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Hypofractionated stereotactic radiotherapy combined with chemotherapy or not in the management of recurrent malignant gliomas: A systematic review and meta-analysis

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ABSTRACT

Hypofractionated stereotactic radiotherapy (HFSRT) is a common salvage treatment for recurrent malignant glioma (MG). However, it remains controversial whether the combination of HFSRT and chemotherapy could improve survival for patients with recurrent MG compared to HFSRT alone. The present systematic review and meta-analysis aims to investigate this question, and tries to determine to what extent the addition of chemotherapy to HFSRT affects survival. A systematic review was performed to analyse the survival for patients treated with HFSRT combined with chemotherapy or not. Hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival (OS) were pooled with random effects; and standard mean difference (MD) with 95% CIs for OS were pooled using the same strategy. A total of 7 studies including 388 patients with recurrent MG were eligible for our study. The OS survival of patients receiving combination therapy ranged from 8.7 to 23 months, and the median OS of patients underwent HFSRT ranged from 3.9 to 12 months. The meta-analyses resulted in the pooled HR of 0.44 (95% CI 0.30-0.65, $p < 0.0001$) (Cochran Q statistic 4.70, P = 0.320, $I^2 = 14.8\%$) and pooled standard MD of 0.80 months (95% CI 0.41–1.18, $p < 0.001$) (Cochran Q statistic 10.16, $p = 0.71$, $I^2 = 50.8\%$). The present study suggests that HFSRT + chemotherapy confers a slight survival improvement for patients with recurrent MG as compared with sole HFSRT management. To draw a more solid conclusion, greater investigation is warranted.

1. Introduction

Malignant glioma is the most frequent brain malignancy in adults, accounting for more than 70% of all the malignant brain tumors. [1] The standard of care for MG is maximal safe surgical resection plus radio-chemotherapy followed by the maintenance of temozolomide (TMZ) [2]. Though the standard treatment results in prolonged survival duration for patients, the high aggressiveness of MG makes tumor recurrence inevitable [3]. Almost all patients recurred within 2 years after initial treatment [4,5].

To date, several treatment options for recurrent MG are employed in clinical practice, including re-resection, re-irradiation, chemotherapy, or combination of them. [6] Re-irradiation appears to be advantageous because of the good feasibility and acceptable side-effect, considering that more than 90% of the recurrences occur within 2 cm of the initial lesions [7–9]. Among the modalities of re-irradiation, HFSRT, usually delivered with a fraction dose of >2 Gy, has been increasingly used in patients with recurrent MG. [10]. Hypofractionated stereotactic radiotherapy has the advantages of deciding a precise and accurate irradiated dose, the ability to deliver a large total dose and short treatment duration [11]. Over the years, many studies reported good outcomes for patients with recurrent MG treated with HFSRT. In these studies, some employed HFSRT alone for patients, while other employed HFSRT in combination with chemotherapy for patients. Consequently, the question is raised whether the addition of chemotherapy to HFSRT can result in better local tumor control for recurrent MG than HFSRT alone did. To our best knowledge, it remains controversial. Some researchers suggested that the combination of HFSRT and chemotherapy could lead to prolonged survival [12–16]; other researchers indicated in their studies that there did not show statistically significant difference between these two treatment modalities [17–21], while the addition of chemotherapy could induce severe toxicity [22].

Given the controversy of the question aforementioned, we conducted a systematic review and meta-analysis of the available data from the published literature to determine whether and to what extent the addition of chemotherapy to HFSRT affects survival in recurrent MG compared to HFSRT alone.

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2. Methods

2.1. Search strategy

Two of the authors (Y.J.H and C.D) independently conducted a literature search in the electronic databases PubMed and EMBASE in Jan 2019, using the following terms: 'recurrent high-grade glioma*', 'recurrent high grade glioma*', 'recurrent malignant glioma*', 'recurrent glioblastoma*', 'hypofractionated', 'fractionation', 'fractionated', 're-irradiation', and 'reirradiation'. The search was limited to publications in human subjects published in English language. The reference lists of all studies included in the present systematic review and meta-analysis and of all relevant review articles were hand-searched. All studies obtained by this process were subsequently screened by 2 reviewers independently. Consensus was reached through discussion when disagreement occurred. In addition, the corresponding authors of the studies included in this systematic review and meta-analysis were contacted to gain essential data which were critical to perform a meta-analysis, such as hazard ratio (HR), confidence interval and P value.

2.2. Study selection

The titles and abstracts were checked to exclude the studies which did not involve HFSRT or chemotherapy for patients with recurrent MG. Subsequently, full-texts of the potentially eligible studies were assessed according to inclusion and exclusion criteria. Inclusion criteria were as follows: 1) patients were historically diagnosed with MG; 2) the initial treatment was maximal safe resection and conventional fractionated stereotactic radiotherapy followed by concurrent and adjuvant chemotherapy; 3) data (HR, confidence interval) in terms of comparison between two interventions could be obtained directly or through information provided in included studies. Exclusion criteria included 1) patients who were newly diagnosed with gliomas or MG, 2) patients < 5 years old, and 3) studies were case reports, reviews, surveys, or editorials. Study selection was performed by two reviewers independently and disagreements were solved by means of discussion.

2.3. Data extraction

Data extraction was conducted independently by 2 of the authors (L.F.Z and C.D). The following data were recorded: study characteristics, patient data, and treatment outcomes.

2.4. Data extraction and meta-analysis

Data including study characteristics, demographic characteristics, and treatment outcomes were extracted. Meta-analysis of HR relevant to OS was conducted to determine whether there was a difference between two treatment modalities. It describes how likely (or unlikely) is the occurrence of the event in a participant at a certain moment, if this participant is given the treatment to be evaluated instead of the control treatment. [23] The log HR (logHR) and the standard error of log HR (SElogHR) were used in our meta-analysis. HR and its confidence interval were obtained by the approaches described as follows: [24] 1) calculated from the value of the log-rank statistic and the log-rank statistic variance; 2) calculated from p value of the log-rank test or Cox regression and the total number of patients and deaths in every group; and 3) calculated from the Kaplan-Meier curves if number of patients of both groups are provided. The values of HR and its confidence interval were calculated using WPS office 2016, according to the methodology described by Parmar et al. [24], and Tierney et al. [25] The isolation of the Kaplan-Meier curves was performed with the software Engauge Digitizer (Version 4.1, Mark Mitchell, 2002).

To clarify to what extent the addition of chemotherapy to HFSRT affects survival outcomes in recurrent MG compared to HFSRT alone, meta-analysis of MD relevant to OS was conducted. The estimation of mean and standard deviation of OS was based on the method described by Hozo et al. [26]

Heterogeneity across the included studies was assessed by the Cochrane's *Q*-test I^2 statistic. There exists heterogeneity if $P < 0.01$ and $I^2 > 50\%$, while a lack of heterogeneity if $P > 0.01$ and $I^2 < 50\%$. Random-effects model was employed in our meta-analysis. Sensitivity and subgroup analysis were used to explore the causes of heterogeneity. Publication bias was assessed by funnel plots and by analytic methods (e.g. Begg's test and Egger's test). All statistical analyses were performed using STATA version 14 (Stata Corp LP, 1985–2015). All reported p-values were two-sided and $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Literature search

The initial search using the strategy described above resulted in a total of 317 studies. After removing duplicates, 204 records were remained. Based on checking titles and abstracts of the potentially eligible studies, 42 full-text studies were retained to be reviewed. Meanwhile, 2 additional full-text articles obtained through reading relevant review articles were also reviewed in detail. Among the 44 studies, 37 studies were removed with detailed reasons. Finally, a total of 7 studies were included in systematic review. [12–14,16,18–20] As for meta-analysis of HR, two studies were excluded because data essential for meta-analysis cannot be obtained [18,19]. As a result, 5 studies were included to perform a meta-analysis of HR [12–14,16,20]. The search process is illustrated in Fig. 1.

3.2. Study characteristics

The main characteristics of the included studies are summarized in Table 1. The present study included 4 retrospective studies and 3 prospective studies, with the sample sizes ranging from 21 to 147. Among the 7 studies, 3 employed HFSRT plus TMZ as combination therapy; 2 employed HFSRT plus bevacizumab (BEV) as combination therapy; and 2 employed various chemotherapeutic agents as concurrent treatment with HFSRT. Regimens of chemotherapy were reported in 2 out of the seven studies. The median total dose of the included studies ranged between 15 and 37.5 Gy, and the median dose per fraction (reported in 7 studies) ranged between 2.5 and 6 Gy. Six studies provided the median follow-up periods, with the range between 6 and 21 months. Three studies provided median time interval between first-line treatment and re-treatment, ranging from 12 to 30 months.

3.3. Patient characteristics

The overall number of the patients involved in our systematic review and meta-analysis was 388. Two hundred patients received HFSRT plus chemotherapy, and 188 were treated with HFSRT alone. Besides, a total of 320 patients were diagnosed with recurrent grade VI glioma (GVIG), and the other 68 patients were diagnosed with recurrent grade III glioma (GIIIG). The median age and its range were reported in all included studies, with the median age varying from 45 to 62 years. Karnofsky performance status (KPS) was given in 5 out of the 7 included studies and all were greater than 80. Tumor volume was provided in all included studies and the median tumor volume varied from 8.54 to 35.01 cm^3. Patient characteristics are outlined in Table 2.

3.4. Overall survival and progression-free survival

Overall survival was the major outcome of all the studies included in our study. In the 7 included studies, median OS (after treatment for recurrence) of patients receiving combination therapy ranged between 8.7 and 23 months, while this measure for patients receiving HFSRT

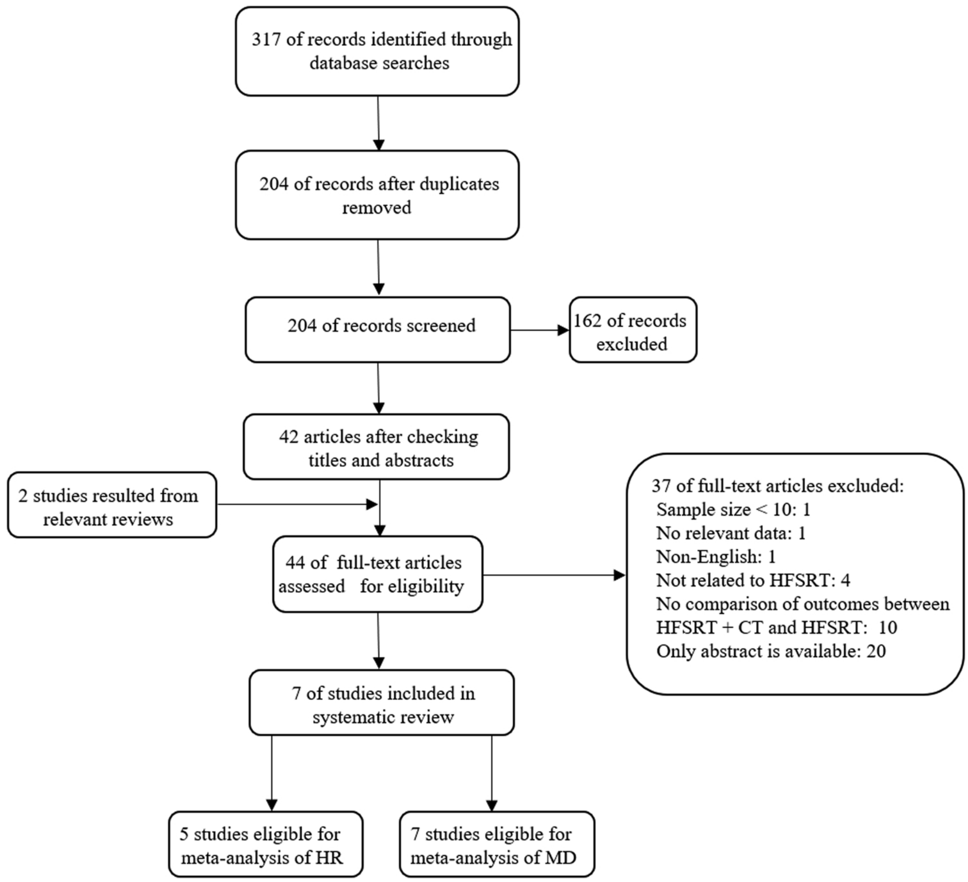

Fig. 1. Flowchart of the steps of the systematic review and meta-analysis. n, number of studies; HFSRT, hypofractionated stereotactic radiotherapy; CT, chemotherapy; HR, hazard ratio; MD, mean difference.

solely was between 3.9 and 12 months. Three out of the 7 included studies presented statistically significant difference (P < 0.05) between these two treatment approaches, while the other 4 studies did not observe a statistically significant difference. Although the difference was not statistically significant, 3 out of the 4 studies showed a trend for favorable survival benefit for patients who underwent HFSRT plus chemotherapy as compared to those treated with only HFSRT. However, Fogh et al. [18] reported an analogous median overall survival of patients treated with HFSRT plus chemotherapy or not, with the median OS of 11 and 10 months (P = 0.791), respectively.

PFS was provided in 3 studies, with 2 calculated from the date of retreatment and 1 from the date of initial diagnosis. Two out of the three studies presented a positive association between combination therapy and survival, whereas Miwa et al. [20] did not observe a statistically significant association. They reported the median progression-free survival of patients treated with HFSRT plus chemotherapy or not of 6 and 5 months (P = 0.447), respectively. The treatment outcomes of the included studies are illustrated in Table 3.

3.5. Meta-analysis

The pooled HR regarding OS between combination therapy (HFSRT plus chemotherapy) and HFSRT alone was significantly reduced and in favor of combination therapy (378 patients, HR 0.44, 95% CI 0.30-0.65, P < 0.0001, inverse variance fixed-effects model) (Fig. 2), while statistically significant heterogeneity was not identified (Cochran Q statistic 4.70, P = 0.320, I^2 = 14.8%).

In the analysis of standard MD, HFSRT + chemotherapy resulted in slight prolongation in OS compared to HFSRT (standard MD 1.34, 95% CI 0.48–2.20, p = 0.002). However, significant heterogeneity was noted (Cochran Q statistic 67.57, P < 0.05, I^2 = 91.1%). By sensitivity analysis, we found that heterogeneity mainly originated from the study by Cuneo et al. [12] Repeat analysis of MD revealed acceptable heterogeneity after removing this study (Cochran Q statistic 10.16, p = 0.71, I^2 = 50.8%) (Fig. 3), and obtained comparable OS (standard MD 0.80, 95% CI 0.41–1.18, P < 0.001).

A funnel plot to evaluate publication bias requires at least ten studies to be included in a meta-analysis, otherwise, the test power will be too low to assess the symmetry of the funnel plot. Considering only 5 studies included in our meta-analysis, we did not generate a funnel plot.

4. Discussion

Recurrence of MG seems to be inevitable under the present clinical treatment mainly due to the aggressiveness of malignant tumor and generation of resistance to chemotherapy. In recurrent setting, the optimal treatment remains to be established, and many treatment approaches are salvage in nature. Hypofractionated stereotactic radiotherapy features a shortened duration and precise dose delivery in the management of recurrent patients, especially for those with relatively large tumors. Over the last two decades, this treatment modality has been widely used in intracranial neoplasms, including recurrent MG. According to literature review, the median OS of recurrent MG patients since HFSRT ranged from 8 to 18 months, and the side-effects were well tolerable. [14,27]

In contrast to the management strategy for newly diagnosed MG, the role of chemotherapy is obscure in the management of relapsed MG. In the treatment of relapsed MG, it remains controversial whether the addition of chemotherapeutic agents to HFSRT could achieve a prolonged survival in comparison to survival by HFSRT alone. Some investigators contend that the addition of chemotherapy could exert a positive impact in extending survival. The study by Lee et al. [16]

Table 1
Characteristics of the studies included in the systematic review and meta-analysis.

Author & year	Study type	Sample size	Treatment modality	Regimen of chemotherapy	Outcome	Median total dose	Median dose per fraction	Chemotherapeutic agent (s), percent	Median follow-up, months (range), months	Median time between initial therapy and salvage re-irradiation, (range), months
Lee et al. 2018 [16]	Prospective	25	HFSRT vs. HFSRT & TMZ	N/R	OS, PFS	37.5 Gy	2.5Gy	TMZ, 52%	13 (4-41)	30 (12-72)
Miwa et al. 2014 [20]	Prospective	21	HFSRT vs. HFSRT & TMZ	TMZ: 200 mg/m2/day for 5 days, 3 or more cycles after HFSRT	OS, PFS	30 Gy	5 Gy	TMZ, 62%	12	12 (3-48)
Mckenzie et al. 2013 [19]	Retrospective	35	HFSRT vs. HFSRT & BVZ	N/R	OS	30 Gy	6 Gy	BVZ: 86%	N/R	N/R
Cuneo et al. 2012 [12]	Retrospective	63	HFSRT vs. HFSRT & BVZ	N/R	OS, PFS	15 Gy	N/R	BVZ: 66.7%	6.5	N/R
Fogh et al. 2010 [18]	Retrospective	147	HFSRT vs. HFSRT & various agents	N/R	OS, PFS	35 Gy	3.5 Gy	Various agents: 32.7%	21 (4-221)	N/R
Fokas et al. 2009 [13]	Prospective	53	HFSRT vs. HSRT & various agents	N/R	OS, PFS	30 Gy	3 Gy	Various agents: 47.2%	8 (2-31)	N/R
Grosu et al. 2005 [14]	Retrospective	44	HFSRT vs. HFSRT & TMZ	TMZ: 200 mg/m2/day for 5 days, 1-2 two cycles before HFSRT and four to four cycles after	OS	30 Gy	5 Gy	TMZ: 66%	6	16

Abbreviation: HFSRT, hypofractionated stereotactic radiotherapy; TMZ, temozolomide; BVZ, bevacizumab; N/R, not reported; OS, overall survival; PFS, progression-free survival.

reported a significant difference in OS of patients receiving HFSRT in combination with TMZ or not (P = 0.033). Cuneo et al. [12] reported in their study that the combination of HFSRT and BVZ resulted in the median OS of 11.2 months, and the median OS by HFSRT alone was 3.9 months (P = 0.005). Besides, the study by Haque et al. [28] showed that addition of chemotherapy to HFSRT was associated with improved OS (HR = 0.57, 95% CI 0.49–0.67; P < 0.001). However, there exists opposite viewpoint, especially the study by Fogh et al., [18], which included the most patients so far. In their study, median OS of patients underwent HFSRT combined with chemotherapy or not were comparable (HFSRT + chemotherapy: 11months, HFSRT: 10 months; P = 0.791). It should be noted that numerous chemotherapeutic agents were used in their study, and they did not take mutation of O6-methylaguanine-DNA-methyltransferase (MGMT) or isocitrate dehydrogenase (IDH) into account.

In the present study, the results of meta-analyses suggest that the addition of chemotherapy to HFSRT could confer a slight survival advantage over HFSRT. The combination of HFSRT and chemotherapy surely improve survival duration; however, the pooled standard MG of 0.80 months is disappointed, which suggests that the role of chemotherapy may be relatively feeble in treating recurrent MG. As for PFS, a narrative analysis was conducted due to lack of sufficient data. In fact, PFS is the best measure to evaluate the efficacy of treatment for cancer patients.

O6-methylaguanine-DNA-methyltransferase is a DNA repair protein that protects glioblastoma multiforme (GBM) tumor cells from alkylating agents. [29] The MGMT methylation status prognosticates response to TMZ in newly diagnosed GBM; however, it influence on survival of patients with recurrent MG has not been clarified clearly. In the present study, only the study by Lee et al. [16] takes MGMT methylation status into consideration; however, the Cox regression analysis showed that MGMT did not exert an impact on survival. The study by Minniti et al. [30] identified MGMT methylation status a statistically significant factor on survival in univariate analysis, but it did not affect survival in multivariate analysis. In our study, we did not analyze the influence of MGMT methylation status on survival due to the lack of sufficient data.

The main side-effect of HFSRT is radiation necrosis, with the incidence ranging from 0 to 64% in the published articles. It has been proposed that a cumulative dose of more than 100 Gy tends to induce radiation necrosis. The study by Lee et al. [16] reported the radiation necrosis rate of 64%, and more than 90% of the patients received cumulative dose of >100 Gy, which may partly account for the high incidence of radiation necrosis. [31,32]. According to the study by Fogh et al. [18] (147 patients), only the patient who received an irradiated dose of 40 Gy experienced grade 3 CNS toxicity in the form of severe headache, and the all the patients completed the prescribed radiation dose without interruption. In addition, a systematic review of stereotactic radiosurgery for recurrent MG reported a pooled value of radiation necrosis rate of 5.9% [17]. The diagnosis of radiation necrosis should be differentiated from pseudoprogression and tumor progression. According to the meta-analysis by Abbasi et al., [33] the incidence of pseudoprogression after chemoradiotherapy was up to 36% in the patients who were diagnosed with tumor progression through imaging. Similarly, pseudoprogression may account for a certain proportion of the cases that are diagnosed with radiation necrosis [34]. To date, there is no single diagnostic imaging modality which allows the differentiation of necrosis from pseudoprogression or tumor recurrence. The main method to differentiate these changes after radiotherapy is based on the combination of DWI/DTI, MRS, and PET/SPECT, because each modality has varying sensitivity and specificity [33]. In addition, characteristics specific to these changes also help differential diagnosis. However, although the utilization of these imaging modalities, the differential diagnosis between these changes remains challenging. A better understanding of the biology and molecular changes after radiotherapy may be important to establish a non-invasive modality to distinguish

Table 2
Patients characteristics of included studies.

Study	Number of patients				Median age (range), years	Median KPS (range)	Tumor volume (range), ml
	HFSRT plus CT	HFSRT	GIVG	GIIIG			
Lee et al. 2018 [16]	13	12	25	0	45 (23–61)	90 (60–100)	32 (4–90)
Miwa et al. 2014 [20]	13	8	21	0	53.9 (22–76)	80 (60–90)	27.4 (3.4–102.9)
Mckenzie et al. 2013 [19]	30	5	32	3	62 (16–76)	80 (50–100)	8.54 (0.4–46.56)
Cuneo et al. 2012 [12]	42	21	49	14	47 (19–76)	80 (50–90)	4.8
Fogh et al. 2010 [18]	48	99	105	42	53 (19–86)	–	22 (0.6–104)
Fokas et al. 2009 [13]	25	28	53	0	53 (22–71)	–	35.01 (3–204)
Grosu et al. 2005 [14]	29	15	35	9	50 (36–73)	80 (40–100)	15 (1–61)

Abbreviation: CT, chemotherapy, HFSRT, hypofractionated stereotactic radiotherapy; GIVG, grade IV glioma; GIIIG, grade III glioma; KPS, Karnofsky Performance Status.

Table 3
Outcome measures in the combination treatment and re-irradiation alone.

Study	Median OS, months			Median PFS, months		
	Combination treatment	Re-irradiation alone	P values	Combination treatment	Re-irradiation alone	P values
Lee et al. 2018 [16]	23	12	0.033	–	–	–
Miwa et al. 2014 [20]	12	6	0.079	6	5	0.447
Mckenzie et al. 2013 [19]	8.7	6.9	0.9	–	–	–
Cuneo et al. 2012 [12]	11.2	3.9	0.005	5.2	2.1	0.014
Fogh et al. 2010 [18]	11	10	0.791	–	–	–
Fokas et al. 2009 [13]	11	8	0.1466	14*	9*	0.031
Grosu et al. 2005 [14]	11	6	0.04	–	–	–

Abbreviation: OS, overall, survival; PFS, progression-free survival.
* progression-free survival after initial diagnosis.

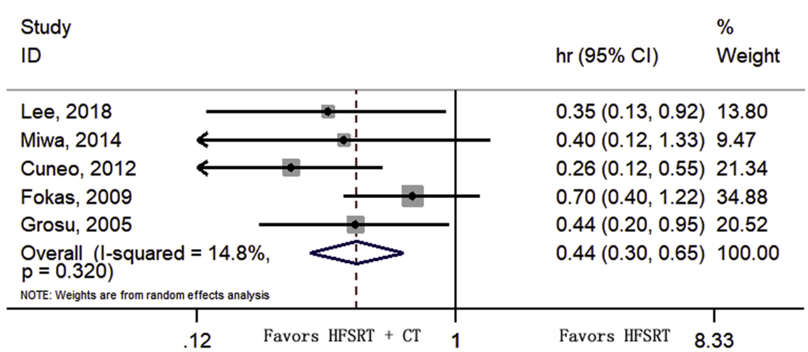

Fig. 2. Forest plot of quantitative synthesis of hazard ratios (HR) and their corresponding 95% confidence intervals (95% CIs) with all the studies in the meta-analysis. HFSRT, hypofrationated stereotactic radiotherapy; CT, chemotherapy.

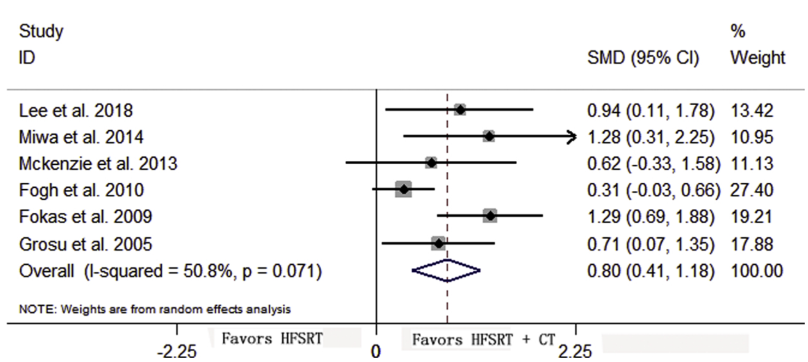

Fig. 3. Forest plot of the pooled mean difference (MD) and its corresponding 95% confidence intervals (95% CIs) of all cohorts comparing median overall survival (OS) between HFSRT + chemotherapy (CT) vs HFSRT. Values presented were obtained by random-effects model. HFSRT, hypofractionated stereotactic radiotherapy.

radiotherapy-related changes [35]. According to a recent systematic review including 26 studies, Hu et al. [36] revealed that the pooled necrosis rate after HFSRT was 5% (3–7%). Considering the confounding of pseudoprogression, the real rate of radiation necrosis in clinical practice may be lower than that reported in literatures and acceptable. Thus, although the advancement of methods to differentiate the aforementioned radiation changes is warranted, the control of radiation necrosis after HFSRT is not so pessimistic.

The toxicity of chemotherapy mainly includes hematologic toxicity, gastrointestinal perforation, fatigue, and hypertension. Across the published studies employing HFSRT + chemotherapy for recurrent MG, the most frequently occurring toxicities are grade 2 or 3, and grade 4 toxicity (life-threatening toxicity) occurred with a low incidence. Clarke et al. [7] reported a study employing HFSRT + BEV for 15 patients, and 1 patient developed grade 4 hypertension. Jia et al. [37] reported no occurrence of toxicity related to treatment in their study (22 patients). The study involving 54 patients by Minniti et al. [30] reported grade 4 lymphocytopenia in 3 patients (5%). Taken together, toxicities related to combination treatment of HFSRT and chemotherapy were well tolerated by recurrent patients.

The results of the present study should be interpreted conservatively, due to the inherent limitation of the included studies. The primary limitation of the included studies is the observational nature. It is because of the lack of randomized clinical studies that makes the nonrandomized studies eligible to be included. The lack of randomization cannot ensure the comparability of baseline characteristics between patients treated with HFSRT in combination with chemotherapy or not. Only two out of the seven studies provided the comparison of baseline characteristics of patients in two groups. [12,14] Furthermore, the majority of studies included in the present study did not take the mutation of IDH-1/2 into consideration, nor did these studies analyze 1p/19q status of patients. The mutation of IDH-1/2 predicts better prognosis for patients with MG [38]. The status of 1p/19q is an important biomarker for patients with MG, and the codeletion of 1p/19q is predictive of better response to chemotherapy and longer survival [39]. For patients with GIIIG or GVIG, the status of 1p/19q may differ a lot. However, we cannot conduct an analysis of these aspects, which weakens the reliability of our outcome. Selection bias is another inherent limitation. In the present study, the median KPS of patients in all included studies is equal to or more than 80. The performance status is an important prognostic factor for recurrent patients. Consequently, these selected patients tend to have prolonged survival so that they cannot represent the general population of patients with recurrent MG.

5. Conclusion

In the salvage management of recurrent MG, HFSRT is a critical choice, and whether the addition of chemotherapy to HFSRT could improve survival is in debate. Our results suggest that HFSRT combined with chemotherapy achieve a slight survival advantage in comparison to HFSRT alone. Nonetheless, considering the presence of some shortcomings of the present article, well-designed randomized trials are needed to draw a more solid conclusion.

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