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Review article

The efficacy of hypofractionated radiotherapy (HFRT) with concurrent and adjuvant temozolomide in newly diagnosed glioblastoma: A meta-analysis

L'efficacité de la radiothérapie hypofractionnée avec le témozolomide concomitant et adjuvant dans le glioblastome nouvellement diagnostiqué : une méta-analyse

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ABSTRACT

Purpose. – The efficacy of hypofractionated radiotherapy (HFRT) in glioblastoma (GBM) without age restrictions remains unclear. The aim of this meta-analysis is to access the survival outcomes of HFRT in these patients.
Methods. – A comprehensive electronic literature search of PubMed, Web of Science and Cochrane Library was conducted up to June 1, 2020. The main evaluation data were the overall survival (OS) rate at 12 months and 24 months and the progression-free survival (PFS) rate at 6 and 12 months. The secondary evaluation data was the incidence of radionecrosis and adverse events. The study was performed using R "meta" package.
Results. – Eleven studies met the inclusion criteria, which totally contained 484 participants. The 12-month OS and 24-month OS rate of HFRT in GBM were 71.3% and 34.8%, while the 6-month PFS and 12-month rate were 74.0% and 40.8%. Compared to low-BED (biological equivalent dose) schedules (< 78 Gy), high-BED schedules may increase survival benefit both in PFS-6 ($P = 0.003$) and PFS-12 ($P = 0.011$), while the difference did not show on OS. Different dose per fraction had no significant effect on both OS and PFS. Incidence of radionecrosis was 14.2%. Although the overall incidence of adverse reactions cannot be quantified, the toxicity of HFRT was acceptable.
Conclusions. – Compared with survival data for standard treatment, HFRT seemed to improve overall survival and progression-free survival, while high BED schedules may future increase benefit on PFS. Meanwhile, the toxicity of HFRT was tolerable. Further randomised controlled clinical studies are needed to confirm these findings.

Mots clés :
Radiothérapie hypofractionnée
Glioblastome
Survie
Méta-analyse

RÉSUMÉ

Objectif de l'étude. – L'efficacité de la radiothérapie hypofractionnée dans le glioblastome sans limite d'âge reste incertaine. L'objectif de cette méta-analyse était d'accéder aux résultats de survie chez ces patients.
Méthodes. – Une recherche documentaire électronique complète sur PubMed, Web of Science et Cochrane Library, a été menée jusqu'au 1er juin 2020. Les principales données d'évaluation étaient le taux de survie globale à 12 et 24 mois et ceux de survie sans progression à 6 et 12 mois. Les données d'évaluation secondaires étaient l'incidence de la radionécrose et des événements indésirables. L'étude a été réalisée à l'aide du R « meta » *package*.

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Résultats. – Onze études répondaient aux critères d'inclusion, qui incluaient au total 484 participants. Les taux de survie globale à 12 mois et à 24 mois étaient de 71,3 % et 34,8 %, ceux de survie sans progression à 6 mois et à 12 mois de 74,0 % et 40,8 %. Par rapport aux programmes à faible BED (*Biology Effective Dose*) (< 78 Gy), les fortes BED peuvent augmenter le taux de survie sans progression à 6 ($p = 0{,}003$) et 12 mois ($p = 0{,}011$), mais pas celui de survie globale. Différentes doses par fraction n'ont eu aucun effet significatif à la fois sur la survie globale et la survie sans progression. L'incidence de la radionécrose était de 14,2 %. Bien que l'incidence globale des effets indésirables ne puisse être quantifiée, la toxicité de la radiothérapie hypofractionnée était acceptable.
Conclusions. – Comparée aux données de survie pour le traitement standard, la radiothérapie hypofractionnée semble améliorer les taux de survie globale et de survie sans progression, tandis que les BED élevés peuvent augmenter celui de survie sans progression. La toxicité de la radiothérapie hypofractionnée est tolérable. D'autres études cliniques contrôlées randomisées sont nécessaires pour confirmer ces résultats.

1. Introduction

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumour in adults and remains extraordinarily poor prognosis due to its greatly aggressive behaviour [1,2]. Despite constant effort, little progress has been made to improve the overall survival (OS) or progression-free survival (PFS) time. The largest and feasible resection range is believed to significantly improve overall survival and progression-free survival [3]. However, invasive behaviour and importance of brain tissue make it highly difficult to attain a goal of gross total resection. Systematically comprehensive treatments, including radiotherapy (RT) concurrent/adjuvant with temozolomide (TMZ) after surgery, have been considered as optimal therapy [2]. Conventional fractionated radiotherapy (CRT) to a total dose of 60 Gy delivered at 2 Gy per fractions in 30 days is considered to tolerable with acceptable neurotoxicity [4]. However, the optimised dose and fraction of radiotherapy have not been determined.

With the development of radiotherapy technology, the optimisation of dose fraction in external beam radiotherapy has gained wide interest. One of the potential therapies is to improve the survival of GBM is hypofractionated radiotherapy (HFRT). Compared to CRT, HFRT delivers a higher dose per fraction (>2 Gy) and fewer exposure times, which have a potential advantage of increasing cells killing [5–7]. In addition, shorter treatment times may be associated with higher quality of life for patients with poor prognosis [8]. Several randomised phase 3 trials have investigated the efficacy of hypofractionation in elderly patients [9–11]. Based on results of these trials, the American Society of Clinical Oncology (ASCO) and the American Society for Radiation Oncology (ASTRO) guideline recommend that it is appropriate for elderly patients or patients with poor performance status to receive hypofractionated radiotherapy [12]. However, the efficacy of hypofractionated radiotherapy across all ages and performance status in newly diagnosed glioblastoma remains unclear. Therefore, we performed a meta-analysis to access the overall efficacy of HFRT in GBM without age restrictions.

2. Methods

2.1. Study eligibility criteria and selection

This study was prepared based on the preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines for reporting systematic reviews [13]. Nowadays, the randomised control trial about HFRT without age restrictions in newly diagnosed GBM is rare. Thus, any phase trial about this research direction was all included. The study should be designed to evaluate the efficacy of HFRT in newly diagnosed GBM. Eligible patients enrolled should have normal hematologic, renal, hepatic function and have no restriction on age. Patients enrolled less than 10 were excluded because of relatively high bias. Standard temozolomide regimen (concurrent: 75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy; adjuvant: 150 to 200 mg per square meter for 5 days during each 28-day cycle) was supposed to be used in every patient at the beginning of trial though someone may terminate chemotherapy because of adverse effect. The neoadjuvant temozolomide regimen (used temozolomide before radiotherapy) was allowed. Study did not provide specific survival data or survival curve (Kaplan–Meier curve) was excluded.

2.2. Data sources and search strategy

The electronic database of PubMed, Web of Science and Cochrane Library were systematically searched from their inception to June 1, 2020. The search term comprised synonyms for "glioblastoma", "radiation", "hypofractionated", "temozolomide", and "survival". Reference lists of accepted studies and bibliographies of reviews were manually searched in order not to miss other relevant studies. Two investigators (Longbin Guo and Xuanzi Li) independently performed the literature search, screened titles and abstracts, and selected relevant full articles and assessed their eligibility. Different opinions between two investigators were resolved by consensus or by consultation of a third investigator (Shasha Du).

2.3. Literature quality evaluation

It was inappropriate to evaluate literature quality using the Newcastle-Ottawa scale (NOS) [14] because most of the studies included were single arm trial. Referring to the NOS, we set some criteria to evaluate literature quality accommodating this study purpose and including:

- study population clearly defined;
- cohort representative for the population of GBM patients;
- treatment volumes specifically defined;
- dose constraints well defined;
- clear and specific treatment process;
- follow-up long enough for outcomes to occur;
- adequacy of follow-up;
- assessment of outcome well performed;
- toxicities and comparison well recorded.

The complete scale is presented in Supplement Table S1.

2.4. Data extraction

Clinical endpoints including PFS-6 (PFS rate at 6 months), PFS-12 (PFS rate at 12 months), OS-12 (OS rate at 12 months) and OS-24 (OS rate at 24 months) were the primary survival data to extract. The incidence of severe acute/late toxicity and radionecrosis, which were defined by Common Terminology Criteria for Adverse Events, were also extracted for additional analysis. When survival data only provided in survival curve (Kaplan–Meier curve), figures were digitised to extract numeric data using Engauge Digitizer 10.12 (https://github.com/markummitchell/engauge-digitizer/).

2.5. Statistical analysis

Analyses were performed using R version 3.5.1 (https://cran.r-project.org/) with the "meta" package and Microsoft Excel 2016. The overall survival proportion was calculated with corresponding 95% confidence intervals (95%CI). Heterogeneity was assessed by calculating Cochran Q test and inconsistency index test (I^2 test). Random effects model was used in case of the existence of heterogeneity, defined as a P-value of Cochran Q test < 0.1 and I^2 > 50% [15], whereas fixed effects model was used in the opposite case. In the subgroup analysis, effects models of both subgroups were unified according to overall effects model. A two-tailed P-value < 0.05 was considered statistically significant.

3. Results

3.1. Search results

A total of 253 studies were identified after electronic and manual searches. After exclusion based on title and abstract, 105 full-text articles of potential interest were reviewed. After further evaluation, eleven studies (10 prospective single arm trials, 1 retrospective case-control study and 1 phase II randomised trial) were included [16–26]. No additional articles were identified in reference lists of accepted studies and bibliographies of reviews. Fig. 1 shows a flowchart for procession of studies selection.

3.2. Study characteristics and quality evaluation

Biologically effective dose (BED) of every radiation schedule were calculated in order to access the efficacy between different studies. Calculation method was in accordance with the following formula:

$$\mathrm{BED} = D * \left(1+\frac{d}{\alpha/\beta}\right)$$

where D means total dose, d means dose fraction, α/β means α/β ratio. Here α/β ratio was set as 10 conventionality.

shows the specific characteristics of eleven included studies. Though a little different, most of the radiation target volumes were defined as contrast-enhancing residual tumour plus surgical cavity with about 0.5 cm margin; hence, the bias from this were acceptable. The age range of the population included in the study was 16 to 82 years old, and most of them were middle-aged and elderly people (50s–60s), in line with the age distribution of GBM (Table 1). Since a certain percentage of studies did not record MGMT promote methylation and IDH-1 mutation in detail, they were not displayed. Except study of Shenouda et al. [22] used the neoadjuvant plus standard temozolomide regimen, other studies all used standard temozolomide regimen.

Referring to the NOS, we performed a particular literature evaluation scale to evaluate each study (Supplement Table S1). In general, the included studies could completely record important information of trial. However, the existence of prospective single arm trials and retrospective case-control study made overall research somewhat heterogeneous and limited the quality of reporting.

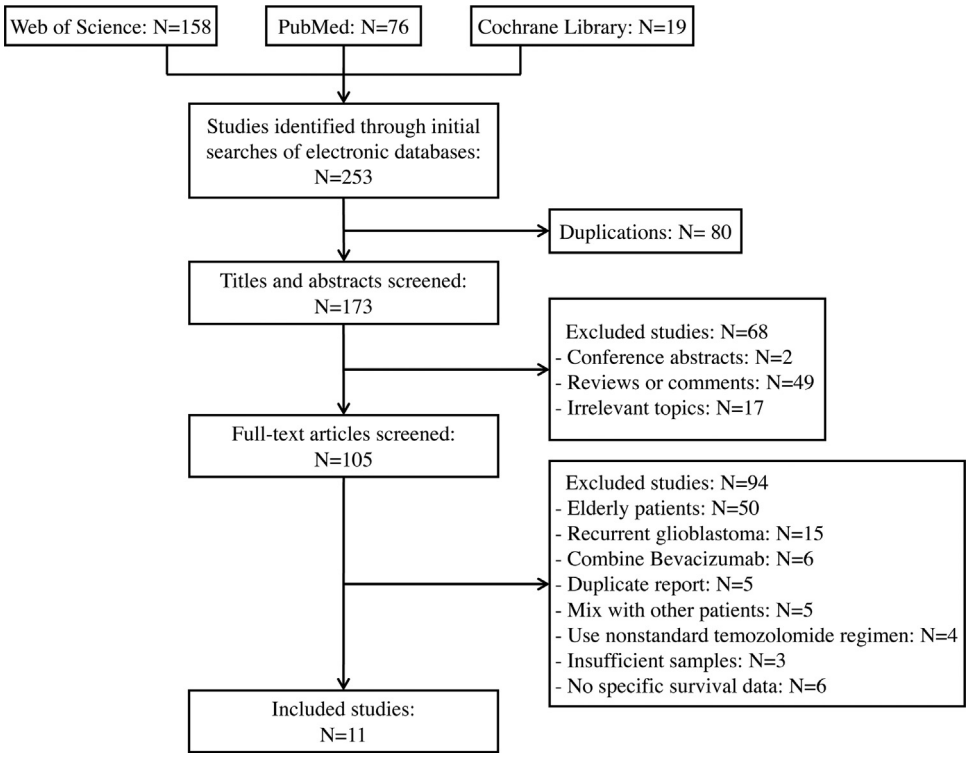

Fig. 1. Flow diagram showing the study screening process.

Table 1
The basic characteristics of clinical trials included in the meta-analysis.

	Year	Patients	Median age (range)	KPS	Target volume	Total dose (Gy)	Dose fractions	Fraction	BED (Gy)	mFollow-up time	mOS	mPFS	OS-12 months	OS-24 months	PFS-6 months	PFS-12 months	Acute toxicity ≥ G3	Late toxicity ≥ G3	Radionecrosis
Iuchi	2016	46	65.5 (40–80)	?	Contrast-enhancing residual tumour plus surgical cavity +0.5 cm	68	8.5	8	125.8	16.3	20	9.7	69.6%	42.8%	65.2%*	43.5%*	Skin rash 2.2%	Pneumonitis 2.2% Fatigue 4.3% Bone marrow suppression 2.2% Liver dysfunction 17.8% Anemia 17.8% Lymphocytopenia 45.7% Neutropenia 6.5% Thrombocytopenia 2.2%	43.50%
					Contrast-enhancing residual tumour plus surgical cavity +2 cm	40	8.0	5	72.0										
					High-intensity region on FLAIR	32	8.0	4	57.6										
Jastaniyah	2013	25	53.1 (22.6–73.4)	≥ 70	Contrast enhancement on T1-w +1.5 cm	60	2.7	22	76.4	12.4	15.7	6.7	68%*	20%*	60%	38%	Pneumonia infection 4%		
Hematological 8%		–																	
Mallick	2018	45	45 (16–65)	≥ 70	T1 contrast-enhancing tumour +1.5 cm	60	3.0	20	78.0	11.4	25.18	13.1	75.6%*	66.7%*	93.3%*	64.4%*	Thrombocytopenia 8.9%	?	2.2%
					Enhancing tumour and edema as seen in the preoperative T2 weighted/ T2 flair MRI + 1.5–2 cm	50	2.5	20	62.5										
Navarria	2017	98	61 (23–77)	≥ 60	Entire surgical cavity plus eventual residual tumour after surgery or abnormality on the T1-weighted post-contrast MPRAGE and 11CMETPET in case of biopsy +0.5 cm	60	4.0	15	84.0	–	15.9	10	71.4%	31.7%	87.8%*	42.9%	?	?	20.0%
Panet-Raymond	2009	35	63 (31–78)	All	Contrast-enhancing residual tumour plus surgical cavity	60	3.0	20	78.0	12.6	14.4	7.7	57.1%*	8.6%*	62.9%*	31.4%*	Nausea and emesis 2.9%	0	–
					Contrast-enhancing residual tumour plus surgical cavity +1.5 cm	40	2.0	20	48.0										
Scoccianti	2018	24	61 (43–78)	≥ 70	Contrast-enhancing residual tumour plus surgical cavity +0.8 cm	67.5	4.5	15	97.9	–	15.1	8.6	65.6%	20.8%*	66.7%*	41.2%	0	Neutropenia 4.2% Thrombocytopenia 8.3%	4.2%

Table 1 (*Continued*)

	Year	Patients	Median age (range)	KPS	Target volume	Total dose (Gy)	Dose fractions	Fraction	BED (Gy)	mFollow-up time	mOS	mPFS	OS-12 months	OS-24 months	PFS-6 months	PFS-12 months	Acute toxicity ≥ G3	Late toxicity ≥ G3	Radionecrosis
					Contrast-enhancing residual tumour plus surgical cavity +1.8 cm	52.5	3.5	15	70.9										
Shenouda	2016	50	60 (31–79)	>60	Surgical cavity and/or postoperative contrast-enhancing lesion on MRI +0.5 cm	60	3.0	20	78.0	22.3	22.3	13.7	78.0%*	49.70%	86.0%*	52.0%*	Hepatotoxicity 2%	Pancytopenia 2% Fatigue 8% Nausea and vomiting 6% electrolyte imbalance 6%	14.0%
					Surgical cavity and/or postoperative contrast-enhancing lesion on MRI +1.5 cm	40	2.0	20	48.0										
Terasaki	2011	26	61 (39–79)	≥50	Enhancing primary tumour site +2.5 cm	45	3.0	15	58.5	20	15.6	9.6	57.7%*	23.1%*	65%	34.6%*	Neutropenia 12%		
Thrombocytopenia 4%	0	7.7%																	
Ye	2015	16	65 (50–82)	≥40	Contrast-enhancing tumour +1 cm	36	6.0	6	57.6	9	14	5	75%*	43.8%*	50.0%*	6.3%*	0	Hematological 12.5%	–
Yoon	2013	39	55 (19–72)	All	Contrast-enhancing residual tumour plus surgical cavity +0.3 cm	50	5.0	10	75.0	16.8	16.8	6.8	69.2%	38.5%	61.5%*	25.6%	Hepatotoxicity 2.6%	Leukopenia 2.6%	
Thrombocytopenia 7.7% Hepatotoxicity 2.6%	17.9%																		
					Contrast-enhancing residual tumour plus surgical cavity +1.3 cm	40	4.0	10	56.0										
					Contrast-enhancing residual tumour plus surgical cavity +2.3 cm	30	3.0	10	39.0										
Zhong	2019	80	50 (24–75)	All	Contrast-enhancing residual tumour plus surgical cavity +0.3 cm	64	2.4	27	80.4	16	21	15	77.6%	41.6%	85.0%*	56.0%	Neutropenia 1.3% Anemia 2.5% Thrombocytopenia 2.5%	?	3.7%
					Contrast-enhancing residual tumour plus surgical cavity +1.3~2.3 cm	60	2.2	27	72.5										
					Contrast-enhancing residual tumour plus surgical cavity +2.3~4.3 cm	54	2.0	27	64.8										

*: extract from survival curve; ?: not clearly described; –: not mentioned.

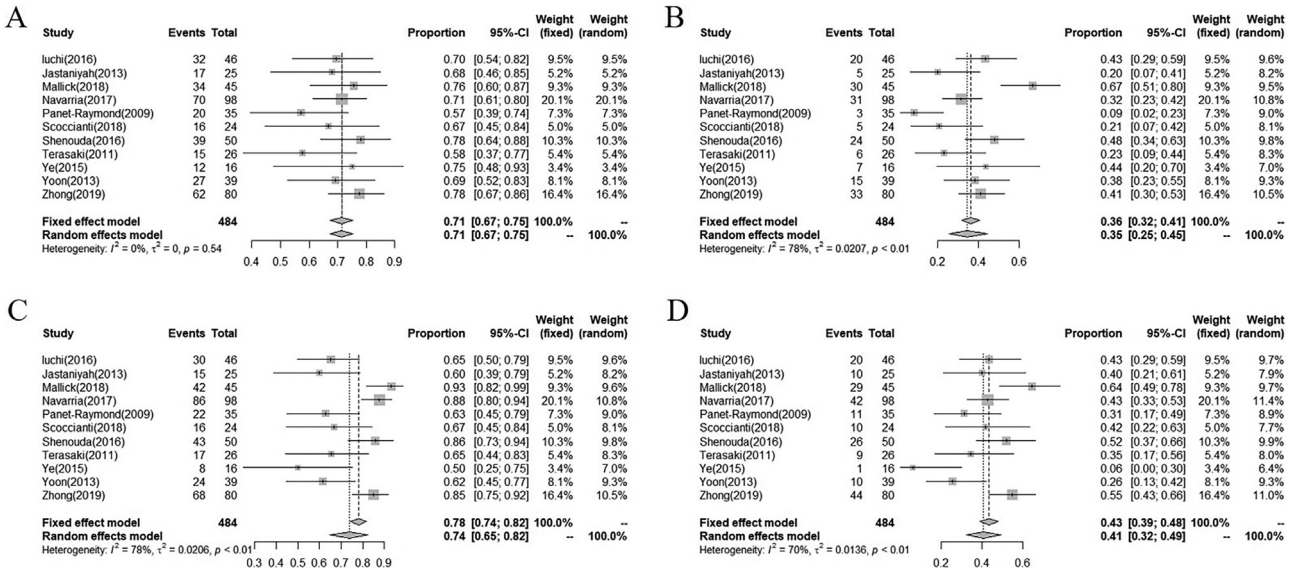

Fig. 2. Forest plots for the overall survival rate at (A) 12 months and (B) 24 months, and the progression-free survival rate at (C) 6 months and (D) 12 months, according to study design in GBM patients receiving HFRT. CI: confidence interval.

Table 2
Comparison of various clinical endpoints between different BED and dose fraction schedules.

		OS-12		OS-24		PFS-6		PFS-12	
		n	Rate	*n*	Rate	*n*	Rate	*n*	Rate
Overall	344	71.4%	179	34.8%	371	74.0%	212	40.8%	
BED	<78Gy	71	67.1%	33	30.6%	64	60.5%	30	26.6%
	≥78Gy	273	72.5%	146	36.7%	307	80.2%	182	47.9%
P-value		0.272		0.500		**0.003**		**0.011**	
Dose fraction	<4Gy	187	72.1%	89	34.0%	207	77.9%	129	47.5%
	≥4Gy	157	70.6%	78	34.9%	164	68.6%	83	33.0%
P-value		0.714		0.917		0.333		0.081	

Bold values indicate significant difference.

3.3. OS

Overall survival was one of the primary clinical endpoints of interest in this study. A total of 344 and 179 patients have a 12-month and 24-month survival time, separately. The overall OS-12 rate was 71.3% (95%CI 67.2%–75.5%) using fixed effects model because of the non-existent heterogeneity (I^2 = 0%, P = 0.54), while the overall OS-24 rate was 34.0% (95%CI 23.5%–45.2%) using random-effects model due to the heterogeneity (I^2 = 78%, P < 0.01) (Fig. 2A&B, Table 2). The highest rate of OS-12 and OS-24 were 78.0% and 66.7% in different trials [18,22], while the lowest, 57.1% and 8.6% separately, were both in a study [20]. In order to evaluate whether the neoadjuvant TMZ regimen will affect the efficacy of HFRT, we compared the OS rate of the neoadjuvant regimen plus standard temozolomide group and the standard regimen group (Supplement Fig. S1A&B). The results showed that there was no statistical difference in OS-12 (P = 0.253) or OS-24 (P = 0.102) between the two groups.

To further investigate whether different BEDs and dose per fraction will affect survival time, we performed a subgroup analysis using the median as the cut-off point (Table 2). However, no statistically significant difference was found between different BEDs or dose fraction schedules.

3.4. PFS

Another important clinical endpoint, progression-free survival, was analysed subsequently. For the PFS-6 rate, a total of 371 patients reach this clinical endpoint. Meta-analysis indicated the overall PFS-6 rate was 74.0% (95%CI 64.7%–82.3%) using random-effects model determined by a heterogeneity (I^2 = 78%, P < 0.01) (Fig. 2C). The highest PFS-6 rate (93.3%) was reported by a study that used a higher BED schedule [18], while the lowest (50.0%) appeared in a study that used the lowest BED schedule [24]. Meanwhile, 212 patients had a 1-year progression-free survival time. Similarly, the extremum values of PFS-12 rate were showed in two identical studies [18,24], and the rate was ranged from 6.3% to 64.4%. Due to the heterogeneity (I^2 = 70%, P < 0.01), the overall PFS-12 rate was calculated as 40.8% (95%CI 32.5%–49.4%) using random-effects model (Fig. 2D). Similar to OS, the two temozolomide regimens combined with HFRT showed no significant difference in PFS-6 (P = 0.060) or PFS-12 (P = 0.148) (Supplement Fig. S1C&D).

The BED subgroup analysis revealed significant difference of progression-free survival time divided by 78 Gy (the median of entire BEDs). It was showed that high-BED schedules (≥ 78 Gy) were better than low-BED schedules (< 78 Gy) both at 6 months (80.2% vs. 60.5%, P = 0.003) and 12 months (47.9% vs. 26.6%, P = 0.011) (Table 2). No significant differences were observed for different dose per fraction.

3.5. Radionecrosis and toxicity

Radionecrosis was observed in 14.2% (95CI 5.9%–25.0%) of patients in 7 studies (Supplement Fig. S2). An obvious extreme value from the study of Iuchi et al. [16], whose the incidence rate of radionecrosis was 43.5% and twice that of the second highest, may

relatively reduce the reliability of the overall rate. The highest BED schedule, as well as the only one beyond 100 Gy, possibly led to this paranormal event.

The meta-analysis to explore the toxicity of hypofractionated radiotherapy was unable to perform due to the various record formats of adverse events from every study. However, it seemed to have a higher risk of late grade 3/4 toxicity in high-BED schedules (Table 1). Lymphocytopenia, thrombocytopenia and hepatotoxicity appeared frequently in overall trials.

4. Discussion

Due to high invasiveness, the prognosis of glioblastoma is extremely poor even after receiving comprehensive treatment. In the field of radiation oncology, researchers have focused on whether increasing the dose or changing the dose-fractionated mode could improve outcome of GBM. RTOG9803 prospectively evaluated the survive difference of GBM after increasing the total dose from 60 Gy to 84 Gy in a conventional fractionated mode [27]. The results showed that higher total dose could achieve better survival in GBM patients with smaller plan target volume (PTV2 < 75 cc). However, for three-dimensional conformal radiotherapy in conventional fractionated mode, increasing the dose to 84 Gy will significantly increase the treatment time and medical costs. With the development of radiotherapy technology, simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT) can increase the total dose without increasing the radiation exposure times, which the treatment time and medical costs will not increase. Moreover, previous studies have confirmed that glioma is a type of tumour resistant to radiotherapy [28,29]. Therefore, hypofractionated radiotherapy with increased dose per fraction may achieve better curative effects in GBM. The results of previous related clinical trials have demonstrated that in elderly GBM patients, HFRT and CRT have similar efficacy, and the incidence of complications is also similar. Therefore, ASCO and ASTRO guidelines have recommended HFRT for elderly GBM patients [12]. However, in the entire GBM population, the efficacy and safety of HFRT have not been carefully studied so far.

For the sake of comprehensively evaluating the efficacy and safety of HFRT in newly diagnosed glioblastoma without age restrictions, we performed this meta-analysis. Little significance of overall survival was detected after our analysis. Seventy percent (71.3%, 95%CI 67.2%–75.5%) of patients with newly diagnosed received HFRT more likely to survival 1 year and about one third (34.0%, 95%CI 23.5%–45.2%) more likely to survival 2 year. As a contrast, the overall survival rates of CRT from Stupp et al. [2] were 61.1% (95%CI 55.4–66.7%) and 26.5% (95%CI 21.2%–31.7%), respectively. In the last few years, several extensive clinical trials using CRT plus TMZ reported OS-12 rate was ranged between 62.1%–71.8% and OS-24 rate was ranged between 16.2%–33.7% [30–34]. Although the comparison of survival rates in different clinical studies is not very rigorous, the results show that HFRT has a tendency to improve prognosis relative to CRT.

Meanwhile, we found that newly diagnosed GBM tend to achieve a better progression-free survival undergoing high-BED schedule HFRT in PFS. The overall rate of PFS-6 and PFS-12 were 74.0% (95%CI 64.7%–82.3%) and 40.8% (95%CI 32.5%–49.4%), respectively. For comparison, Stupp et al. [2] reported that PFS-6 and PFS-12 rate of GBM patients who treated with CRT + TMZ were 53.9% (95%CI 48.1–59.6%) and 26.9% (95%CI 21.8%–32.1%). Besides, the rate of PFS-6 (CRT + TMZ) from several studies was ranged between 47.2%–60.2%, while that of PFS-12 (CRT + TMZ) was ranged between 12.2%–39.8% [30–34]. Similarly, the results showed a potentially trend that the efficacy of HFRT was better than CRT in progression-free survival. Further analysis revealed high-BED schedule achieved significantly preferable progression-free survival time than low-BED schedule both at 6 months (80.2% vs. 60.5%, $P = 0.003$) and 12 months (47.9% vs. 26.6%, $P = 0.011$). Here, we noticed that higher BED was associated with better PFS while higher dose fraction was not. This seems uncommon effect may cause by the potential radiation brain injury while treated by higher dose fraction and, meanwhile, relatively moderate dose fraction and high-BED schedule could lead to better PFS in GBM. At the same time, the advantages of hypofractionation, including increasing cell damage by a higher total dose, may help to limit GBM growth and prolong progression-free survival [35,36].

Limited by the various record format from including studies, the safety of HFRT could not be systematically analysis. High-BED schedules were seemed to slightly induce more late-grade 3/4 adverse events, however, without statistical analysis (Table 1). Lymphocytopenia, thrombocytopenia and hepatotoxicity were three of the most common adverse events in overall trials. However, it should be noted that compared with radiotherapy, these three complications are more common in temozolomide chemotherapy [37]. At the same time, these complications did not increase significantly, compared with standard treatment [2], which shows that the toxicity of HFRT in GBM is tolerable. Radionecrosis was observed in about fourteen percent (14.2%, 95CI 5.9%–25.0%) of patterns underwent hypofractionated radiotherapy. The incidence of radionecrosis was acceptable, except that from the extreme high BED schedule (BED = 125.8 Gy). In summary, hypofractionated radiotherapy was well tolerated and did not distinctly increase the risk of adverse events while receiving a proper high BED schedule.

Due to the several limitations in this study, these findings are supposed to be cautiously comprehended. Firstly, the reliability of analysis was affected by small number of trials and patients included, which could not be well representative of the population intended to be analysed. Secondly, the studies included were almost single-arm trial, except 1 retrospective case-control study conducted by Navarria et al. [19] and a phase II randomised trial conducted by Mallick et al. [18]. Lower level of evidence and significant overall heterogeneity may reduce the accuracy of this study. Notwithstanding confounding factors were restricted as well as possible, random-effects model was used to minimise the bias from the difference of baseline characteristics, such as radiation target volumes, extent of resection, the constituent ratio of KPS. Because of several studies not recording MGMT promoting methylation and IDH-1 mutation in detail, information about IDH and MGMT were not extracted, although the mutation status of IDH and MGMT promoting methylation could deeply influence GBM's clinical and biological characteristics [38,39]. Moreover, age is a well-known important prognostic factor for GBM, but because the included studies do not always give detailed patient age distribution, it is impossible to analyse the efficacy of HFRT in different age groups. In addition, the studies we included comprised of studies on the neoadjuvant temozolomide regimen, which may also introduce bias. After our analysis, we found that the efficacy of these two regimens was similar and may have less influence on the overall results. Finally, because of the incomplete outcome data, systematic measurement error was of inescapability while extracting numeric data from survival curve figures.

The results of our study are similar to previous randomised clinical studies and retrospective studies on elderly GBM patients. Compared with CRT, HFRT does not show a significant impact on the survival time or complications of GBM patients. However, patients in these studies are usually carefully selected and have relatively good performance status, which sometimes do not reflect the real-world situation. A real-world analysis based on the National Cancer Database indicated that HFRT was associated with worse outcome compared to CRT for elderly GBM patients [40], but it is also important to note that in the real world, because elderly

and low KPS patients need to complete treatment as soon as possible, the proportion of these patients who choose HFRT is relatively high, and the prognosis of these GBM patients is actually poor. On the other hand, patients with better physical conditions tend to choose CRT. This may be one of the reasons why HFRT is less effective than CRT in real-world studies. Anyway, these different views warn us that it's necessary to collect more data to future study the specific efficacy of HFRT on GBM. Recently, a multicentre phase III trial in newly diagnosed glioblastoma comparing standard radiochemotherapy to radiochemotherapy with simultaneous integrated boost (72 Gy/30F) have been conducting and the outcome is worthy of expectation [41].

5. Conclusion

As far as we know, this study is the first systematic analysis to evaluate the efficacy of hypofractionated radiotherapy in newly diagnosed glioblastoma without age restrictions. By shortening overall treatment time, hypofractionation not only could increase tumour cell kill from a higher dose per fraction, but also reduce demands on medical resources. Compared to conventional radiotherapy, HFRT tends to improve prognosis of GBM. In addition, we found that high-BED schedule hypofractionated radiotherapy could prolong GBM progression-free survival in the future. The risk of toxicity did not show an obvious increasing trend and was acceptable while undergoing a proper high BED schedule. Further research including phase II/III random control trials to evaluate the efficacy of hypofractionated radiotherapy and explore optimal hypofractionation schedule for newly diagnosed glioblastoma at all ages are recommended.

Authors' contributions

SD and CR conceived the study. LG designed study eligibility criteria and selection. LG, XL and SD captured and selected citations. CR, YC and RL extracted data. LG performed all statistical analysis. LG and XL drafted the manuscript. All authors contributed to manuscript revision, read and approved the final version.

Availability of data and materials

No data, models, or code were generated or used during the study.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.canrad.2020.08.049.

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