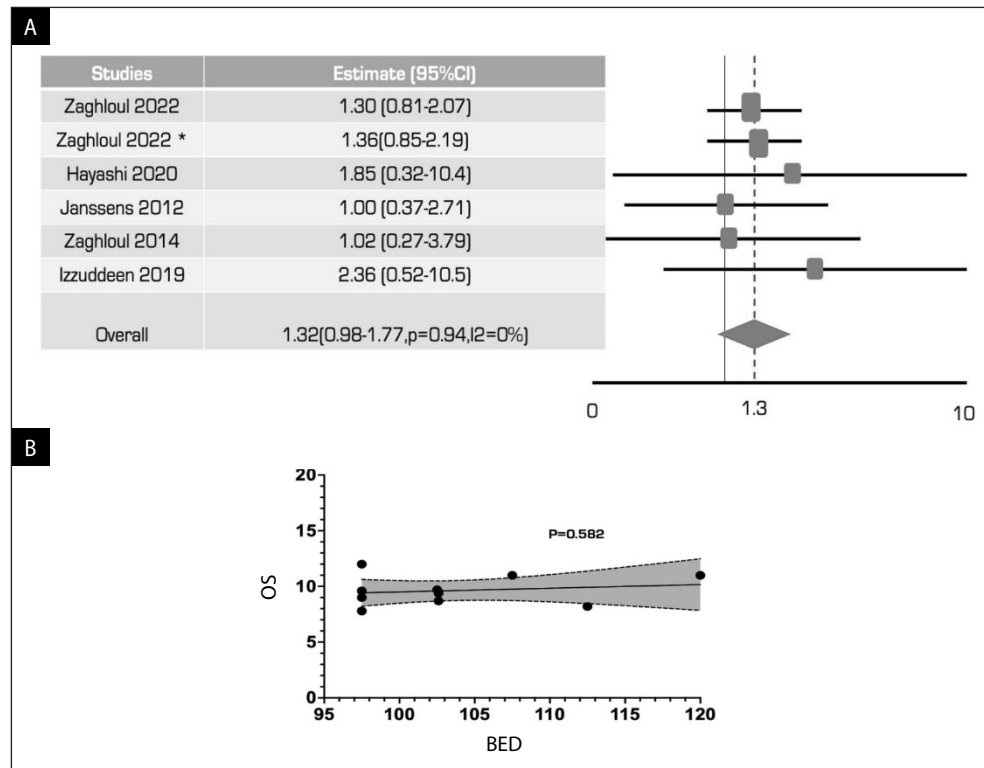


Figure 1. **A.** Meta-analysis of include studies for overall survival; **B.** Metaregression analysis for the relationship between biologically effective dose (BED) and median overall survival (OS). CI — confidence interval

Table 2. Metaregression analysis of factors influencing the overall survival or progression free survival in diffuse intrinsic pontine gliomas

Variable	β	P
Progression free survival (5 studies, n = 518)		
BED Gy2 (97–112)	–0.036	0.187
Chemotherapy (Yes vs. No)	0.221	0.781
Study design (RCT vs. R)	–0.371	0.660
Overall Survival (n = 5 studies, n = 518)		
BED Gy2 (97–112)	0.005	0.800
Chemotherapy	0.510	0.395
Study design (Phase II)	0.297	0.761

BED — biologically effective dose; RCT — randomized controlled trial; R — retrospective

compared with 7.3 months in the CFRT (95% CI: 4.2–7.9 months), translating into a mean difference of –0.58 (95% CI: –1.5–0.35, $p = 0.20$, $I^2 = 20\%$) with no significant difference between the arms. In the meta-regression analysis, no significant relationship between BED, chemotherapy combination, study design, and median OS was observed (Tab. 2 and Fig. 2B).

Toxicity

Two studies reported grade 1/2 dysphagia and skin toxicity. No significant difference was observed between HFRT and CFRT for grade 1/2 dysphagia RR = 1.43 (95% CI: 0.56–3.66, $p = 0.00$, $I^2 = 0\%$, Supplementary File — Fig. S2A), or skin toxicity RR = 1.02 (95% CI: 0.79–1.33, $p = 0.90$, $I^2 = 0\%$, Supplementary File — Fig. S2B). Pooling all grade 1/2 toxicities, no significant toxicity was observed with an RR of 1.06 (95% CI: 0.84–1.34, $p = 0.88$, $I^2 = 0\%$, Supplementary File — Fig. 2C). No grade 3 or 4 toxicity was reported in the HFRT arms. Izzuddeen et al. reported only one case of grade 3 toxicity, a subdural hemorrhage, in the CFRT arm receiving combined temozolomide [14].

Risk of bias in the included studies and publication bias

Figure S3A in Supplementary File presents the risk of bias summary per domain for individual studies and for all included studies. Most studies showed a low risk of bias per domain, but 40% of the included studies (2/5) scored overall as hav-

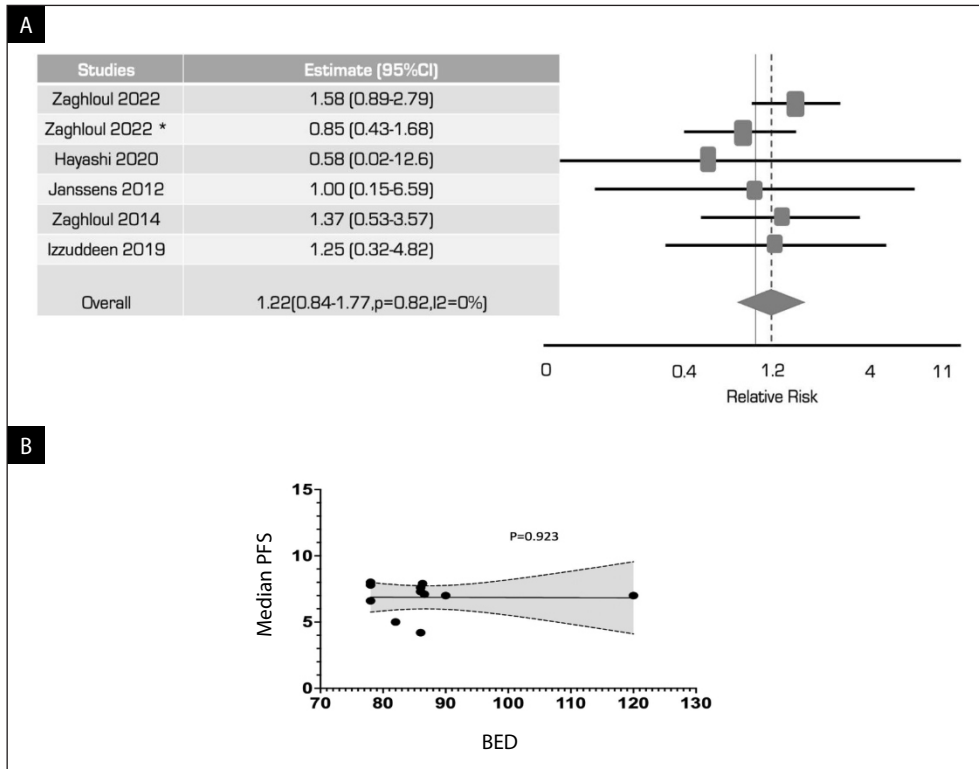


Figure 2. A. Meta-analysis of include studies for progression free survival; B. Metaregression analysis for the relationship between biologically effective dose (BED) and median progression free survival (PFS). CI — confidence interval

ing some concerns. We found no evidence of bias across trials for OS (Supplementary File — Fig. S3B).

Discussion

Our meta-analysis, encompassing five relevant studies published from 2013 to 2023, comparing HFRT and CFRT for DIPG, showed similar 1-year OS and 1-year PFS rates, with only one case of grade 3 toxicity in patients who received concurrent CFRT-temozolomide.

In the meta-regression analysis, no significant relationship between RT BED and OS/PFS was observed, suggesting that HFRT is a viable alternative to CFRT for DIPG patients. Furthermore, HFRT had the advantage of shortened overall treatment time (OTT) with no difference in treatment interruptions or rates of re-irradiation.

The median OS was nine months in both HFRT and CRT arms, confirming the poor prognosis of DIPG and the palliative nature of the treatment. Radiotherapy is the standard for DIPG because it may help improve symptoms, reduce steroid dependency, and improve quality of life. However,

CFRT with an OTT of about six weeks is not an ideal treatment option for patients with a life expectancy of less than 12 months. Although our findings agree with previous meta-analyses, the sample size gathered here allows us to hypothesize that HFRT is not inferior to CFRT¹⁶. The difference found in OS between the arms was 7%; to obtain a true difference in favor of HFRT, 332 patients would be required to be sure at 90% that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) excludes a difference in favor of the CFRT arm more than 7%. Therefore, it is reasonable to assume that HFRT may produce similar outcomes to CFRT.

In our meta-analysis, the toxicity rate was similar after HFRT or CFRT. The comparison of acute toxicity between the two arms, including skin reactions and dysphagia, showed no significant differences, even when we combined all reported grade 1-2 toxicity. Besides, no grade 3–4 RT-related acute toxicity was detected in patients who underwent HFRT, which provides similar safety of HFRT compared to CFRT.

The poor survival rate has led to several attempts at new treatment strategies [17–22]. The attempt to

combine radiotherapy with chemotherapy failed to improve OS [17–22]. In our meta-regression, studies using chemotherapy showed no significant benefit in OS or PFS with the addition of chemotherapy to radiotherapy. This lack of clinical benefit with the combined treatment agrees with data from a recent population-based study that investigated the treatment outcomes in a large sample (253 patients) of brain stem tumors [20]. In this real-world study, the use of chemotherapy regimens has increased over the last 20 years, but with no significant improvement in OS or PFS [23].

Moreover, although we have included retrospective studies with a higher risk of bias in the present meta-analysis than RCTs, the study design was not associated with OS or PFS in the meta-regression analysis.

Overall, these results demonstrate that HFRT is not inferior to CFRT, and future research integrating molecular mechanisms, such as mutations that change the H3 histone variants H3F3A, H3F3B, and H3K27M, could employ HFRT safely with the same efficacy as CFRT². Hence, the results of the NCT02274987 trial concerning the tumor genomic profile as a predictive tool are awaited. In contrast, reirradiation tolerance is also being evaluated in the NCT04670016 study.

Furthermore, it is essential to highlight the importance of shorter radiation courses not only in DIPG, especially in light of a long term global scarcity of linear accelerators (linacs) [24–26]. Utilizing ultra-hypo or hypofractionated radiation schedules not only enhances the convenience of radiotherapy for patients and their families but also mitigates the financial strain related to travel and time off work [27–36]. Additionally, such approaches have the potential to allow treatment centers to alleviate capacity constraints [27–36].

Although our analysis has found positive results with HFRT, it has some limitations that deserve to be mentioned: the small sample size and the inclusion of retrospective series are the main drawbacks. An additional restriction in the present study stems from the absence of detailed information regarding steroid dependence, treatment interruptions, and quality of life among DIPG patients in the trials under evaluation. As a result, evaluating any alterations within these domains was not feasible. Another limitation is linked to the use of three-dimensional conformal (3D) radiation in all stud-

ies. Therefore, these results do not apply to more advanced radiation techniques like IMRT, VMAT, IGRT, or proton beam. Nevertheless, even with these caveats, the current meta-analysis achieved a high statistical power by obtaining a large sample size, with no heterogeneity in the outcomes and reducing bias in the studies and publications, which supports the use of HFRT as a treatment option for DIPG.

Conclusion

Our meta-analysis comparing HFRT and CFRT for DIPG showed that HFRT yields similar 1-year OS and PFS rates as CFRT, with no grade 3 or higher toxicity observed. No relationship between BED and chemotherapy was observed in the treatment outcomes. Therefore, these findings support HFRT as a viable alternative to CFRT.

Data availability

Research data are stored and will be shared upon request to the corresponding author.

Conflict of interest

F.Y.M. reports previous consulting fee from Elekta and honoraria from Astra Zeneca, both outside the current work. G.N.M. reports previous honoraria from Varian and Astra Zeneca, both outside the current work. All other authors have no competing interests.

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Ethical statement

Ethical approval was not necessary for the preparation of this article.

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