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Hypofractionated radiotherapy versus conventional radiotherapy for diffuse intrinsic pontine glioma
A systematic review and meta-analysis

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Abstract

Background: The standard treatment for diffuse intrinsic pontine glioma (DIPG) is radiotherapy, although conventional fractionated radiotherapy (CFRT) may not be in the best interest of the patient. Instead, hypofractionated radiotherapy (HFRT) may shorten the treatment period and reduce related costs for this treatment, which is typically palliative in nature.

Methods: This systematic review and meta-analysis evaluated survival outcomes among patients who received HFRT or CFRT for DIPG. The PubMed, Medline, EMBASE, Cochrane Central Register, and Scopus databases were searched to identify relevant studies. Overall survival was the primary outcome of interest and progression-free survival was the secondary outcome of interest.

Results: The search identified a total of 2376 reports, although only 4 reports were ultimately included in the meta-analysis. The studies included 88 patients who underwent HFRT and 96 patients who underwent CFRT. Relative to CFRT, HFRT provided comparable outcomes in terms of overall survival (hazard ratio [HR]: 1.07, 95% confidence interval [CI]: 0.77–1.47) and progression-free survival (HR: 1.04, 95% CI: 0.75–1.45).

Conclusions: The results of this meta-analysis suggest that CFRT and HFRT provide similar survival outcomes for patients with DIPG.

Abbreviations: CFRT = conventional fractionated radiotherapy, CI = confidence interval, DIPG = diffuse intrinsic pontine glioma, HFRT = hypofractionated radiotherapy, HR = hazard ratio, OS = overall survival, PFS = progression-free survival, SE = standard error.

Keywords: diffuse intrinsic pontine glioma, hypofractionated radiotherapy, meta-analysis

1. Introduction

Diffuse intrinsic pontine gliomas (DIPG) have a poor prognosis and are the leading cause of brain tumor-related deaths among pediatric patients.[1] The median overall survival (OS) in these

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cases is <12 months, with OS rates of only 30% at 1 year and 10% at 2 years.[1–3] Patients with DIPG may present with neurologic symptoms that include cranial nerve disorders, cerebellar ataxia, and long-tract signs.[4] Unfortunately, given the vital nature of the brainstem and the infiltrative growth of DIPG, gross total resection is generally impossible, although stereotactic biopsy can be performed in select cases.[5] Based on these factors, the standard treatment for DIPG is radiotherapy, which can improve or stabilize the patient's neurologic symptoms and decrease the need for corticosteroids.[4] Conventional fractionated radiotherapy (CFRT) is typically used in this setting and takes approximately 6 weeks (generally 54 Gy in 30 fractions). However, given the median survival of <12 months, this treatment is considered palliative, and prolonged treatment periods reduce the patient's quality of life. Thus, hypofractionated radiotherapy (HFRT) may be useful in this setting, based on its shorter treatment time, fewer hospital visits, and decreased use of treatment resources.[6]

Janssens et al[7] performed a matched cohort analysis to compare outcomes between HFRT (44.8 Gy in 16 fractions or 39 Gy in 13 fractions) and CFRT, which revealed that HFRT provided equivalent survival outcomes with a lower treatment-related burden. Zaghloul et al[8] performed the first prospective randomized controlled trial to confirm this result, which revealed no significant differences in the median values for OS and progression-free survival (PFS) between the HFRT (39 Gy in 13 fractions) and CFRT groups. However, the small sample size was insufficient to conclusively determine non-inferiority, which is

related to the low incidence of DIPG. Therefore, this systematic review and meta-analysis aimed to confirm whether HFRT and CFRT provided similar survival outcomes among patients with DIPG.

2. Methods

2.1. Search strategy

The systematic review aimed to identify reports that compared survival outcomes between HFRT and CFRT among patients with DIPG. The PubMed, Medline, EMBASE, Cochrane Central Register, and Scopus databases were searched without any language restrictions. The search terms were designed to provide maximum sensitivity: (diffuse intrinsic pontine glioma) or (diffuse brainstem glioma) or (midline glioma) and (radioth* or radia*). Ethical approval are not necessary because this study was not direct enrollment of human.

2.2. Selection criteria

Two authors (JWP, JP) independently reviewed the search results to identify studies that compared HFRT to CFRT and enrolled >20 patients with DIPG. Eligible reports were required to include specific data regarding the OS and PFS outcomes. However, reports were considered ineligible if they were letters, conference papers, review articles, case reports, or part of a book. In the event that the search identified both a pilot study and a definitive study, the definitive study was selected for inclusion.

2.3. Data extraction

The 2 reviewers independently extracted data regarding the patient eligibility criteria, interventions, and survival outcomes. The primary outcome of interest was OS and the secondary outcome of interest was PFS. Data from all included studies were re-reviewed by another reviewer, and any discrepancies were resolved via discussion until all reviewers achieved complete agreement regarding the extracted data.

2.4. Statistical analysis

The data analysis was performed using Cochrane's Review manger (version 5.3). Treatment efficacy was judged based on the hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and PFS. If the HR or CI values were not reported, these values were calculated based on the number of events and median survival. The standard error (SE) values were calculated based on the CI values.[9] Heterogeneity testing was performed, and a fixed-effect model was used in instances with an I^2 of <50% or a P-value of >0.1. A funnel plot and Egger test were used to identify publication bias. Differences were considered statistically significant at P-values of <0.05.

3. Results

3.1. Search results and study characteristics

The review identified 2376 reports, although only 1629 reports remained after duplicate publications were removed. A further 1615 reports were excluded after the titles and abstracts were screened, and 10 additional reports were excluded after a full-text review (Fig. 1). All screened abstracts were written in English, and

the reports to be read in full text were also written in English. Thus, the meta-analysis ultimately included data from 4 articles (Table 1).[10,11,7,8] Two studies were randomized controlled trials[11,8] and 2 were retrospective studies,[10,7] that included one matched cohort analysis.[7] The eligible reports were published during 2013 to 2020. The studies evaluated 194 patients, including 88 patients who underwent HFRT (39 Gy in 13 fractions or 44.8 Gy in 16 fractions) and 96 patients who underwent CFRT (total dose: 50.4–60 Gy). Adjuvant temozolomide was concurrently administered with the radiotherapy in one trial.[11]

3.2. Survival outcomes

The fixed-effect model was selected based on the findings for OS ($I^2 = 0$ and $P = .97$) and for PFS ($I^2 = 0$ and $P = .56$). Relative to CFRT, HFRT provided comparable outcomes in terms of OS (HR: 1.07, 95% CI: 0.77–1.47) and PFS (HR: 1.04, 95% CI: 0.75–1.45). The results are shown in Figs. 2 and 3.

3.3. Toxicity

Janssens et al[7] reported that HFRT had a significant shorter median treatment time than CFRT (20 days vs 41 days, $P < .01$). Three reports described toxicity-related data,[11,7,8] albeit with very different criteria. The only reported grade 3 toxicity involved a single case of subdural hemorrhage in the CFRT plus temozolomide arm from the study by Izzuddeen et al.[11] There were no statistically significant differences in grades 1 and 2 toxicities from the other 2 studies.[7,8]

3.4. Sensitivity analysis and publication bias

Table 2 shows the results of the sensitivity analysis for OS, which failed to detect significant heterogeneity. Figures 4 and 5 show the funnel plot results for OS and PFS, which failed to detect significant publication bias.

4. Discussion

There is a growing interest for the use of HFRT for glioblastoma in elderly patients,[12–16] and to treat breast cancer,[17–19] and prostate cancer.[20–24] This strategy aims to reduce treatment costs and hospital visits, while providing similar treatment outcomes.[25–27] Treatment costs and patient convenience are important factors for breast cancer cases with a good prognosis, and the HFRT strategy may even improve the quality of life for elderly patients with glioblastoma who have a poor prognosis.[27] Similar to glioblastoma, DIPG has a very poor prognosis and most patients die within 1 year, which generally makes the treatment palliative in nature.[1,2,4] Radiotherapy is the treatment of choice for DIPG because it may help improve symptoms, reduce steroid dependency, and improve quality of life. Moreover, a treatment period of approximately 6 weeks is not ideal for patients who are expected to survive for <1 year, and Negretti et al[6] have reported that HFRT was effective and required a shorter treatment duration for DIPG.

Haas-Kogan et al[28] estimated that the α/β ratio of $p53$ mutated glioblastoma was 2 Gy. According to a linear-quadratic model, a relatively low α/β ratio may be sensitive to high fraction
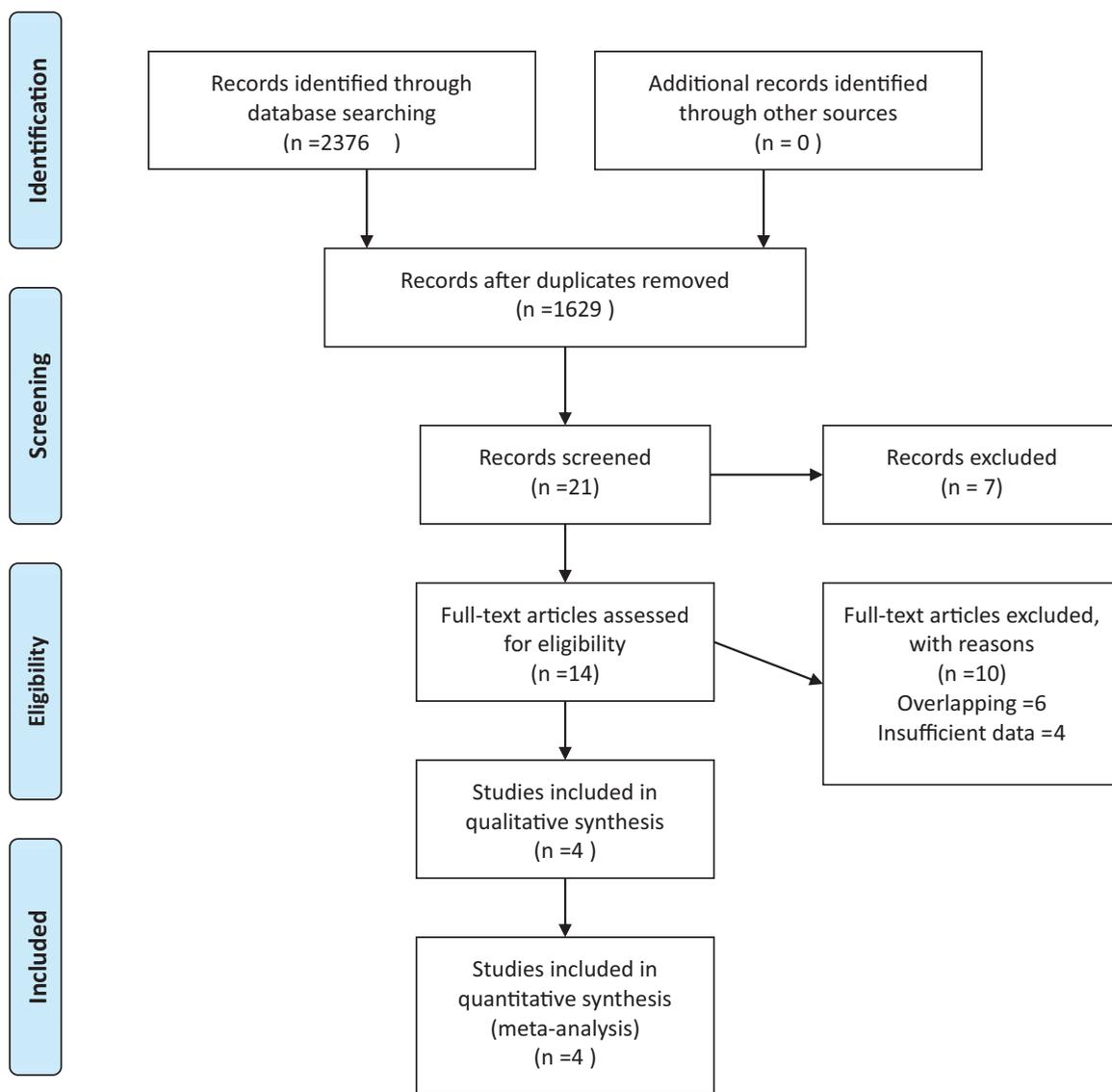
Figure 1. PRISMA flow chart.

sizes.[29] The biologically effective dose (BED) can be calculated using the following formula:

$$BED = nd(1 + d/\alpha/\beta)$$

n is a number of fractions and d is the dose per fraction.[10]

The BEDs from the 2 schedules of 44.8 Gy per 16 fractions and 39 Gy per 13 fractions were calculated to be 107.52 and 97.5 Gy, respectively; these values were similar to 102.6 Gy, the BED from

Table 1

Summary of the included studies.

| Study	Country	Year	Number (CFRT/HFRT)	Randomization	Median age	Dose	Chemoradiotherapy
Hayashi[10] (2020)	Japan	2000–2018	15/9	No	6.3 (1.6–14)	50.4–59.4 Gy/28–33 fx. vs 44.8 Gy/16 fx.	No
Izzuddeen[11] (2020)	India	2016–2018	18/17	Randomized phase II	7 (4–35)	60 Gy/30 fx. vs 39 Gy/13 fx.	Yes (concurrent and adjuvant temozolomide)
Jansssens[7] (2013)	Netherlands, UK, Canada, Belgium	2002–2010	27/27	Matched cohort	7.5 (3.7–13.7)/7.3 (2.8–14.6)	54 Gy/30 fx. vs 44.8 Gy/16 fx. or 39 Gy/13 fx.	No
Zaghloul[8] (2014)	Egypt	2007–2011	35/36	Randomized phase III	7.9 ± 3.6	54 Gy/30 fx. vs 39 Gy/13 fx.	No
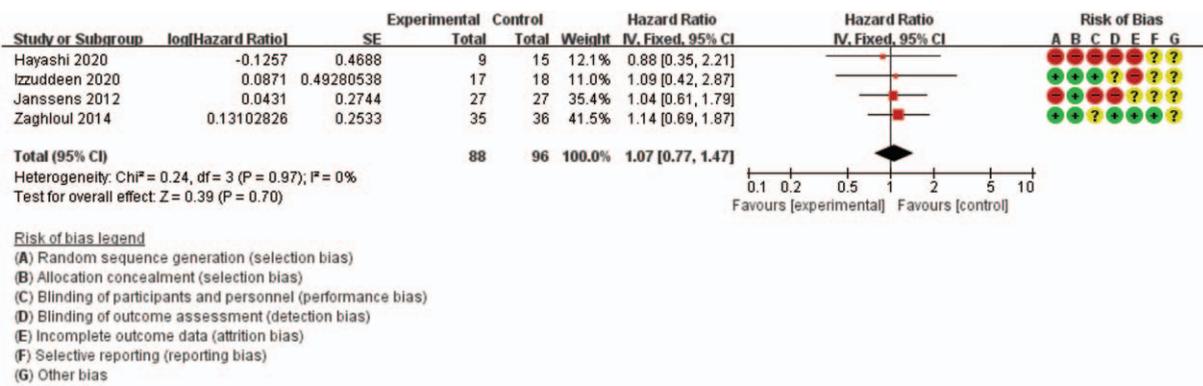
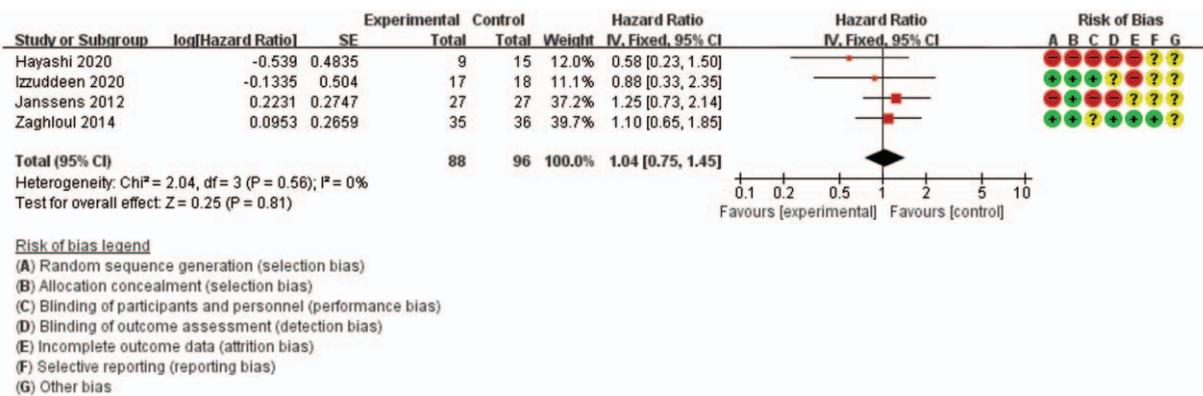**Figure 2.** Forest plot of overall survival.

Figure 3. Forest plot of progression-free survival.

the conventional fractionation schedule. Therefore, the biological effects of HFRT and CFRT might be similar.

This meta-analysis revealed no significant differences in OS and PFS between the CFRT and HFRT groups. Zaghloul et al[8] performed the first phase III randomized controlled trial that compared HFRT (39 Gy in 13 fractions) to CFRT (54 Gy in 30 fractions) in pediatric patients with DIPG. The study enrolled 80 patients, but only randomized 71 patients, and ultimately failed to detect significant differences in OS and PFS. Moreover, the differences in the 18-month rates were only 2.2% for OS and 1.2% for PFS, with CI values (–21–25% for OS and –20–22% for PFS) that substantially exceeded the required non-inferiority margin (20%). A second phase II randomized controlled trial was performed by Izzuddeen et al,[11] which only included 35 patients. This is likely related to the difficulty in enrolling a large sample of patients, given the low incidence of DIPG. Therefore, a meta-analysis is likely necessary to determine whether HFRT and CFRT provide equivalent outcomes for DIPG cases.

Table 2

Sensitivity analysis for overall survival.

Excluded study	Hazard ratio	95% confidential interval
Hayashi 2020	1.09	0.78–1.54
Izzuddeen 2020	1.06	0.67–1.49
Janssens 2013	1.04	0.61–1.79
Zaghloul 2014	1.02	0.67–1.54

Several systematic reviews have evaluated the role of HFRT to treat DIPG. Hu et al[30] performed a systematic review of the Cochrane database to identify phase III randomized controlled trials, although their review only identified the Zaghloul et al[8] study. Gallitto et al[31] also performed a systematic review that compared CFRT, HFRT, and hyperfractionated radiotherapy for DIPG. Their search identified 49 CFRT, 7 hyperfractionated radiotherapy, and 3 HFRT studies, although they failed to detect significant differences between HFRT and CFRT in terms of the median OS (9.0 months vs 9.4 months) and time to progression (5.0 months vs 7.6 months). However, that review did not employ a meta-analysis to compare HFRT and CFRT, and only included 2 studies that were published before 2019.[7,8] However, 2 related reports were published in 2020, which facilitated our meta-analysis of the outcomes after HFRT and CFRT.[10,11]

The HFRT and CFRT strategies appear to have similar toxicities. Zaghloul et al[8] reported various acute toxicities in the 2 groups, which included skin reactions, hearing issues, decreased appetite, dysphagia, fatigue, insomnia, nightmares, and seizure, although there were no significant differences between the HFRT and CFRT groups. Other studies[10,11,7] failed to identify any grade 3–4 radiotherapy-related acute toxicities in patients who underwent HFRT, and the HFRT and CFRT strategies appeared to provide a similar efficacy. Zaghloul et al[8] evaluated steroid discontinuation, which occurred in 6 HFRT cases and 5 CFRT cases, and also noted that the HFRT group exhibited significant improvements in neurologic conditions (cranial nerve disorders and ataxia). Janssens et al[7] reported that steroid treatment could
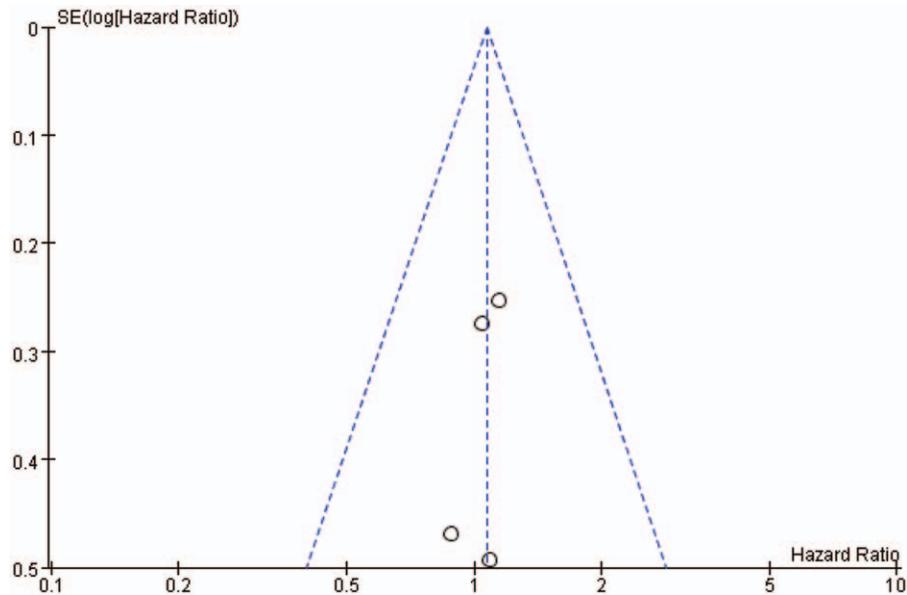
Figure 4. Funnel plot of overall survival.

be temporarily discontinued for 78% of patients in the HFRT group, and that the treatment duration was significantly shorter for HFRT than for CFRT (20 days vs 41 days, $P < .01$).

Several treatment strategies have been attempted for DIPG. Unfortunately, chemotherapy failed to improve survival in these cases.[32] Reirradiation is an attractive option to improve the prognosis with minimal toxicity for patients who experience disease progression after radiation therapy.[33] However, future strategies should be based on our increasing understanding of the radiological, molecular, and clinical characteristics of DIPG, such as mutations that affect the H3 histone variants H3F3A and HIST1H3B.[34,35]

The present study has several limitations. For example, 2 of the 4 studies used a retrospective design, which might have introduced significant bias. However, Janssens et al[7] used a matched cohort design with well-balanced treatment arms. Hayashi et al[10] involved a retrospective review of a small sample of patients, although the sensitivity analysis revealed that study had a minimal effect on the heterogeneity in our findings. There is an ongoing phase III randomized trial that is comparing HFRT (39 Gy in 13 fractions and 45 Gy in 15 fractions) to CFRT (54 Gy in 30 fractions) among a larger sample of patients (NCT01878266: https://clinicaltrials.gov/ct2/show/study/NCT01878266).
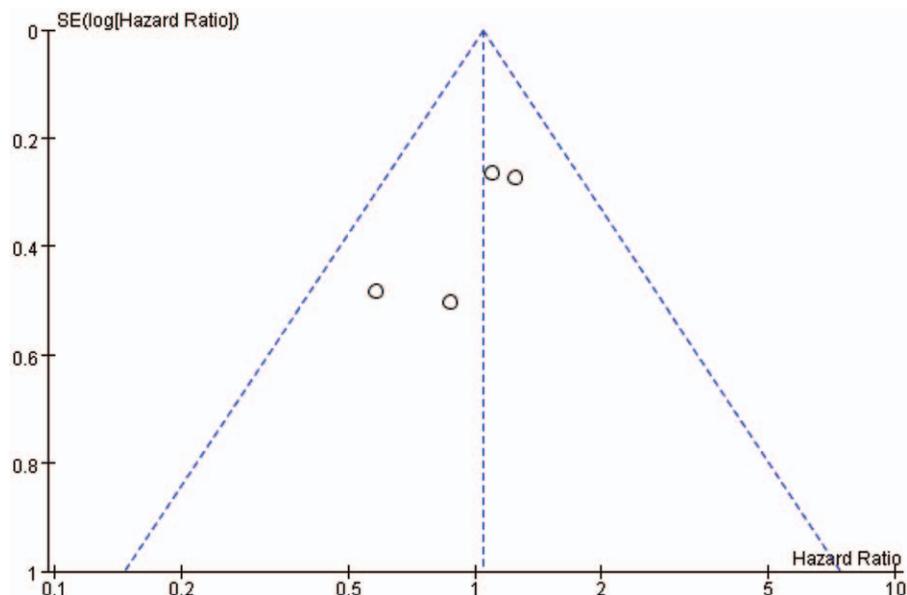

Figure 5. Funnel plot of progression-free survival.

In conclusion, this systematic review and meta-analysis revealed that HFRT and CFRT provided similar survival outcomes for patients with DIPG. Furthermore, HFRT and CFRT may have similar treatment toxicities. Thus, HFRT may be considered a standard treatment given its benefits in terms of decreased treatment burden, fewer hospital visits, and increased quality of life. Nevertheless, the small sample size and retrospective design of some studies highlights the need for larger randomized controlled trials to confirm this benefit.

Author contributions

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