REVIEW

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Evaluating the Role of Re-Irradiation in the Management of DIPG: A Systematic Review and Meta-Analysis of Current Evidence

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Abstract

Objective: Overall survival (OS) of patients with diffuse intrinsic pontine glioma (DIPG) is poor. Re-irradiation (re-RT) represents an emerging strategy aimed at improving outcomes for patients who experience recurrence or progression after initial radiation therapy (RT). While re-RT is increasingly used at progression, its survival benefit lacks robust quantification. This systematic review and meta-analysis aims to evaluate the impact of re-RT timing on OS and toxicity in pediatric DIPG. **Methods:** This review was conducted in the PubMed/MEDLINE, Europe PMC, and Scopus (2014-2024), following PRISMA guidelines. Meta-analysis used random-effects models to pool OS after re-RT (primary outcome). Heterogeneity was quantified via I^2 statistics. Secondary outcomes included symptom improvement and grade ≥3 toxicity. **Result:** Fourteen studies (n=357) were included. The pooled median OS after re-RT was 9.5 months (95%CI: 5.34-13.71), though substantial heterogeneity existed (I^2=98.9%, p <0.001). Patients receiving re-RT had longer median OS from diagnosis than non-re-RT counterparts (20.8 vs. 8.3 months). Neurological symptom improvement occurred in 64-100% of patients, with triad symptoms (ataxia, cranial neuropathy, long-tract signs) showing greatest responsiveness. Only 1.4% (5/357 patients) experienced grade ≥3 complications (dysphagia, pontine necrosis, hemorrhage). The pooled hazard ratio (HR) or re-RT versus non-re-RT groups was 0.43 (95%CI: 0.28-0.67), indicating a 57% reduction in mortality risk. **Conclusion:** This meta-analysis establishes that re-RT confers a statistically significant and clinically meaningful survival extension (median 9.5 months post re-RT), with low severe toxicity risk. While high heterogeneity reflects protocol variations (e.g., longer OS with >30 Gy regimens), re-RT consistently outperforms non-re-RT approaches. Re-RT also significantly reduces mortality risk (HR=0.43). We recommend standardized regimens using 1.8-2.0 Gy per fraction (≤24 Gy total) to optimize survival while minimizing toxicity. Future trials should prioritize dose optimization and patient stratification.

Keywords: Re-Irradiation- DIPG- Overall Survival

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Introduction

Diffuse intrinsic pontine glioma (DIPG) is a highly aggressive brainstem tumor predominantly affecting children [1, 2]. It presents considerable difficulties in diagnosis, treatment, and prognosis. Despite advancements in treatment, DIPG continues to be one of the most aggressive and fatal pediatric brain tumors, with a median survival duration of six to nine months post-diagnosis [3–6]. Since its introduction, radiation therapy (RT) has served as the cornerstone treatment for DIPG [3, 7, 8]; however, due to the tumors' aggressive characteristics, recurrence is unavoidable [5, 9–12]. Incorporating advanced imaging techniques facilitates improved evaluation of tumor progression and treatment response, thus assisting in the decision-making process regarding the optimal timing for re-irradiation (re-RT). With the guidance of advanced imaging techniques, re-RT shows significant potential in the assessment of tumor progression and response to treatment of DIPG [13, 14]. Furthermore, the exploration of concurrent therapies, including chemotherapy and immunotherapy, indicates that a multimodal strategy may improve the effectiveness of re-RT.

Re-RT signifies a novel approach designed to enhance outcomes for patients facing recurrence or progression following initial RT [1, 6, 11–21]. Conventional RT for DIPG typically involves focal irradiation at 54–60 Gy, administered in daily fractions of 1.8 to 2 Gy, following

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established consensus guidelines that seek to optimize local control while reducing toxicity to adjacent tissues. For re-RT, emerging research indicates that administering doses of 20 to 30 Gy in fractions of 1.8 to 3 Gy may lead to improved survival rates with manageable toxicity, especially when treatment is initiated at least 6 months after the initial RT improve survival with manageable toxicity. For instance, Gallito et al. [24] revealed that re-RT (with a median dose of 20 Gy) provided a median progression-free survival advantage of 2.4 months and an overall survival benefit of 3.8 months, with longer intervals between RT sessions (>12 months) associated with better outcomes. Consequently, the choice to undertake re-RT should be tailored to the individual, taking into account the patient's clinical condition, prior treatment history, and the potential advantages and disadvantages of these shortcomings. This review seeks to synthesize existing evidence regarding the timing, protocols, and outcomes of re-RT in pediatric DIPG, emphasizing the identification of optimal strategies and areas for future research. This review synthesized evidence on re-RT timing, protocols, and outcomes in pediatric DIPG, highlighting optimal strategies and future research priorities.

Through the synthesis of data from recent studies conducted between 2014 and 2024, we aim to offer insights that may guide clinical practice guidelines on the most effective strategies for managing recurrent DIPGs while prioritizing patient well-being. Our analysis will utilize a variety of sources to ensure a thorough examination of pertinent research findings. As we progress, it is crucial for radiation oncologists to stay updated on the most recent research findings and clinical practices to deliver optimal care for patients facing this disease.

Materials and Methods

Search Strategy

A comprehensive systematic search was conducted using the following databases, adhering to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Statement 2020 guidelines: PubMed/MEDLINE, Europe PMC, and Scopus. The search was conducted from 1 January 2014 until 25 October 2024, without any language limitations. In concordance with the population, intervention, comparison, and outcome framework (Supplementary Table S1), keywords were formulated as shown in Supplementary Table S2. The titles and abstracts of shortlisted studies from the given databases were screened independently. The reference lists of selected studies were also sought, and duplicates were then removed.

Inclusion and Exclusion

The inclusion criteria comprised clinical trials enrolling pediatric patients of any gender with progressive DIPG or re-RT first progression, patients with or without treatment history, and any previous methods of early DIPG diagnosis, whether through imaging only or with confirmation by biopsy.

Studies involving adolescent patients and animal samples were not included. Case reports or case series with a sample size of less than three, brief reports, further re-RT, and letters to the editor were excluded. Use of systemic therapy was not an exclusion criterion.

Data Extraction

The data were extracted as follows: Author, Year, Title, Intervention given, Method of administration; Number of patients with DIPG, Median age at initial diagnosis (in years), Median time from initial RT to re-RT, Outcome measures; Median overall survival (OS, in months), Median progression-free survival (PFS, in months), Complications related to re-RT (specifically ≥ grade 3), re-RT dose and fractions given, and additional systemic therapy. The primary outcomes evaluated were OS and PFS. Secondary outcomes included clinical/neurological symptom improvement (assessed via changes in ataxia, cranial neuropathy, long-tract signs, performance status, and/or quality of life before and after re-RT), tumor response, and toxicity profiles (incidence and severity of complications ≥ grade 3). In addition, also look for changes in symptoms from before therapy and after re-RT.

During the inclusion phase, individual study data were prepared in a presentable format, and the concluding remarks were also added. Existing neurological deficits that existed prior to re-RT were only included in complications counts if they were reported to have worsened following the radiation; otherwise, all other neurological problems were included if they occurred subsequently and were attributable to re-RT.

Statistical Analysis

Descriptive statistics were performed in Microsoft Excel (2016) using means, medians, ranges, and interquartile ranges (IQR). The mean age was weighted according to the number of patients in each study. The lack of individual data points across studies prevented the computation of standard deviation and median for age and follow-up calculations.

Due to anticipated heterogeneity, we performed a meta-analysis of overall survival (OS) using a random-effects model (Restricted Maximum Likelihood estimator). Pooled estimates are reported with a 95% confidence interval (CI). Heterogeneity was quantified using the I^2 statistic and Cochran's Q test. Influence diagnostics (Cook's distance, covariance ratios) assessed outlier impact. Publication bias was evaluated via funnel plot symmetry, Egger's regression, and fail-safe N tests.

A separate random-effects meta-analysis pooled hazard ratios (HR) for overall survival comparing re-RT versus non-re-RT groups. The natural logarithm of HR and standard error (SE) were extracted from studies, with results exponentiated for clinical interpretation.

Study Selection and Risk of Bias Descriptive

The process of article selection was done independently by the authors. The title and abstract were initially reviewed, and then the full text was read. Afterward, the studies were critically evaluated to determine methodological quality and eligibility. The Cochrane Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was used to assess the risk of bias in

the included reviews [25]. This tool comprised seven domains. (1) Bias due to confounding; (2) bias due to selection of participants; (3) bias in classification of interventions; (4) bias due to deviations from intended interventions; (5) bias due to missing data; (6) bias in the measurement of outcomes; (7) bias in the selection of the reported result. Any disagreements in the study review were resolved through discussion among authors until an agreement was reached.

Results

Literature Search

During phase I, the identification phase, 441 studies were identified, and 80 articles were discarded due to duplication. In phase II, the screening phase, 361 study titles and abstracts were screened, of which 323 were omitted as they did not warrant inclusion against the inclusion criteria. Subsequently, 28 studies were reviewed and assessed for eligibility. Then, 14 studies were excluded for the reason that the research was a case report, adolescent patients, or letters to editor. In phase III, the inclusion phase, a total of 14 trials from 2014-2024 were included in this study. The study selection process is based on the PRISMA 2020 diagram flow explained in Figure 1.

Clinical Features and Demographics

All study designs of the included articles consist of retrospective cohort and clinical trials. The total sample was 357 participants, consisting of children who were diagnosed with diffuse intrinsic pontine glioma (DIPG) and underwent RT and/or re-RT. The median age at initial diagnosis ranged from 5.5 to 8 years, and the median time from initial RT to re-RT ranged from 7.1 to 14 months. The total dose used in re-RT treatment varies with a range from 18 to 60 Gy and is delivered in 1.3 to 3 Gy per fraction. As many as 10 studies reported the use of additional systemic therapy during therapy with re-RT. The main characteristics of all the included studies are listed in Table 1.

Re-Irradiation Protocols

The patient's head was immobilized using a thermoplastic mask. Patients who were unable to follow instructions or remained immobile during the treatment were anesthetized. A non-contrast simulated computed tomography scan was registered with MR brain imaging to depict the target and normal tissue. The gross tumor volume included all gross tumors on MRI. The planning target volume was the gross tumor volume plus a 3 to 5 mm geometric margin. Treatment was delivered with intensity-modulated radiation therapy (IMRT) [16, 22].

Both conventional (dose/fraction: 1.8-2.0 Gy) and hypofractionated (dose/fraction: >2.0 Gy) radiotherapy regimens were permitted during initial radiotherapy. At first progression, a radiotherapy regimen consisting of at least ten fractions was required for analysis. At progression, the clinical target volume included the tumor as defined by FLAIR (if available) or T2-weighted MRI images with a margin of 0.0-1.0 cm. The margin was adjusted for bony structures and the tentorium. An additional margin of between 0.2 and 0.5 cm was added to create the planning target volume [19].

Treatment dose was determined using a phase 1-2 utility-based adaptive Bayesian design. Dose determination began at 24 Gy in 12 fractions, representing a biological equivalent dose (BED) of 40 Gy ($\alpha/\beta = 3$). The second (26.4 Gy in 12 fractions) and third (30.8 Gy in 14 fractions) dose levels represented BED escalations of 14% (biological effective dose (BED = 45.76 Gy) and 17% (BED = 53.39 Gy), respectively. Chemotherapy was not given with re-RT [16].

Survival Outcomes

The median OS from initial diagnosis across all studies was 16,45 (IQR: 14.4-18.6) months in DIPG patients [1, 2, 15–19, 21, 22, 23, 26–29]. From one study that examined OS based on time, it was found that OS at 12, 18, and 24 months was around 95 ± 4.9%, 37.2 ± 11.1%, and 15.9 + 8.4% [26]. In addition, in another study comparing OS in patients who underwent re-RT with those who did not undergo re-RT, the results obtained were OS at 6, 9, 12, and 18 months were 100 versus 95%, 87 versus 67%, 71 versus 33% and 23 versus 10% [19]. Other studies also showed that OS in patients who underwent re-RT was higher, namely 20.8 months compared to 8.3 months in those who only underwent RT [6].

Several studies also stated that several patients died during the study period. Two patients died due to intra-tumoral hemorrhage (days 84 and 126) and 3 patients could not receive complete treatment due to a rapid deterioration of their general health condition and died within 1 month [2, 26]. Whereas in another study, after a mean observation period of 15.5 months post-diagnosis, 40 patients (93%) died. The mean time from re-RT to death was 4.2 months (range within 0.6–10.3 months) [17].

Meta-Analysis of Overall Survival

The meta-analysis included 14 studies with 357 patients. The pooled median OS after re-RT was 9.52 months (95%CI: 5.34-13.71; Figure 3). Extreme heterogeneity was observed (I^2=98.9%, Q=538.48, p <0.001), attributable to clinical variability in re-RT protocols. For example, Wawrzuta et al. [29] reported an OS of 29.73 months (95% CI: 22.89-36.58) using 20-24 Gy regimens, while Janssens et al. [19] reported 14.770 months (95%CI: 13.55-15.85) with 18-30 Gy.

Hazard Ratio Analysis

Six studies reported hazard ratios for survival comparing re-RT versus non-re-RT groups. The pooled analysis demonstrated a significant survival advantage of re-RT (HR=0.43, 95%CI: 0.28-0.677; p=0.004; Figure 4), indicating a 57% reduction in mortality risk. Heterogeneity was low (I^2=26.9%, Q=5.56; p=0.35), reflecting consistent treatment effects across protocols.

Influence Diagnostics

Cook's distance analysis identifies Wawrzuta et al. [29] (distance = 0.45) and Lobon-Iglesias et al (2017) (distance = 0.17) as disproportionately influential (Supplementary

Table 1. Patient Demographics and Characteristics of Included Studies

No.	Study	N	Median age at initial diagnosis (yrs)	Median time from initial RT to re-RT (mo)	Additional systemic therapy	Re-RT total dose/fx given (Gy)		Median PFS (mo)	Median OS from initial diagnosis (mo)	Complications related to re-RT (≥ grade 3)
						Total dose	Fx			
1	Amsbaugh et al. 2019 [16]	12	N/A	12.3	No	24, 26, & 30.8	2-2.2	N/A	19.5	1 grade 3 hypoxia & dysphagia
2	Chavaz et al. 2022 [18]	25	8	7.1	Yes	18-30	1.8-2	8	13.7	N/A
3	Freese et al. 2017 [22]	3	6	14	No	20	2	9	17.3	N/A
4	Janssens et al. 2017 [19]	31	6	N/A	Yes	18-30	1.8-3	8.2	13.7	N/A
5	Kline et al. 2018 [6]	12	5.5 (re-RT), 8 (re-RT+Nivo)	11.8	Yes	24 (2 px: + 12 Gy boost)	2-2.4	7.7 (re-RT), 9.6 (re-RT+Nivo)	20.8	N/A
6	Krishnatry et al. 2021 [26]	20	7.5	8.4	Yes	30.6 (WBI), 21.6-30.6 (focal), & 39-45 (responders)	1.8	8.4	16.6	2 intracranial haemorrhage post-RT
7	Lassaletta et al. 2018 [15]	16	5.87	13	Yes	21.6-36	1.8-3	10.5	19.26	1 pontine necrosis
8	Lobon-Iglesias et al. 2018 [2]	14	6.5	9.4	No	N/A	N/A	N/A	11.3	N/A
9	Mankuzhy et al. 2024 [27]	20	5	8	Yes	20-30 & 30-60	2 & 3	N/A	15.5	N/A
10	Massimino et al. 2014 [21]	24	7.4	N/A	Yes	19.8	1.8	8.5	14.6	N/A
11	Panizo-Morgado et al. 2024 [17]	44	7.8	10.2	Yes	20-30.6	1.3-2.5	10	15.1	1 hydrocephalus (shunt required)
12	Pillay-Smiley et al. 2024 [28]	113	N/A	9.5	N/A	25	2.5	N/A	18	N/A
13	Wawrzuta et al. 2024 [29]	18	7.5	N/A	Yes	20 (n=16), 24 (n=2)	2	10	18.2	N/A
14	Zamora et al. 2021 [1]	5	N/A	10	Yes	20-24	2	N/A	16.3	N/A

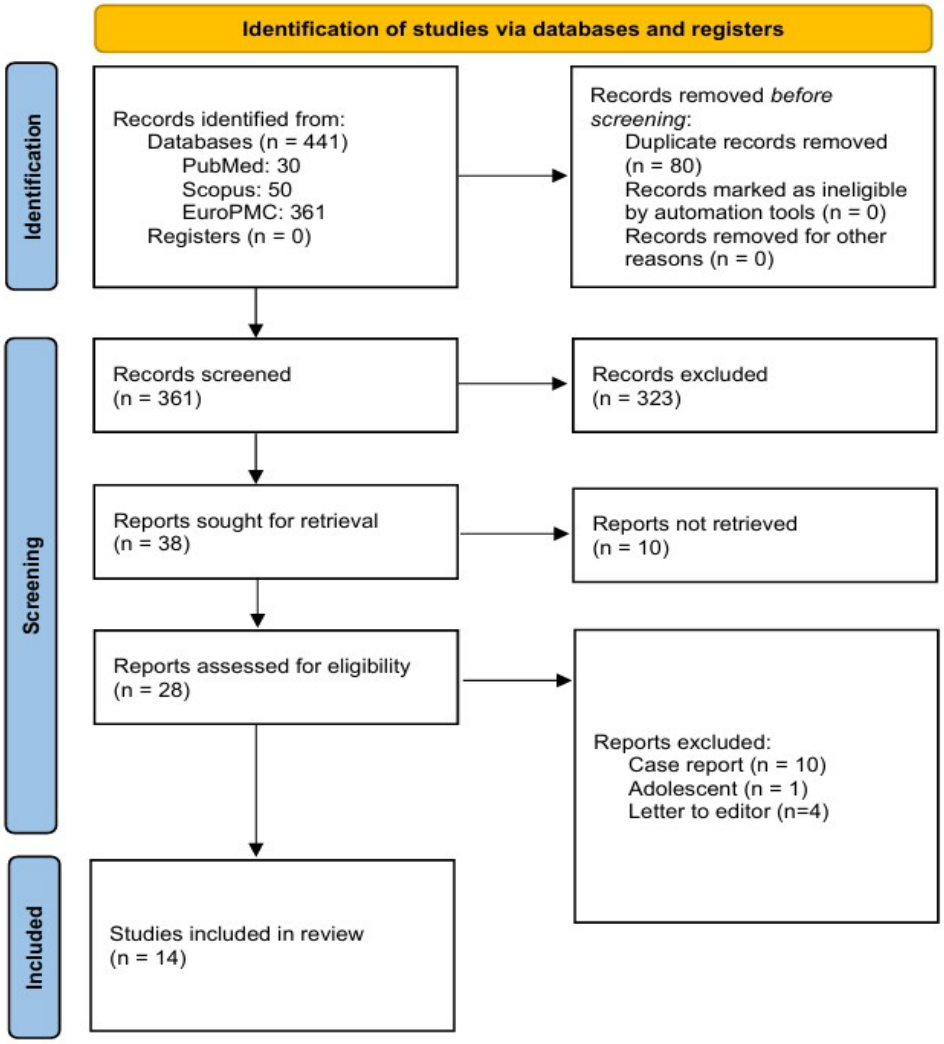

Figure 1. PRISMA Diagram Flowchart.

Figure S2). Covariance ratios <1 (0.54 and 0.96, respectively) confirmed their impact on model stability.

Clinical Improvement

A total of 9 out of 14 studies reported improvement in patients undergoing re-RT [6, 15–19, 22, 26, 29]. The indicators used to measure improvement varied in each study. The most widely used are neurological signs which generally consist of ataxia, cranial nerve, long tract signs, fatigue, and headache. Other indicators also used are 3 domains, triad symptoms, clinical symptoms, performance status, quality of life, and tumor response. Clinical improvement of patients from included studies is summarized in Table 2.

Toxicity Reports

The overall re-RT complication rate with ≥ grade 3 as reported in the included studies was 1.4% (5/357 patients). The complications reported are hypoxia and dysphagia, intracranial hemorrhage, hydrocephalus, and pontine necrosis with brain stem dysfunction and quadriparesis [15–17, 26]. While other patients only experienced mild to moderate toxicity symptoms, such as asthenia, nausea, and hearing impairment [16, 17].

Risk of Bias Synthesis Reports

Studies were assessed as mainly having a low to moderate risk of bias. The main problem that causes bias is that research conducted at different institutions so that the protocols uses are also different, such as the use of varying doses and fractions, which can affect outcomes and cause heterogeneity. In addition, several studies showed missing data, such as detailed clinical data regarding symptoms before and after re-RT and incomplete follow-up, so that the assessment level is moderate to high. Thus, overall studies (5 out of 14 studies) showed moderate bias results, and 5 other studies showed low bias assessment levels. While the remaining 4 studies showed a high risk of bias. The assessment of risk of bias summaries is presented in Figure 2.

Publication Bias Assessment

No evidence of publication bias was detected via funnel plot symmetry (Supplementary Figure S1), Egger's test (t-score=1.3253, p=0.2098), or Kendall's rank correlation (τ=0.2967, p=0.1572). Rosenberg's fail-safe N (5,212) indicated robustness against unpublished null studies. For the HR meta-analysis, funnel plot symmetry (Supplementary Figure S3) and Egger's test (p=0.6990),

Tabel 2. Patient Clinical Improvement of Included Studies

No.	Study	N/Total Sample (%)	Indicator	Improvement
1	Amsbaugh et al. 2019 [16]	10/12 (83.3)	3 domains (imaging, physician assessment of clinical symptoms, and patient/family-reported QoL)	10 patients in at least 1 domain, 6 in 2 domains, and 3 in all domains
2	Chavaz et al. 2022 [18]	16/25 (64)	Triad symptoms (cerebellar signs, cranial neuropathy, long-tract signs)	16 patients in at least 1 symptoms, 10 in at least 2 symptoms, and 6 in all
3	Freese et al. 2017 [22]	2/3 (66.7)	Clinical symptoms	Improvement in dysphagia, headaches, and cranial nerve deficits
4	Janssens et al. 2017 [19]	24/31 (77)	Performance status & Neurological signs	Performance status (n = 16) or a neurological sign (ataxia, n = 11; cranial nerve palsy, n = 11; long tract signs, n = 10; fatigue, n = 6; headache, n = 5)
5	Kline et al. 2018 [6]	12/12 (100)	Clinical symptoms & Quality of life	Symptom improvement and regained function important to quality of life, such as ambulation and swallowing
6	Krishnatry et al. 2021 [26]	20/20 (100)	Neurological deterioration (clinical criteria)	All patients had at least 2/3 clinical criteria and 3/3 in 6 patients
7	Lassaletta et al. 2018 [15]	13/16 (81%)	Neurological symptoms	13 patients improved after re-RT, in 6 patients the recovery was full
8	Lobon-Iglesias et al. 2018 [2]	N/A	N/A	N/A
9	Mankuzhy et al. 2024 [27]	N/A	N/A	N/A
10	Massimino et al. 2014 [21]	N/A	N/A	N/A
11	Panizo-Morgado et al. 2024 [17]	34/44 (77.3) & 21/35 (60)	Neurological symptoms & Tumour response	34 patients improved in neurological deterioration & 21 in tumour response from MRI assessment
12	Pillay-Smiley et al. 2024 [28]	N/A	N/A	N/A
13	Wawrzuta et al. 2024 [29]	14/18 (78)	Neurological symptoms	Improvement without adverse event of grade >2 toxicity
14	Zamora et al. 2021 [1]	N/A	N/A	N/A

or Kendall's rank correlation (τ=-0.4667, p=0.2722). Rosenberg's fail-safe N (36) indicated robustness against unpublished null studies

Discussion

Clinical Benefits

One of the leading causes of death from central nervous system malignancies in children is diffuse intrinsic pontine glioma (DIPG). DIPG is an aggressive tumor that represents 75% to 80% of brainstem tumors in children and 10% of all pediatric central nervous system tumors [30]. Due to local infiltration and brainstem localization, the disease cannot be treated with surgical resection. Therefore, the only available treatment modality is radiotherapy, which is traditionally delivered via conventional fractionated radiation therapy (CFRT) with a total dose of 54 Gy and hypofractionated radiation therapy (HFRT) with a total dose of 39 Gy divided into 13 fractions [31, 32]. Research by Zaghloul et al., comparing conventional and hypofractionated radiotherapy, showed that HFRT was not inferior to CFRT [33]. Radiotherapy is effective as a palliative treatment by providing temporary symptom relief and increasing the overall survival (OS) of patients by several months [7].

A study conducted by Amsbaugh et al. on 12 DIPG patients who underwent re-RT showed that clinical improvement was observed in all but 1 patient, and quality of life improved in almost two-thirds of all patients. Radiographic improvement was seen in 8 patients (66.7%). Clinical improvement at 1 month was observed in 11 patients (91.7%). Of the 11 patients with assessable quality of life (QoL) data, 63.6% had QoL improvement [16]. Another study by Chavaz et al. assessed improvement based on a triad of neurological symptoms consisting of cerebellar signs (CB), cranial neuropathy (CN), and long-tract signs (LT). Of the 25 patients, 16 patients (64%) experienced clinical benefit in at least one of the three triad symptoms, 10 (40%) in at least 2 symptoms, and 6 (24%) experienced improvement in all three triad domains [18]. This is in accordance with previous studies, that the majority of patients who underwent re-RT therapy experienced symptom relief [34].

Based on the doses used, Chavaz et al. found that

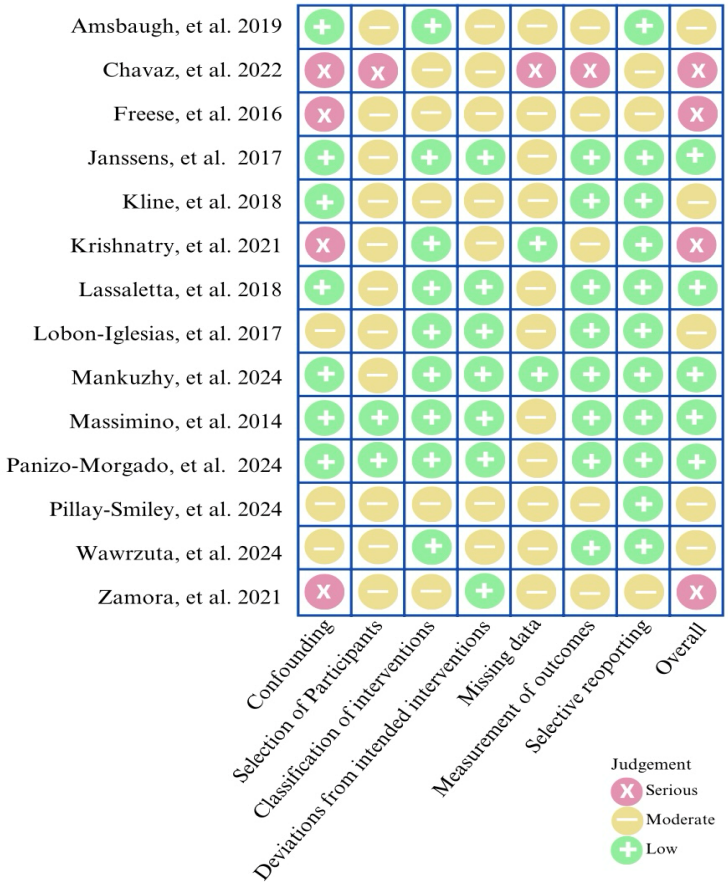

Figure 2. Risk of Bias Summaries with ROBINS-I Tool Summary

a total dose of <20 Gy was associated with a global clinical response rate of 71% of cases, while patients receiving ≥20 Gy had clinical benefit in 82% of cases. Different re-RT dose regimens did not provide evidence of differences regarding CN signs, LT, headache, and fatigue improvement. However, DIPG patients receiving re-RT doses ≥20 Gy may experience slightly better improvement regarding ataxia [18]. In addition, the study by Krishnatry et al. also showed better safety and outcomes with higher doses of 39.6 to 45 Gy. The study also found that a dose of 43 Gy seemed to provide the best results [26]. This is in line with the study by Dassi et al., which showed good

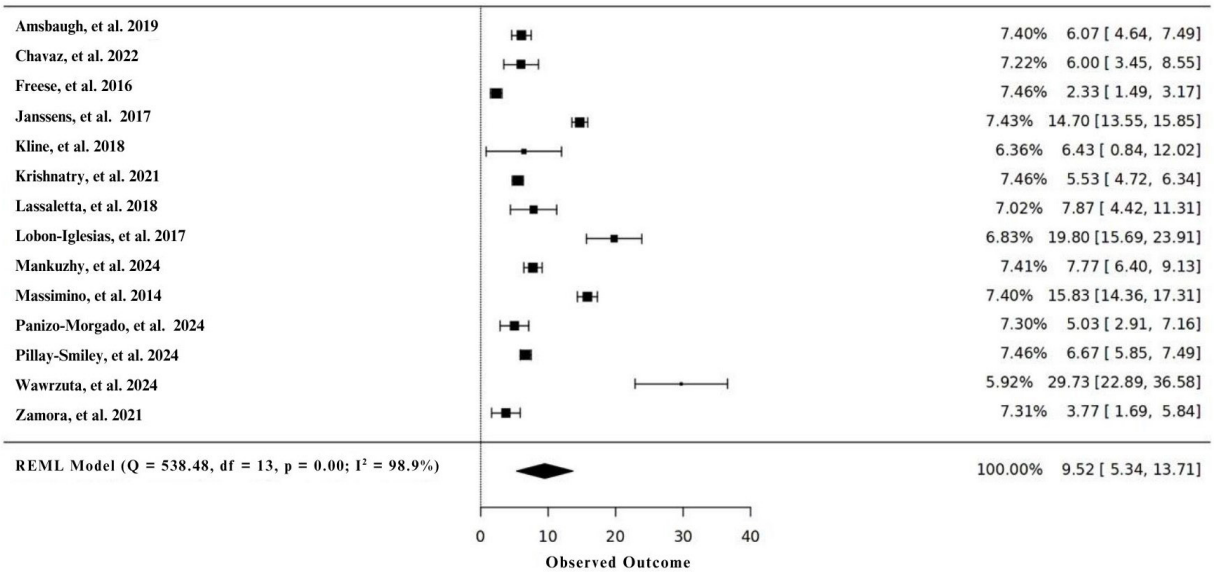

Figure 3. Forest Plot of Pooled Overall Survival After Re-Irradiation in Diffuse Intrinsic Pontine Glioma: Random-Effects Meta-Analysis

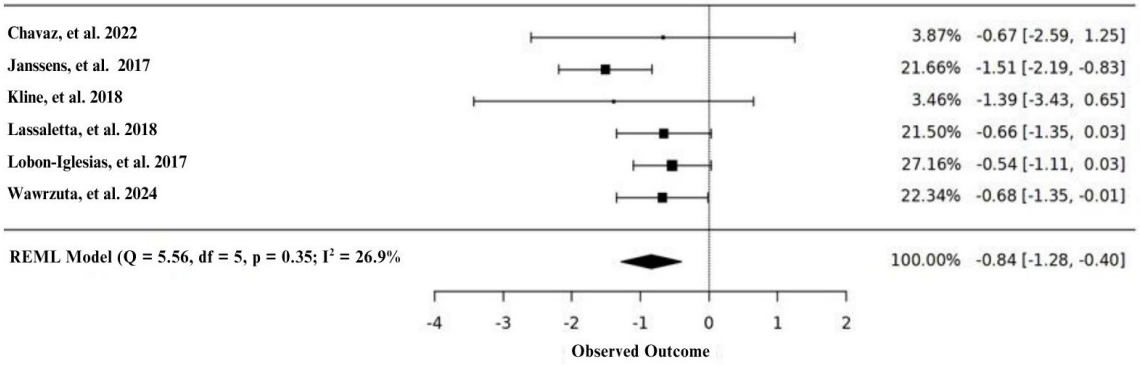

Figure 4. Forest Plot of Pooled Hazard Ratio for Overall Survival: Re-Irradiation vs. Non-Re-Irradiation Groups

results in using doses above 30 Gy (13 patients with good clinical status received more than 50 Gy), without reporting serious side effects [35].

Toxicity Concerns

Of the total patients, it was reported that 5/357 patients (1.4%) experienced serious complications. One patient suffered from pontine necrosis with brainstem dysfunction and quadriparesis after receiving 30 Gy in 10 fractions. This severe toxicity may be related to the higher fraction size delivered in this case (3 Gy) [15]. The other case was that of severe hypoxia due to dysphagia during a 30.8 Gy over 14 fraction regimens [16]. This suggests avoiding larger fraction sizes whenever possible to minimize the risk of complications. Although DIPG appears radioresistant to relatively high initial doses (54 Gy), doses of 24 to 30 Gy over 10 to 17 fractions have been reported to have minimal toxicity and have shown some efficacy in repeat RT. Future larger standardized trials will improve understanding of appropriate thresholds, considering patient age, time since initial RT, incidence of radiation necrosis, and practical considerations such as the timing of hypofractionated RT versus standard RT [11].

Lassaletta et al. and Amsbaugh et al. recommend that re-RT for DIPG use fraction sizes in the range of 1.8-2.0 Gy and should not exceed 24 Gy in 12 fractions [15,16]. Current practice is to offer re-RT as standard palliative care for patients who progress more than 6 months after the initial RT, as these patients are most likely to benefit from re-RT. Based on time to recurrence, there are dose guidelines divided into 6-12 months and more than 12 months. If re-RT is given between 6 and 12 months from the initial RT, then 30.6 Gy in 17 fractions is prescribed. However, if re-RT is given more than 12 months from the initial RT, then 36 Gy in 20 fractions is prescribed [12].

Based on the overall results of the study, the median time interval to the nearest re-RT from the initial RT was 7 months [18]. Another study by De Pietro et al. recommended a re-RT time of at least 6 months between 2 radiation treatments which was associated with better outcomes. In addition, RT with a dose of 54–60 Gy in 1.8–2.0 Gy per fraction remains the standard of care, but its role is mainly palliative and provides only temporary relief. When performing re-RT, it is essential to keep the dose as low as possible to the normal brain tissue surrounding the recurrent tumor and sensitive structures such as the brainstem, spinal cord, and optic apparatus. Therefore, high-precision stereotactic techniques in re-RT will allow highly accurate patient positioning and dose delivery and may replace conventional RT in clinical practice [36].

Sources of Heterogeneity

The extreme heterogeneity (I^2=98.9%) in OS outcomes reflects critical variations in reRT protocols. Studies using >30 Gy doses (e.g., Krishnatry et al. 2021) reported longer OS (16.6 months), while hypofractionated regimens (<20 Gy) showed poorer outcomes (Panizo-Morgado et al. 2024; 5.03 months). Wawrzuta et al.'s [29] outlier result (29.73 months) may reflect unique patient selection criteria or concurrent therapies. Future trials should standardize dosing intervals and patient stratification.

Outcomes

Several studies conducted research comparing OS in patients who underwent re-RT and those who did not undergo re-RT or only underwent RT. Of the 8 studies that reported PFS values, the median value was 9.1 months with a range of 8 to 10.5 months [15, 17–19, 21, 22, 26, 29]. The study by Kline et al. compared PFS values in RT patients with or without nivolumab and showed a significant difference, 7.7 months compared to 9.6 months with nivolumab. Meanwhile, the PFS results after re-RT showed no significant difference, namely 4.1 and 4.2 months with nivolumab [6]. From the initial diagnosis, the median OS from across all studies was 16,45 months (range 11.3-20.8 months) [1, 2, 15–19, 21, 22, 26–29]. Kline et al. study also showed a significant difference in OS with 20.8 months in patients who underwent re-RT compared to 8.3 months in those who only underwent RT [6]. Thus, patients with DIPG who received re-RT at the time of recurrence showed better OS compared to those who received only RT at the time of diagnosis.

Higher doses of radiotherapy during re-RT were associated with longer patient survival. Patients receiving >20 Gy had an estimated median survival of 21.1 months, compared with 14.9 months for those receiving ≤20 Gy. Re-RT can prolong survival by several months and maintain satisfactory functional status. However, optimizing the dose and fraction of re-RT, as well as

combining it with other therapies, is still needed [17]. Every patient who underwent re-RT experienced an improvement in clinical symptoms. These results support the use of re-RT in the setting of recurrent DIPG, not only to improve OS, but also quality of life through symptom relief [6].

Study Limitation

There are several limitations to this study. Because this study conducted a review with the majority of retrospective studies, there is the potential to cause bias in the results. In addition, the sample size of the studies used was also limited with different protocols used. While publication bias was absent, our meta-analysis is limited by high heterogeneity and retrospective data. Influence diagnostics highlight that pooled OS (Supplementary Figure S2) is sensitive to outlier studies, necessitating cautious interpretation. Nevertheless, we re-demonstrate the poor prognosis of this disease and the potential benefits of re-RT. These findings should be explored in further clinical trials to prove safety, characterize side effects, and clinical outcomes when administered to a larger sample size. While certain trials have shown effectiveness with prolonged survival rates, the results are not generalizable and should be supported by further controlled clinical trials to prove their benefits.

In conclusion, despite advances in radiation, systemic treatments, and advances in cancer research, survival rates for children diagnosed with DIPG have not improved significantly in the past two decades. While re-RT is not a cure and may not apply to every diagnosis, the results of this study suggest that re-RT is a positive step toward improving the prognosis of this disease. Overall, this review recommends that re-RT for DIPG use fraction sizes in the range of 1.8-2.0 Gy and should not exceed 24 Gy in 12 fractions to optimize outcomes.

This meta-analysis confirms that re-RT reduces mortality risk by 57% (HR=0.43) and extends median survival after progression by 9.5 months after progression, establishing it as a high-impact intervention for recurrent DIPG.

Author Contribution Statement

All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by E.N. and N.R. The first draft of the manuscript was written by E.N. and N.R., all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data

The data supporting the findings of this systematic review and meta-analysis are derived from previously published studies, which are cited in the article. No new datasets were generated or analyzed during the current study. Data extraction sheets and analysis code are available from the corresponding author upon reasonable request.

Registered Dataset or Clinical Trials

This systematic review and meta-analysis was not prospectively registered in any database

Body Approved

Ethical approval was not required for this study as it is a systematic review and meta-analysis of previously published data and does not involve direct participation of human subjects.

Ethical Issue

No ethical issues were identified in this study, as it involved the analysis of previously published data and did not involve direct interaction with human or animal subjects.

Conflict of interest

The authors have declared that no conflict of interest exists.

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