Acta Neurologica Belgica
https://doi.org/10.1007/s13760-020-01533-w

ORIGINAL ARTICLE

Treatments of gliosarcoma of the brain: a systematic review and meta-analysis

Xing Wang[1] · Jiao Jiang[2] · Meixi Liu[3] · Chao You[1,4]

Received: 9 June 2020 / Accepted: 20 October 2020

Abstract

Gliosarcoma (GSM) is a rare central nervous system tumor. Clinical management of it is similar to glioblastoma (GBM). However, due to a few comparative studies exist, uncertainty and disagreements remain in the literatures. To assess the available evidence on the value of different treatments and to carry out an up-to-date evaluation to summarize the evidence for the optimal treatment in GSM patients. Free words were used to search for the relevant studies without language limitations in electronic databases including PubMed, Ovid EMBASE, Cochrane Central Register of Controlled Trials from inception to September 15, 2019. Pooled hazard ratio (HR) with 95% confidence interval (CI) were calculated using a random-effects model. The main endpoint was all-cause mortality. Overall, 10 studies published between 2008 and 2018 including 803 patients were selected for the meta-analysis. Temozolomide (TMZ)-dominated chemotherapy was associated with a reduced risk of overall survival (OS), with HR 0.49 (95% CI 0.37–0.66). The pooled HR of OS was 0.40 (95% CI 0.29–0.56) between radiotherapy and without radiotherapy. The pooled HR (0.52, 95% CI 0.32–0.85) indicated gross total resection (GTR) had a positive impact on OS in GSM. In patients with GSM, survival benefits as currently performed are associated with TMZ-dominated chemotherapy and high-dose radiotherapy. Our systematic review and meta-analysis also demonstrate GTR is associated with a reduction in all-cause mortality in patients with primary GSM.

Keywords Gliosarcoma · Radiotherapy · TMZ · GTR · Survival

Introduction

Gliosarcoma (GSM), characterized by a mixture of glial and sarcomatous histopathologic compositions, is a rare but highly malignant glioblastoma (GBM) that accounts for 2–8% of high-grade gliomas (HGG) [1–4]. GSM has gained widespread acceptance gradually since 1955 when Feigen et al. [4] first described. At present, it is generally accepted that the clinical characteristics of GSM are similar to GBM. However, GSM seems to metastasize much more frequently than GBM, as the incidence of extracranial metastases has been reported up to 11% [5, 6].

To date, various risk factors have been considered to influence the survival among individual patients with GSM, including age, Karnofsky score (KPS), the extent of resection (EOR), preoperative and postoperative neurological function, and application of adjuvant therapies [7, 8, 9, 10]. To decrease the mass effect and to reduce the tumor burden necessitate gross total resection (GTR) of tumor tissues. However, GTR is not always possible due to the invasive, infiltrative and metastatic nature of GSM. Besides, extended

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13760-020-01533-w) contains supplementary material, which is available to authorized users.

✉ Chao You
dr.chaoyou@outlook.com

1 Department of Neurosurgery, West China Hospital, Sichuan University, No. 37, St. Guoxuexiang, Chengdu 610041, Sichuan, People's Republic of China

2 Department of Dermatology, The Second Xiangya Hospital, Central South University, Changsha 410008, Hunan, People's Republic of China

3 Department of Rehabilitation, Huashan Hospital, Fudan University, Shanghai 200040, People's Republic of China

4 West China Brain Research Centre, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, People's Republic of China

Published online: 06 November 2020

resection for achieving GTR may lead to motor and language deficits and a decrease in the quality of survival. As such, surgical removal is unlikely to be curative and whether extensive resection generates favorable outcome in a long term in patients with GSM is unclear [11, 12].

Radiotherapy has been suggested as mandatory to improve the long-term outcomes of patients, because it may improve long-term outcomes and increases survival by 8–15 weeks [1, 13]. However, due to insufficient data, the long-term impact of it on GSM is hard to evaluate. Temozolomide (TMZ) has been proved as the most effective chemotherapeutic drug for the treatment of high-grade gliomas (HGG) [14, 15]. But due to late addition of TMZ in the management of GSM, whether TMZ therapy is beneficial for it is still debatable [16].

Given ongoing debate and uncertainty, we conducted an updated systematic review and meta-analysis to evaluate which therapy methods, including TMZ, radiotherapy, and surgery, determined overall survival (OS) and free progression survival (FPS) in adult patients with GSM in the modern era.

Materials and methods

Protocol and guidance

We followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (checklist available in Supplementary materials) [17], and registered the study on the PROSPERO platform (CRD42020152764).

Data sources and search strategy

A comprehensive search for published literatures was conducted in the PubMed, Ovid EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL). Besides, we checked references of included studies to assess for additional articles. The following keywords and their random combinations were used: gliosarcoma, outcome, temozolomide, radiotherapy. The search was conducted from inception to September 15, 2019. Search strategies are described in eTable 1 in the Supplement.

Selection criteria

All of the following criteria shown are fulfilled: (1) patients: adults (age ≥ 18 years) who were diagnosed with GSM based on 2007 standardized World Health Organization (WHO) classification of brain tumors. (2) interventions and comparators: using one or several of the following management to prolong survival of patients: TMZ-dominated chemotherapy as intervention compared with no TMZ using; radiotherapy as intervention compared with no radiotherapy adoption; GTR compared with no GTR. (3) outcomes: the primary outcome was OS, defined as the length of time from start of treatment for GSM patients to death from any cause. Secondary outcome was FPS, defined as the time from date of treatment to disease progression. Eligible studies should report at least one of them, along with 95% confidence interval (CI). (4) Studies: either cohort studies involved more than 10 patients or randomized controlled trials (RCTs). Detailed information is explained in the following part and eTable 2 in the Supplement. Besides, we excluded studies as one of the following criterions occurs: (1) selected studies without relevant information on the aforementioned data items. (2) studies only referring to animal studies, GBM, other neurogenic tumors including medulloblastoma, ganglioglioma, and optic nerve glioma.

Selection process and data extraction

According to PRISMA guidelines, after deleting duplicates, we excluded publications which were not eligible based on titles and abstracts. Then full-text literatures were reviewed for further included or excluded according to aforementioned inclusion/exclusion criteria.

Two reviewers independently completed the procedures. We contacted the corresponding authors for missing or unreported data if necessary. Disagreements were resolved by consensus or with input from a third independent reviewer.

Study definitions and outcomes of interest

The primary time-to-event outcome was overall survival (OS), the secondary outcome was 6-month (FPS). We used hazard ratios (HRs) to summarize time-to-event outcomes because they accounted for time as well as the number of events. We extracted the HRs and 95% CIs of OS and FPS from multivariate Cox proportional hazard models in the selected studies, otherwise, unadjusted HRs were used. If studies did not provide the above information straightforward, we used a relevant formula to calculate HRs from existing information according to Tierney et al [18].

Subgroup analysis

Subgroup analyses were performed to test interactions based on age (> 60 and ≤ 60 years), sex ratio (female > 35 and ≤ 35%), radiotherapy (RT) dose (> 55 and ≤ 55 Gy), whether containing secondary GSM (yes and no).

Sensitivity analysis

To examined change in the pooled estimates and verify the stability of the results, we conducted sensitivity analyses

for the primary outcome by (1) excluding studies published before 2010; (2) excluding studies containing a secondary GSM; (3) using fixed-effect models; (4) excluding studies without giving HR directly; (5) excluding studies with < 100 patients in total; (6) excluding studies considered as moderate or low methodological quality.

Assessment of risk of bias

We used Newcastle–Ottawa Scale (NOS) to assess the quality of cohort studies [19]. The score was calculated based on the three major domains, with a total maximum of 9 scores. Studies were classified into three types according to the NOS: high-quality studies as ≥ 7 scores, intermediate-quality studies as 4–6 scores, low-quality studies as ≤ 3 scores. For randomized controlled trials, we assessed the risk of bias according to the Cochrane Collaboration Risk of Bias tool across seven domains. Studies with each domain meeting low risk were considered as high-quality.

Two reviewers independently assessed the quality of included studies. Disagreements were resolved by consensus or with input from a third independent reviewer.

Statistical analysis

A random-effects model was performed using the STATA (version 14.0; STATA Corp., College Station, TX, USA), and open-source R (meta package and forestplot package). Other statistical analyses were done in the SPSS (version 22.0; IBM Corp., Armonk, New York, USA). We pooled HRs with the corresponding 95% CIs using the Mantel–Haenszel method in consideration of interstudy heterogeneity. Statistical heterogeneity across the studies was evaluated using the I^2 statistic and I^2 values exceeding 50% were regarded as substantial heterogeneity. For studies with substantial heterogeneity, we conducted further analysis through subgroup and sensitivity analyses to identify the source. Potential publication bias was examined by constructing a funnel plot in which the standard error (SE) of the ln HR was plotted against the HR of the selected outcomes and statistically assessed by Egger's regression test and Begg's adjusted rank correlation test. A reported p value of less than 0.05 was considered statistically significant.

Results

Study identification and characteristics

An extensive bibliographical search strategy identified 340 articles from PubMed, Ovid EMBASE, CENTER, of which 83 were excluded for a duplicate. 257 articles were screened. Among these, papers were excluded for reviews, case reports and case series ($n = 67$), letters and communications or other publication types ($n = 8$). 146 articles were excluded that did not focus on GSM. 36 articles were included for full-text reading Among them, 26 studies were lack of related clinical data ($n = 10$) and nonstandard comparison ($n = 16$). In the end, only 10 studies [20–29] fulfilled our inclusion criteria. The PRISMA flow chart showing the publication screening process and a list of excluded studies with reasons for exclusion are provided in Fig. 1.

The eligible studies were conducted in 6 countries (USA, German, India, France, New Zealand, and South Korea) and articles were published from 2009 to 2018. All of the 10 studies were retrospective cohort studies. Overall, 803 patients were included in the analysis. The number of patients included in each study ranged from 12 to 353, and the mean age ranged from 45 to 75 years old. Most studies focused on primary GSM except two. Table 1 summarizes the characteristics of the studies included in our systematic review and meta-analysis.

Primary outcome: overall survival

The data of GTR was reported in all included studies with a combined total of 803 patients. The effect of GTR on OS appeared to be statistically significant with HR 0.52 (95% CI 0.32–0.85) along with substantial heterogeneity ($I^2 = 71.6\%$). Seven studies with 401 patients reported adopted TMZ-dominated chemotherapy. Overall, TMZ was associated with a significant positive effect on OS with HR 0.49 (95% CI 0.37–0.66) and low heterogeneity across studies ($I^2 = 25.3\%$). Besides, five studies provided OS between radiotherapy group and no radiotherapy group, the results indicated that radiotherapy was associated with a significantly reduced all-cause mortality with HR 0.40 (95% CI 0.29–0.56). The negligible heterogeneity was detected among studies ($I^2 = 7\%$). The results of the primary outcomes are summarized in Fig. 2. After excluding specific studies, the results remained robust in general (eTable 4 in the Supplement).

Secondary outcome: free progression survival

We performed an analysis of three studies that provided FPS in the GTR group and no GTR group. GTR seems unlikely to be associated with a significant reduction in the mortality of patients with GSM, due to the HR 0.77 (95% CI 0.40–1.49). Two studies provided FPS in the TMZ-dominated chemotherapy group compared with the control group. The meta-analysis indicated that the patients with GSM who underwent TMZ-dominated chemotherapy did not benefit more in FPS than who did not according to HR 0.83 (95% CI 0.13–5.40). The results of the secondary outcomes are summarized in Fig. 3.

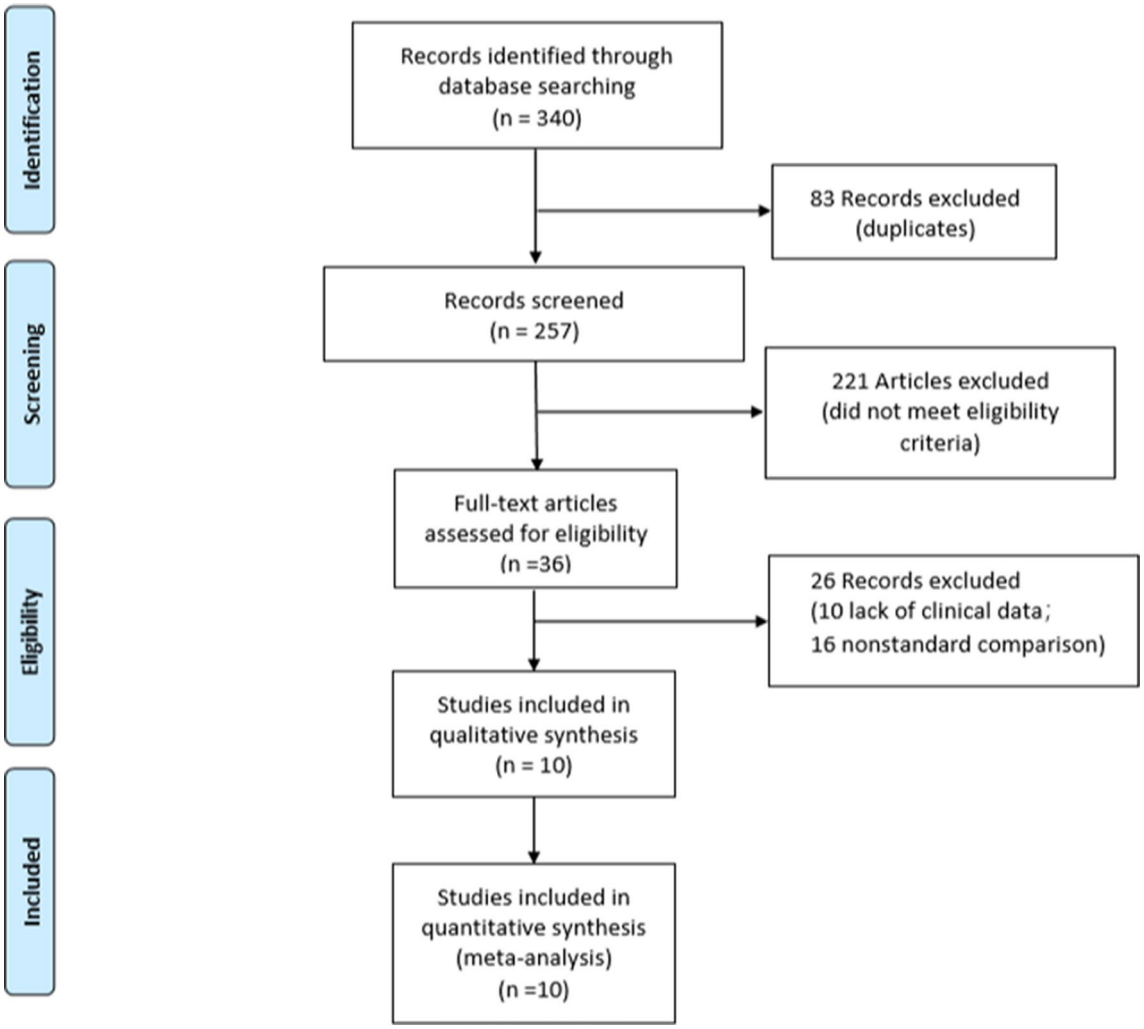


Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram

Subgroup analyses

Subgroup analysis of GTR demonstrated a significantly decreased risk of death in elderly patients (> 60 years old) with HR 0.52 (95% CI 0.32–0.85), female > 35% with HR 0.45 (95% CI 0.26–0.77), RT dose > 55 Gy with HR 0.35 (95% CI 0.14–0.74). Subgroup analysis of chemotherapy demonstrated that more favorable results of OS with patients > 60 years old with HR 0.52 (95% CI 0.44–0.62), RT dose > 55 Gy with HR 0.53 (95% CI 0.42–0.67) and studies without secondary GSM with HR 0.41 (95% CI 0.26–0.65). Among patients underwent radiotherapy, long-term benefits were showed with patients > 60 years old with HR 0.43 (95% CI 0.21–0.85), female > 35% with HR 0.37 (95% CI 0.28–0.49). The results of the subgroup analysis are summarized in Fig. 4.

Risk of bias and publication bias

Study-specific NOS scores and risk-of-bias assessments are summarized in eTable 2 and 3 in the Supplement. Ranging from 5 to 7 among the 10 studies, 3 were considered as high quality [21, 22, 25]. The rest 7 were considered as moderate methodological quality studies [20, 23, 24, 26–29], mainly because the outcomes of interest were emerging at the beginning of study and adjustment for potential confounders was absent.

No publication bias was presented in our meta-analysis. eFigure 1–9 in the Supplement shows the funnel plot, Egger's regression test and Begg's adjusted rank correlation test of included studies representing the association between OS and treatment methods.

Table 1 Study characteristics involving gliosarcoma and different treatment methods

Study	Country	Study design	Total patients	Age (years)	Female (%)	Disease	Surgery	Chemo-therapy	Radiotherapy	Inclusion time		Follow-up (months)
										From	To	
Smith et al. [20]	America	Retrospective	22	62	31.8	GSM	Y	Y	Y	1995	2016	NR
Shin et al. [21]	America	Retrospective	210	75	38.6	Primary GSM	Y	Y	N	2004	2013	8.2
Jain et al. [22]	New Zealand	Retrospective	21	58	38.1	Primary GSM	Y	Y	Y	2000	2013	5.7
Adeberg et al. [24]	Germany	Retrospective	37	60	29.0	Primary GSM	Y	Y	N	2005	2013	NR
Castelli et al. [23]	France	Retrospective	75	65	32.4	Primary GSM	Y	N	Y	1998	2014	12
Rath et al. [25]	India	Retrospective	27	45	25.9	Primary GSM	Y	Y	N	2007	2012	13
Lee et al. [26]	South Korea	Retrospective	26	51	38.5	GSM	Y	Y	Y	1995	2009	NR
Kang et al. [27]	South Korea	Retrospective	12	54	16.7	Primary GSM	Y	N	N	1996	2008	NR
Han et al. [28]	America	Retrospective	20	60.8	40.0	Primary GSM	Y	Y	N	1996	2008	NR
Kozak et al. [29]	America	Retrospective	353	63	38.8	Primary GSM	Y	N	Y	1988	2004	NR

GSM gliosarcoma, *NR* not reported, *Y* yes, *N* no

Discussion

Our meta-analysis of 10 selected studies investigated the efficacy of various treatments among patients with GSM. In our study, we found that both TMZ-dominated chemotherapy and high-dose radiotherapy were highly associated with a reduction in all-cause mortality among GSM patients, with the pooled HR 0.49 (95% CI 0.37–0.66) and 0.40 (95% CI 0.29–0.56) respectively. Despite substantial heterogeneity, GTR might play a clinically favorable prognostic role in patients with GSM with HR 0.52 (95% CI 0.32–0.85). However, the favorable results could not be repeated in FPS among the three inventions.

Compared with other studies

To our knowledge, our study is the only quantitative meta-analysis to explore the association among various therapy methods with OS and FPS in GSM. Existing studies mainly focused on the prognostic factors in GBM and the published systematic review in evaluating the effect of different treatments on patients suffering GSM is sparse. A review in 2015 by Brown et al. [30]. found that GTR essentially improves OS in GBM compared with subtotal resection (STR) regardless of substantial heterogeneity (I^2 as high as 86%), the absolute reduced risk (ARR) of mortality at 1 year was 16.1% with RR 0.62 (95% CI 0.56–0.69) and 10.3% at 2 years with RR 0.84 (95% CI 0.79–0.89). In the same year, an additional systematic review by Loureiro et al. [31]. suggested that neither chemotherapy (HR 0.96 95% CI 0.72–1.27) nor the extent of resection (HR 0.84, 95% CI 0.39–1.79) benefited the prognosis in GBM. The above results were validated by Sun et al. [32].

Our findings that the prognostic value of chemotherapy and extent of resection with favorable survival contrasted with the results of previous publications. We assumed the discrepancy might be explained by rigorous classification, updated data, and methodological differences.

Heterogeneity

The asymmetry in the funnel plot for GTR and OS seemed to be the result of publication bias, in consideration of no publication bias in the subsequent analysis. We assumed it mostly derived from mixing secondary GSM in the analysis. The sensitivity analysis confirmed our speculation. Detailed information of sensitivity analysis is showed in eTable 4 in the Supplement.

Study implications

To date, neurosurgeons have used their clinical experience to decide whether to use TMZ-dominated chemotherapy

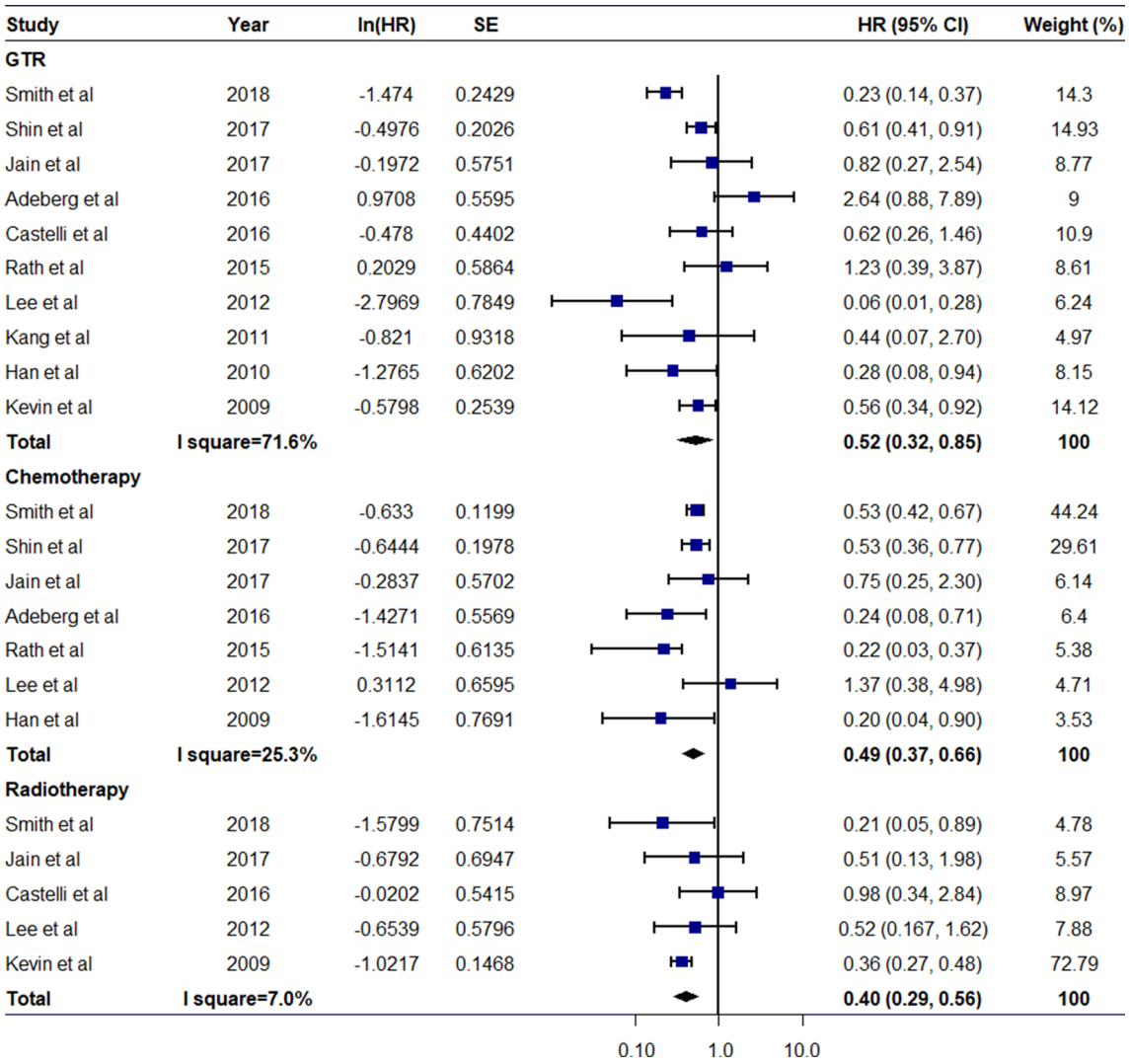


Fig. 2 Meta-analyses for the outcomes of overall survival for GTR, TMZ-dominated chemotherapy and radiotherapy. *CI* confidence interval, *GTR* gross total resection, *HR* hazard ratio, *SE* standard error

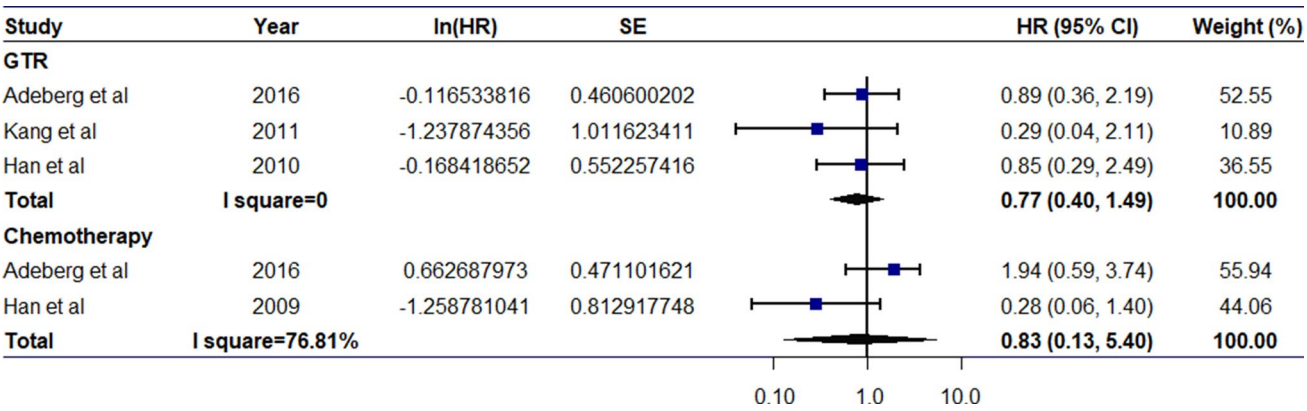
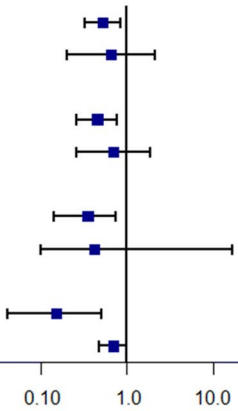


Fig. 3 Meta-analyses for the outcome of free progression survival for GTR, TMZ-dominated chemotherapy and radiotherapy. *CI* confidence interval, *GTR* gross total resection, *HR* hazard ratio, *SE* standard error

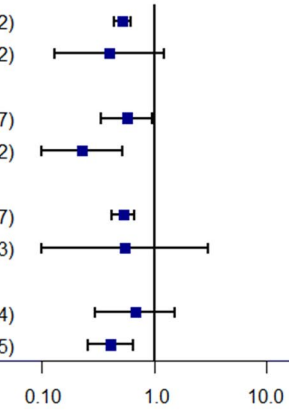
A

Subgroup	Studies	Patients	HR (95% CI)	p value	p for interaction
Age					
>60 years	6	717	0.52, (0.32, 0.85)	0.0001	0.056
≤60 years	4	86	0.65, (0.20, 2.09)	0.456	
Sex					
Female>35%	5	630	0.45 (0.26, 0.77)	0.004	0.363
Female≤35%	5	173	0.70 (0.26, 1.88)	0.482	
RT dose					
>55 Gy	3	71	0.35 (0.14, 0.74)	0.006	0.066
≤55 Gy	2	101	0.42 (0.10, 16.75)	0.643	
Containing secondary GSM					
Yes	2	48	0.15 (0.04, 0.50)	0.002	0.0001
No	8	755	0.69 (0.48, 0.98)	0.037	



B

Subgroup	Studies	Patients	HR (95% CI)	p value	p for interaction
Age					
>60	4	327	0.52 (0.44, 0.62)	0.0001	0.3820
≤60	3	263	0.40 (0.13, 1.22)	0.1090	
Sex					
Female>35%	4	277	0.58 (0.34, 0.97)	0.0390	0.0510
Female≤35%	2	102	0.23 (0.10, 0.52)	0.0001	
RT dose					
>55 Gy	1	22	0.53 (0.42, 0.67)	0.0001	0.8730
≤55 Gy	2	101	0.55 (0.10, 3.03)	0.4940	
Containing secondary GSM					
Yes	2	48	0.68 (0.30, 1.54)	0.3570	0.3520
No	5	353	0.41 (0.26, 0.65)	0.0001	



C

Subgroup	Studies	Patients	HR (95% CI)	p value	p for interaction
Age					
>60	3	412	0.43 (0.21, 0.85)	0.0150	0.5060
≤60	2	47	0.52 (0.22, 1.23)	0.1350	
Sex					
Female>35%	3	400	0.37 (0.28, 0.49)	0.0001	0.3470
Female≤35%	2	59	0.49 (0.11, 2.24)	0.3580	
RT dose					
>55 Gy	2	59	0.53 (0.23, 1.22)	0.3580	0.8900
≤55 Gy	1	26	0.52 (0.17, 1.62)	0.2590	
Containing secondary GSM					
Yes	2	48	0.37 (0.15, 0.91)	0.0290	0.9050
No	3	411	0.48 (0.26, 0.87)	0.0160	

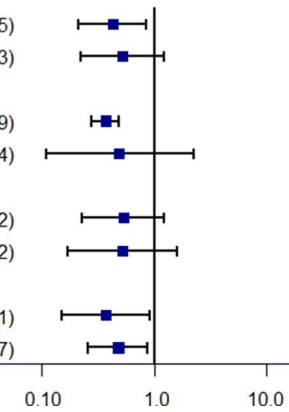


Fig. 4 Subgroup analysis for overall survival of GTR, TMZ-dominated chemotherapy and radiotherapy. *CI* confidence interval, *GSM* gliosarcoma, *GTR* gross total resection, *Gy* gray, *HR* hazard ratio, *RT* radiotherapy, *TMZ* temozolomide

in treating GSM patients for more than 50 years. However, hard evidence is lacking for its indeed efficiency as adjuvant therapy Relevant standard treatments are not been implied in the latest NCCN guidelines of central nervous system cancers. Our meta-analysis showed that TMZ-dominated chemotherapy was significantly associated with a favorable outcome of GSM, as well as high-dose radiotherapy. Thus, we recommend TMZ-dominated chemotherapy and high-dose radiotherapy be used in GSM patients as routine treatments. Moreover, whether GTR benefits for patients with GSM in a long-term warrant further investigation.

Strength and limitations

Strengths of this review include a comprehensive search for evidence, a priori protocol and duplicate assessment of eligibility, risk of bias, and data abstraction. The study includes a rigorous assessment of the credibility of subgroup analyses and the robustness of sensitivity analyses.

We acknowledge the limitations of this systematic review and meta-analysis as follows. First, a major concern was prominent in heterogeneity. A firm conclusion whether GTR in GSM patients benefits for patients remained uncertain. we assumed the heterogeneity was mainly derived from the mixture of primary and secondary GSM. The assumption was confirmed by sensitivity analysis after excluding studies containing secondary GSM. Second, it is noteworthy that no RCTs were included in our analysis, mainly due to ethical issues. And the intrinsic restriction might reduce the level of evidence. However, the "real world" settings are more likely to be representative than RCTs in tumor patients. Third, different definitions of GTR were used by the authors in the individual studies, Two studies (Adeberg et al. and Kang et al. [27]) defined GTR as complete resection of the preoperative contrast-enhancing lesion. While Rath et al. suggested that 90% reduction of tumor volume was a necessary threshold to increase survival in patients with GSM. Forth, secondary GSM was mixed in two studies. Hence, we eliminated the impacts by dropping them out in sensitivity analysis, and the results remained consistent.

Consequently, maximal tumor resection with minimal functional impairment, together with the standard chemotherapy and high-dose radiotherapy, might be the strategy that prolongs survival of GSM patients.

Conclusion

Overall, our results support the hypothesis that TMZ-dominated chemotherapy and high-dose radiotherapy play a clinically useful prognostic role in patients with GSM. However, whether GTR benefits for GSM patients remains uncertain due to significant heterogeneity and poor stability. But still, we conclude that GTR is associated with a decreased risk of all-cause mortality in patients with primary GSM. Nevertheless, in consideration of immanent restrictions of included studies, the results of ongoing and future RCTs are needed.

Author contributions CY was the guarantor of the review. Concept and design: XW, CY; Acquisition, analysis, or interpretation of data: XW, JJ, ML; Drafting of the manuscript: XW, JJ, ML; Statistical analysis: XW, JJ, ML; Supervision: XW, CY.

Funding None.

Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors, thus ethical approval is not required.

Informed consent For this type of study, formal consent is not required.

References

1. Ra M, Feigin I, Ransohoff J 3rd (1976) Clinical and pathological study of 24 cases of gliosarcoma. J Neurosurg 45(4):398. https://doi.org/10.3171/jns.1976.45.4.0398
2. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P (2007) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol Commun 114(2):13
3. Galanis E, Buckner JC, Dinapoli RP, Scheithauer BW, Jenkins RB, Wang CH, O'Fallon JR, Farr G Jr (1998) Clinical outcome of gliosarcoma compared with glioblastoma multiforme: North Central Cancer Treatment Group results. J Neurosurg 89(3):425. https://doi.org/10.3171/jns.1998.89.3.0425
4. Feigin IH, Gross SW (1955) Sarcoma arising in glioblastoma of the brain. Am J Pathol 31(4):21
5. Beaumont TL, Kupsky WJ, Barger GR, Sloan AE (2007) Gliosarcoma with multiple extracranial metastases: case report and review of the literature. J Neurooncol 83(1):39–46. https://doi.org/10.1007/s11060-006-9295-x
6. Frandsen S, Broholm H, Larsen VA, Grunnet K, Moller S, Poulsen HS, Michaelsen SR (2019) Clinical characteristics of gliosarcoma and outcomes from standardized treatment relative to conventional glioblastoma. Front Oncol 9:1425. https://doi.org/10.3389/fonc.2019.01425
7. Meis JM, Martz KL, Nelson JS (1991) Mixed glioblastoma multiforme and sarcoma. A clinicopathologic study of 26 radiation therapy oncology group cases. Cancer 67(9):8. https://doi.org/10.1002/1097-0142(19910501)67:9
8. Weller M, van den Bent M, Hopkins K, Tonn JC, Stupp R, Falini A, Cohen-Jonathan-Moyal E, Frappaz D, Henriksson R, Balana C, Chinot O, Ram Z, Reifenberger G, Soffietti R, Wick W (2014) EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. Lancet Oncol 15(9):e395–e403. https://doi.org/10.1016/S1470-2045(14)70011-7
9. Yi X, Cao H, Tang H, Gong G, Hu Z, Liao W, Sun L, Chen BT, Li X (2019) Gliosarcoma: a clinical and radiological analysis of 48

cases. Eur Radiol 29(1):429–438. https://doi.org/10.1007/s00330-018-5398-y
10. Frandsen J, Orton A, Jensen R, Colman H, Cohen AL, Tward J, Shrieve DC, Suneja G (2018) Patterns of care and outcomes in gliosarcoma: an analysis of the National Cancer Database. J Neurosurg 128(4):1133–1138. https://doi.org/10.3171/2016.12.jns162291
11. Barker FG 2nd, Md P, Chang SM, Gutin PH, Lamborn KR, Larson DA, Malec MK, McDermott MW, Sneed PK, Wara WM, Wilson CB (1996) Radiation response and survival time in patients with glioblastoma multiforme. J Neurosurg 84(3):442–448. https://doi.org/10.3171/jns.1996.84.3.0442
12. Cai J, Wu Y, Mirua T, Pierce JL, Lucero MT, Albertine KH, Spangrude GJ, Rao MS (2002) Properties of a fetal multipotent neural stem cell (NEP cell). Dev Biol 251(2):22. https://doi.org/10.1006/dbio.2002.0828
13. Jaros E, Rh P, Adam L, Kelly PJ, Crawford PJ, Kalbag RM, Mendelow AD, Sengupta RP, Pearson AD (1992) Prognostic implications of p53 protein, epidermal growth factor receptor, and Ki-67 labelling in brain tumours. Br J Cancer 66(0007–0920):13. https://doi.org/10.1038/bjc.1992.273
14. Stupp R, Mason WP, Bent MJ, Weller M, Fisher B, Taphoorn MJB, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO, Mirimanoff RO (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352(1533–4406 (Electronic)):987–996. https://doi.org/10.1056/NEJMoa043330
15. Nabors LB, Portnow J, Ammirati M, Baehring J, Brem H, Butowski N, Fenstermaker RA, Forsyth P, Hattangadi-Gluth J, Holdhoff M, Howard S, Junck L, Kaley T, Kumthekar P, Loeffler JS, Moots PL, Mrugala MM, Nagpal S, Pandey M, Parney I, Peters K, Puduvalli VK, Ragsdale J, Rockhill J, Rogers L, Rusthoven C, Shonka N, Shrieve DC, Sills AK, Swinnen LJ, Tsien C, Weiss S, Wen PY, Willmarth N, Bergman MA, Engh A (2017) NCCN guidelines insights: central nervous system cancers, version 1.2017. J Natl Compr Cancer Netw 15(11):1331–1345. https://doi.org/10.6004/jnccn.2017.0166
16. Walker G, Mr G, Prabhu SS, Brown PD, McAleer MF (2013) Temozolomide use in adult patients with gliosarcoma: an evolving clinical practice. J Neurooncol 112(1):7
17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339:b2700. https://doi.org/10.1136/bmj.b2700
18. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR, Sydes MR (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. BioMed Central. https://doi.org/10.1186/1745-6215-8-16
19. Margulis AV, Pladevall M, Riera-Guardia N, Varas-Lorenzo C, Hazell L, Berkman ND, Viswanathan M, Perez-Gutthann S (2014) Quality assessment of observational studies in a drug-safety systematic review, comparison of two tools: the Newcastle-Ottawa Scale and the RTI item bank. Clin Epidemiol 6:359–368. https://doi.org/10.2147/clep.s66677
20. Smith DR, Wu CC, Saadatmand HJ, Isaacson SR, Cheng SK, Sisti MB, Bruce JN, Sheth SA, Lassman AB, Iwamoto FM, Wang SH, Canoll P, McKhann GM 2nd, Wang TJC (2018) Clinical and molecular characteristics of gliosarcoma and modern prognostic significance relative to conventional glioblastoma. J Neurooncol 137(2):303–311. https://doi.org/10.1007/s11060-017-2718-z
21. Shin JY, Yoon JK, Diaz AZ (2017) Gliosarcoma in septuagenarians and octogenarians: what is the impact of adjuvant chemoradiation? J Clin Neurosci 45:77–82. https://doi.org/10.1016/j.jocn.2017.07.002
22. Jain A, Correia J, Schweder P, McMahon A, Merola J, Aspoas R (2017) Analysis of outcomes of multidisciplinary management of gliosarcoma: a single-center study, 2000–2013. World Neurosurg 106:30–36. https://doi.org/10.1016/j.wneu.2017.06.073
23. Castelli J, Feuvret L, Haoming QC, Biau J, Jouglar E, Berger A, Truc G, Gutierrez FL, Morandi X, Le Reste PJ, Thillays F, Loussouarn D, Nouhaud E, Crehange G, Antoni D, Vauleon E, de Crevoisier R, Noel G (2016) Prognostic and therapeutic factors of gliosarcoma from a multi-institutional series. J Neurooncol 129(1):85–92. https://doi.org/10.1007/s11060-016-2142-9
24. Adeberg S, Bernhardt D, Harrabi SB, Diehl C, Koelsche C, Rieken S, Unterberg A, von Deimling A, Debus J (2016) Radiotherapy plus concomitant temozolomide in primary gliosarcoma. J Neurooncol 128(2):341–348. https://doi.org/10.1007/s11060-016-2117-x
25. Rath GK, Sharma DN, Mallick S, Gandhi AK, Joshi NP, Haresh KP, Gupta S, Julka PK (2015) Clinical outcome of patients with primary gliosarcoma treated with concomitant and adjuvant temozolomide: A single institutional analysis of 27 cases. Indian J Cancer 52(4):599–603. https://doi.org/10.4103/0019-509X.178407
26. Lee D, Kang SY, Suh YL, Jeong JY, Lee JI, Nam DH (2012) Clinicopathologic and genomic features of gliosarcomas. J Neurooncol 107(3):643–650. https://doi.org/10.1007/s11060-011-0790-3
27. Kang SH, Park KJ, Kim CY, Yu MO, Park CK, Park SH, Chung YG (2011) O6-methylguanine DNA methyltransferase status determined by promoter methylation and immunohistochemistry in gliosarcoma and their clinical implications. J Neurooncol 101(3):477–486. https://doi.org/10.1007/s11060-010-0267-9
28. Han SJ, Yang I, Ahn BJ, Otero JJ, Tihan T, McDermott MW, Berger MS, Prados MD, Parsa AT (2010) Clinical characteristics and outcomes for a modern series of primary gliosarcoma patients. Cancer 116(5):1358–1366. https://doi.org/10.1002/cncr.24857
29. Kozak KR, Mahadevan A, Moody JS (2009) Adult gliosarcoma: epidemiology, natural history, and factors associated with outcome. Neuro Oncol 11(2):9. https://doi.org/10.1215/15228517-2008-076)
30. Brown TJ, Brennan MC, Li M, Church EW, Brandmeir NJ, Rakszawski KL, Patel AS, Rizk EB, Suki D, Sawaya R, Glantz M (2016) Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. JAMA Oncol 2(11):1460–1469. https://doi.org/10.1001/jamaoncol.2016.1373
31. Loureiro LV, Victor Eda S, Callegaro-Filho D, Koch Lde O, Pontes Lde B, Weltman E, Rother ET, Malheiros SM (2016) Minimizing the uncertainties regarding the effects of delaying radiotherapy for glioblastoma: a systematic review and meta-analysis. Radiother Oncol 118(1):1–8. https://doi.org/10.1016/j.radonc.2015.11.021
32. Sun H, Du S, Liao G, Xie X, Ren C, Yuan YW (2015) Do glioma patients derive any therapeutic benefit from taking a higher cumulative dose of temozolomide regimens?: a meta-analysis. Medicine (Baltimore) 94(20):e827. https://doi.org/10.1097/md.0000000000000827