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Review

Comparative assessment of the efficacy of gross total versus subtotal total resection in patients with glioma: A meta-analysis

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ABSTRACT

Background: It is controversial whether to plan for a subtotal or gross total resection (GTR) of lesions in patients with gliomas. Several studies have demonstrated that GTR may be superior to subtotal resection (STR) with regard to improving the survival rates of patients with glioma. Thus, the present meta-analysis was designed to compare and evaluate the efficacy of GTR for improving clinical outcomes of patients with glioma.

Methods: We searched the Cochrane Library, PubMed, Embase, and Web of Science for the interval between March 1972 to November 2018 to identify relevant original studies that compared the efficacy of GTR and STR in patients with gliomas. Mean differences (MDs) with 95% confidence intervals (CIs) were estimated to compare the outcomes of the GTR and STR groups. We also performed subgroup and sensitivity analyses to further explore the effects of the extent of surgical resection (EOR) and assess the stability of the combined results. Two external (blinded) reviewers assessed the quality of the trials and the extracted data independently. All statistical analyses were performed using standard statistical procedures provided in Review Manager 5.2.

Results: We included 42 studies (N = 5920 participants) in this meta-analysis. Significantly superior efficacy was detected for GTR to improve overall survival compared to STR (MD 4.01, 95% CI 2.52–5.51; $P < 0.00001$), 5-year survival rate (OR 4.08, 95% CI 3.02–5.52; $P < 0.00001$), progression-free survival (MD 2.08, 95% CI 0.26–3.89; $P = 0.02$), seizure control (OR 4.25, 95% CI 2.99–6.05; $P < 0.00001$), and reducing the incidence of malignant transformation (OR 0.28; 95% CI 0.13–0.60; $P = 0.001$) in patients with glioma.

Conclusions: Our meta-analysis supports the superior efficacy of GTR on survival, functional outcome, tumor progression, seizure control, malignant transformation, morbidity, and mortality in patients with glioma.

1. Introduction

Brain tumors, particularly gliomas, are one of the most common types of primary intracranial tumors [1]. According to the 2012 report from GLOBOCAN, cancers of the brain and central nervous system accounted for 256,000 new cases and 189,000 deaths in 2012 (1.8% of new cancers; 2.3% of cancer deaths) [2]. The highest incidence and mortality rates occurred in more developed regions (Australia/New Zealand, Europe, and North America) and were lowest in Africa and the Pacific [2]. A glioblastoma, classified as a grade IV glioma by the World Health Organization, is a common type of glioma, accounting for 80% of all primary malignant central nervous system tumors [3]. Even though many therapeutic advances have been introduced in the past few decades, such as resection, irradiation with adjuvant temozolomide, and experimental chemotherapy, the overall 5-year survival rate of patients with glioma remains poor [4,5]. Malignant gliomas lead to high rates of morbidity and mortality. Even with optimal treatment, median survival is 12–15 months for glioblastoma and is 2–5 years for anaplastic glioma [6].

Although previous studies have indicated improved clinical outcomes with a greater extent of resection in adults, the efficacy of the extent of surgical resection (EOR) in patients with high-or low-grade gliomas remains a topic of debate, particularly in elderly patients [7–9]. Geriatric patients are often considered poor surgical candidates and suffer from high rates of perioperative morbidity and mortality, because of their coexisting medical comorbidities, polypharmacy, and poor physiological reserves [10–12]. The risks of an extensive resection and only modest apparent survival benefit associated with tumor debulking

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have led some authors to favor biopsy over cytoreductive surgery in elderly patients [13]. Others have advocated for a maximally safe resection [14].

Several studies have focused on the efficacy of EOR in patients with gliomas. However, the results of some studies remain controversial [15–19]. Furthermore, their sample sizes were small [15,20–24]. Therefore, this meta-analysis analyzes and evaluates the efficacy of gross total resection (GTR) and subtotal resection (STR) in patients with glioma. The items evaluated included survival, seizure control, malignant transformation, mortality, and postoperative Karnofsky performance status (KPS), and the results yielded convincing conclusions based on a sufficiently large sample size. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines.

2. Methods and materials

2.1. Inclusion and exclusion criteria

The inclusion criteria for this meta-analysis were: (1) randomized controlled trials and observational studies (prospective and retrospective); (2) patients with a diagnosis of glioma; (3) studies that compared the outcomes of GTR and STR for glioma; (4) relevant outcomes, including survival, seizure control, malignant transformation, mortality, and postoperative KPS were reported or were obtainable.

Exclusion criteria were: (1) trials on animals; (2) abstracts, letters, editorials, expert opinions, reviews, case reports; (3) patients with other primary tumors; (4) studies without sufficient data; (5) duplicate articles; and (6) extent of tumor removal not specified.

2.2. Search strategy

The PubMed, Embase, Cochrane Library, and Web of Science databases were searched for the interval between March 1972 and November 2018. Our Medical Subject Heading (MeSH) search terms terms were: (a) glioma*, brain cancer*, *crania* carcinoma*, and glioblastoma; (b) resection, excision and surgery; (c) outcome, prognosis, survival, and efficacy. References of studies with potential relevance and review studies were screened manually to identify any eligible resources that were not previously identified. Two assessors independently screened the titles and abstracts of each study. After relevant studies were identified, the full texts were obtained for further evaluation.

2.3. Quality assessment

Two reviewers assessed the quality of all of the included studies independently using the 9-star Newcastle-Ottawa Scale (NOS), and the total scores of each study were recorded in a characteristics table. If reviewers held different opinions, they turned to the third reviewer for the final results of the NOS score. The scores were judged according to the three evaluation aspects of NOS: selection, comparability, and outcome between the case and control group. Studies with scores ≥ 6 were considered high-quality studies [25]. A proportion of high-quality studies $\geq 70\%$ were thought good oeverall quality of included studies.

2.4. Data extraction

Data for the analysis were extracted independently by two independent reviewers, and any disagreement was resolved by discussion. If the discussion failed to reach an agreement, they turned to the third reviewer. The extracted contents included study demographics, published year, country, trial design, and outcomes, using a standardized form. This study was performed with strict adherence to the PRISMA and AMSTAR guidelines [26].

Data were entered into RevMan 5.2 software for analysis [27].

2.5. Statistical analysis

Data of comparable outcomes between the GTR and STR groups were analyzed using the standard statistical procedures provided in RevMan 5.2 [27]. The mean difference (MD) of overall survival (OS) or progression free survival (PFS) time and its associated 95% confidence interval (CI) were measured. Heterogeneity between studies was evaluated using the chi-square-based Q statistical test [28], with a *P*-value and I^2 statistic ranging from 0% to 100% to quantify the effect of heterogeneity. $P_{heterogeneity}$ (P_h) ≤ 0.10 was deemed to represent significant heterogeneity [29]. The pooled MD was estimated using a random-effects model (the DerSimonian and Laird method [30]). If statistical heterogeneity was not observed ($P_h > 0.10$), a fixed-effects model (the Mantel–Haenszel method [31]) was used. The effects of outcome measures were considered significant if pooled MDs with 95% CI did not overlap with 0. A subgroup analysis was performed for the pooled results of the effect of OS in patients with glioma according to high-grade glioma and low-grade glioma.

3. Results

3.1. Included studies, study characteristics, and quality assessment

At the beginning of the search, 5876 citation records were obtained; 3755 records were obtained after duplicates were removed. After screening the titles and abstracts of the 3755 citations, 3204 studies were excluded preliminarily, and 551 studies were chosen to gather the full text for further evaluation. After reading the full texts of the 551 studies, 457 studies were excluded for several reasons and 94 full articles were obtained for further evaluation. In the 94 full articles, 52 of them were repeated with other studies and were excluded, then we reserved the ultramodern data or high-quality studies. Eventually, 42 studies [15–24,32–63] (N = 5920 participants) were included in this meta-analysis (Fig. 1). The sample sizes ranged from 11 to 508 patients (Table S1). Thirty-two studies were designed as retrospective studies, and 10 studies (23.8%) were designed as prospective studies. Four studies had a NOS score of 8, 15 studies had a NOS score of 7, 17 studies had a NOS score of 6, and 6 studies had a NOS score of 5. Approximately 85.7% of the studies were of good quality which achieved our requirement.

The detailed search process and summary of the studies are shown in the study flow diagram (Fig. 1). The other characteristics of each study are shown in Table S1.

3.2. Efficacy of GTR for improving OS of gliomas

As shown in Fig. 2, a significant result was obtained with a pooled MD of 4.01 (95% CI 2.52–5.51; $P < 0.00001$) on comparing the effects of GTR and STR for improving the OS of patients with gliomas. The pooled analysis was estimated using random-effects models because significant heterogeneity ($P_h < 0.00001$ and $I^2 = 84\%$) was found among studies. Additionally, we respectively pooled, compared, and analyzed the efficacy of GTR and STR in high- and low-grade glioma. Significant combined results were also observed in both high- and low-grade glioma, with pooled MDs of 3.26 (95% CI 2.10–4.42; $P < 0.00001$) and 3.87 (95% CI 1.76–5.98; $P = 0.0003$), respectively. These results indicate that patients who received GTR experienced longer OS time than those who received STR (Figs. 3 and 4). The analyses were estimated using random-effect models for significant heterogeneity ($P_h \leq 0.10$), except the analysis of the comparison between GTR and STR for high-grade glioma, which was estimated using a fixed-effect model, as no significant heterogeneity was found ($P_h = 0.26$, $I^2 = 19\%$).

As shown in Table 1, we also conducted a subgroup analysis

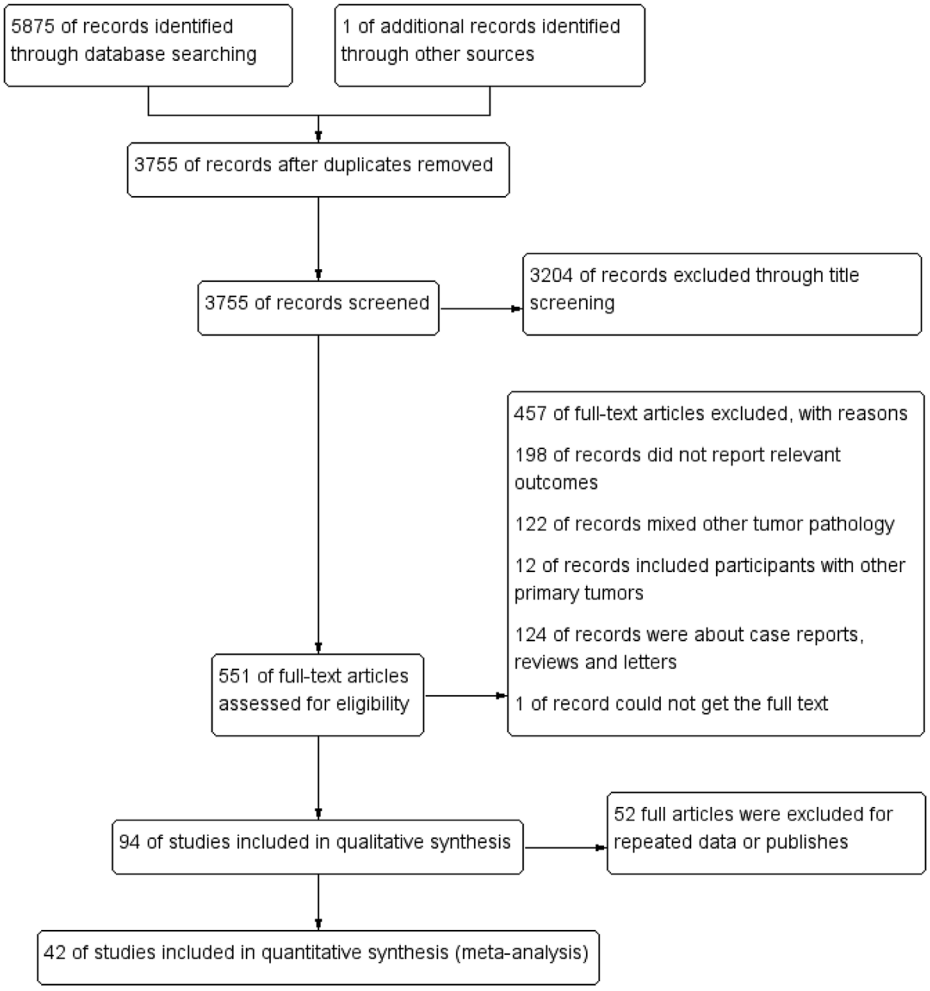

Fig. 1. Flow diagram showing the search strategy for studies included in this systematic review.

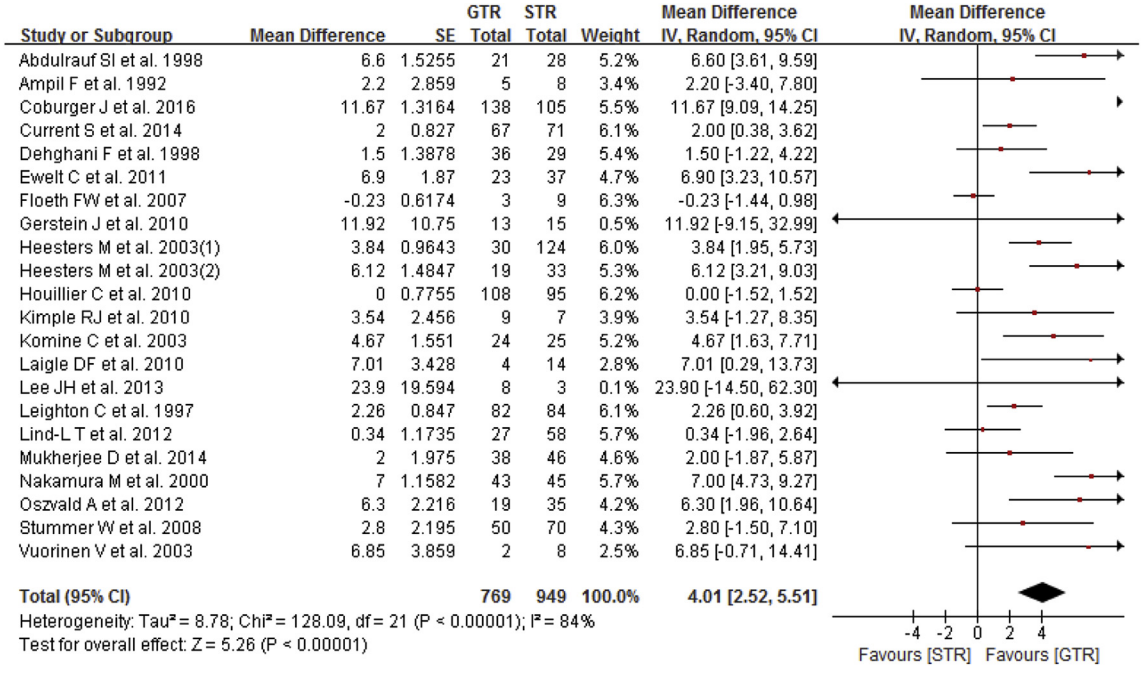

Fig. 2. The comparison between GTR and STR for overall gliomas regarding the overall survival time.

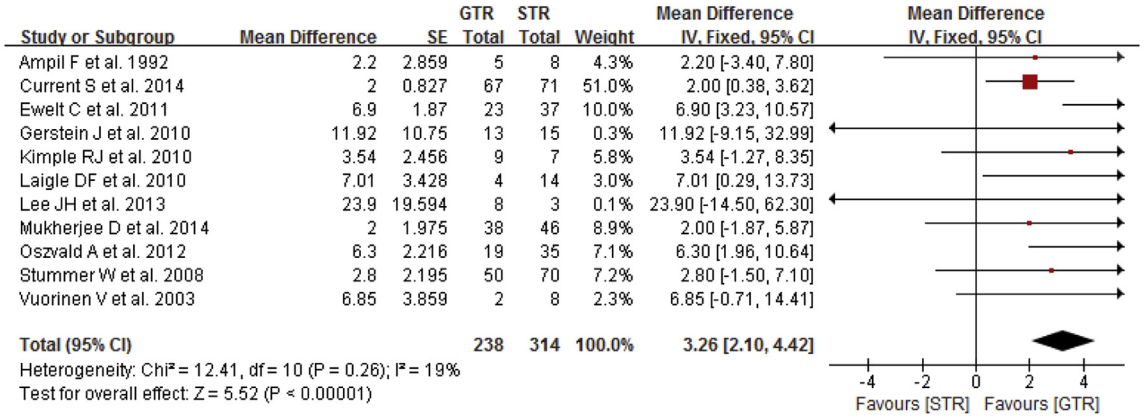

Fig. 3. The comparison between GTR and STR for high-grade glioma regarding the overall survival time.

according to the study design and sample size. Our subgroup analysis results showed that GTR resulted in a significant improvement in OS in all subgroups of patients with glioma when compared with STR. Additionally, we combined the results of our included studies, and the pooled results showed that mean OS increased from 9.34 months (7.84–10.8) in patients with high-grade glioma undergoing resection of any extent to 8.68 months (7.87–9.48) in STR to 14.04 months (95% CI: 12.8–15.2) in the GTR group. Similarly, mean OS in the low-grade glioma group increased from 4.78 years (3.04–6.53) in patients undergoing resection of any extent to 6.68 years (4.19–9.16) in STR to 10.65 years (6.78–14.52) in the GTR group (Table 2).

3.3. Efficacy of GTR for improving 5-year survival rate of glioma

This study also compared and analyzed the efficacy of GTR and STR for improving the 5-year survival rate of low-grade glioma. A combined analysis result of 14 studies showed that GTR was superior for improving the 5-year survival rate of low-grade glioma compared to STR, with a pooled OR of 4.08 (95% CI 3.02–5.52; $P < 0.00001$) (Fig. 5). The analysis was estimated using a fixed-effect model, as no significant heterogeneity was found ($P_h = 0.21$, $I^2 = 23\%$). These results indicate that patients who received GTR experienced a higher 5-year survival rate comparing with those who received STR.

3.4. Efficacy of GTR for improving PFS of glioma

We compared the PFS of patients with glioma who received GTR and STR. The combined results indicated that GTR improved PFS of low-grade gliomas better than that of STR, with a pooled MD of 2.08 (95% CI 0.26–3.89; $P = 0.02$) (Fig. 6). The analysis was estimated using a random-effect model, as significant heterogeneity was found ($P_h < 0.00001$, $I^2 = 90\%$). This result indicates that patients who received GTR experienced longer PFS than those who received STR. The pooled results from all included studies showed that mean PFS increased from 5.47 months (3.54–7.39) in patients with high-grade glioma undergoing resection of any extent to 4.31 months (3.48–5.14) in STR to 7.03 months (5.85–8.23) in the GTR group. Similarly, the mean PFS of patients with low-grade glioma increased from 3.09 years (2.20–3.97) in patients undergoing resection of any extent and 3.41 years (2.09–4.73) in STR to 5.11 years (3.04–7.18) in the GTR group (Table 2).

3.5. Efficacy of GTR for improving seizure control in patients with glioma

We also compared the effects of GTR and STR in seizure control rate of patients with low-grade gliomas. The pooled results showed that seizure control of low-grade gliomas was improved by GTR more than that by STR, with a pooled OR of 4.25 (95% CI 2.99–6.05; $P < 0.00001$) (Fig. 7). The analysis was estimated using a fixed-effect model because no significant heterogeneity was found ($P_h = 0.84$, $I^2 = 0\%$). The result indicates that GTR increased the seizure control rate compared with STR. Similarly, the mean seizure-free rate increased from 68.7% (62.6–74.2) in patients with low-grade glioma undergoing resection of any extent and 54.2% (48.7–59.6) in STR to 81.0% (74.6–86.2) in the GTR group (Table 2).

3.6. Efficacy of GTR for reducing the incidence of malignant transformation and mortality

Our pooled results indicate that GTR was more effective in reducing malignant transformation of low-grade gliomas than STR, with a pooled OR of 0.28 (95% CI 0.13–0.60; $P = 0.001$) (Fig. 8). The analysis was

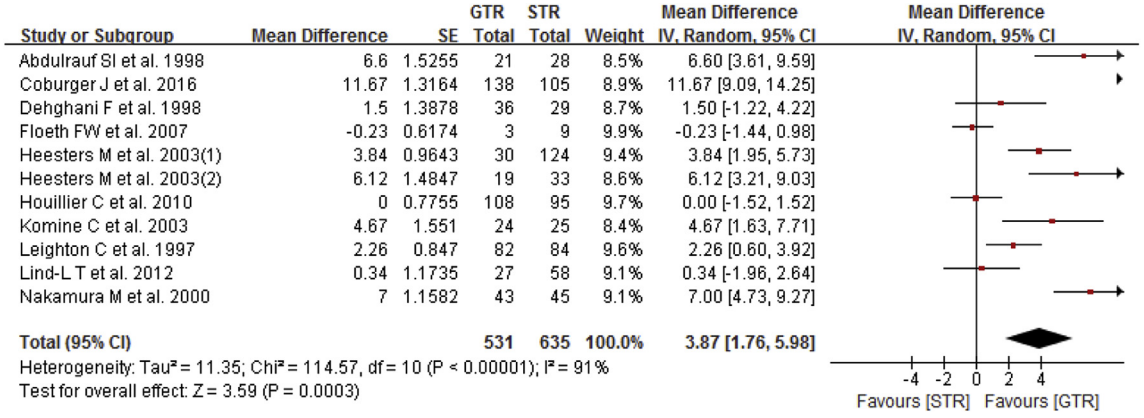

Fig. 4. The comparison between GTR and STR for low-grade glioma regarding the overall survival time.

Table 1
The pooled results of subgroup analysis for the OS of overall gliomas.

Groups/Subgroups	Pooled results			Heterogeneity		
	MD	95% CI	*P* value	I^2	P_h value	Analytical effect model
Grade						
High-grade glioma	3.26	2.10, 4.42	< 0.00001	19%	0.26	Fixed-effect model
Low-grade glioma	3.87	1.76, 5.98	0.0003	91%	< 0.00001	Random-effect model
Study design						
Prospective	3.42	0.50, 6.35	0.02	73%	0.002	Random-effect model
Retrospective	4.22	2.46, 5.99	< 0.00001	84%	< 0.00001	Random-effect model
Sample size						
≤100	4.26	1.74, 6.78	0.0009	80%	< 0.00001	Random-effect model
100–300	3.87	1.26, 6.48	0.004	90%	< 0.00001	Random-effect model

MD, mean difference; CI, confidence intervals.

Table 2
The pooled results of included studies.

Incidence	Resection of any extent	Subtotal resection	Gross-total resection
Low-grade glioma			
Mean overall survival (years)	4.78 (3.04–6.53)	6.68 (4.19–9.16)	10.65 (6.78–14.52)
Mean progression-free survival (years)	3.09 (2.20–3.97)	3.41 (2.09–4.73)	5.11 (3.04–7.18)
Seizure free (%)	68.7 (62.6–74.2)	54.2 (48.7–59.6)	81.0 (74.6–86.2)
Mortality (%)	1.0 (0.5–2.0)	2.3 (1.2–4.4)	3.1 (1.5–6.5)
Malignant transformation (%)	46.5 (28.1–66.0)	47.5 (30.3–65.4)	15.9 (4.2–44.7)
High-grade glioma			
Mean overall survival (months)	9.34 (7.84–10.8)	8.68 (7.87–9.48)	14.04 (12.8–15.2)
Mean postoperative KPS	71.16 (63.29–79.03)	65.16 (47.12–83.2)	75.87 (61.18–89.55)
Mean progression-free survival (months)	5.47 (3.54–7.39)	4.31 (3.48–5.14)	7.03 (5.85–8.23)
Mortality (%)	2.1 (0.01–0.04)	2.8 (0.01–0.11)	1.5 (0.01–0.09)
Morbidity (%)	12.3 (0.09–0.17)	12.7 (0.07–0.22)	6.6 (0.03–0.16)

estimated using a fixed-effect model because no significant heterogeneity was found (P_h = 0.42, I^2 = 0%). Similarly, the mean malignant transformation rate of low-grade glioma decreased from 46.5% (28.1–66.0) in patients undergoing resection of any extent and 47.5% (30.3–65.4) in STR to 15.9% (4.2–44.7) in the GTR group (Table 2).

However, our results showed a difference in mortality between patients with low- and high-grade glioma. The mean mortality rate of patients with low-grade glioma increased from 1.0% (0.5–2.0) in patients undergoing resection of any extent and 2.3% (1.2–4.4) in STR to 3.1% (1.5–6.5) in the GTR group, but the mean mortality rate in patients with high-grade glioma decreased from 2.1% (0.01–0.04) undergoing resection of any extent and 2.8% (0.01–0.11) in STR to 1.5% (0.01–0.09) in the GTR group; the mean morbidity rate decreased from 12.3% (0.09–0.17) in patients undergoing any extent of resection and 12.7% (0.07–0.22) in STR to 6.6% (0.03–0.16) in the GTR group (Table 2).

4. Discussion

The role of increasing EORs in the surgical management of glioma remains controversial. When multiple degrees of resection can be achieved safely, it is controversial whether to plan for an operative strategy involving STR or GTR of the lesion. This controversy is based in the unclear benefits and concerns about higher rates of mortality and

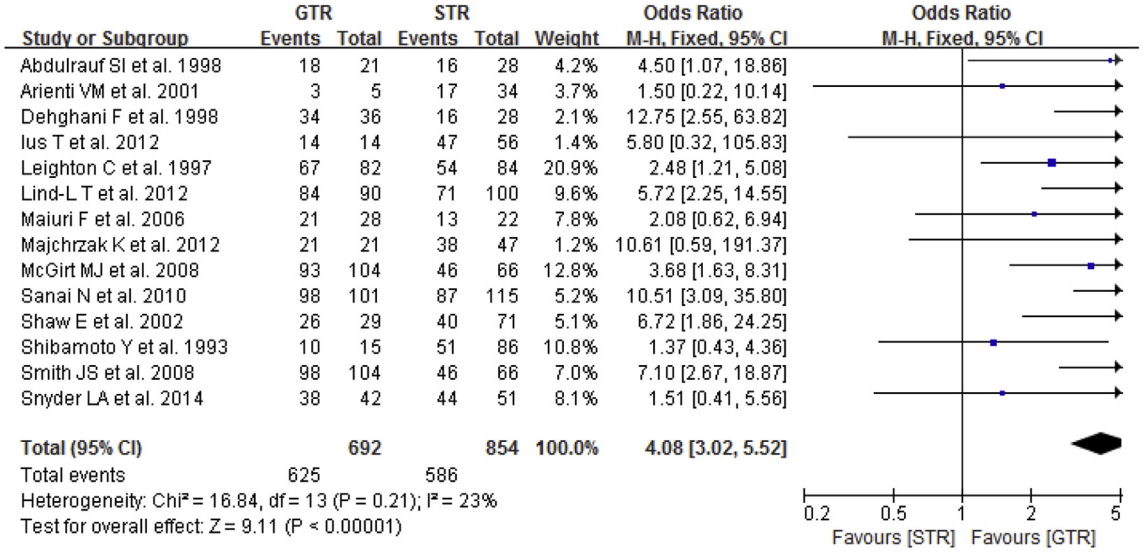

Fig. 5. The comparison between GTR and STR for low-grade glioma regarding the 5-year survival rate.

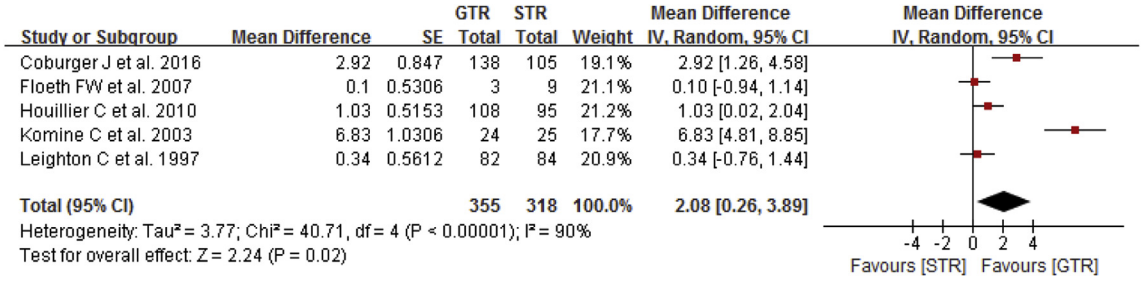

Fig. 6. The comparison between GTR and STR for low-grade glioma regarding the progression-free survival.

morbidity associated with more extensive grades of resection. Hence, these patients occasionally undergo biopsy or partial resection followed by adjuvant therapy. We performed a comprehensive review and critical appraisal of the current published data to compare and evaluate the efficacy of GTR for improving clinical outcomes in patients with glioma.

Our systematic review and meta-analysis demonstrated significant benefits associated with increasing safe EORs in the management of gliomas, in terms of OS, PFS, seizure control, and delaying malignant transformation of low-grade glioma, without increasing postoperative mortality or morbidity. Some early studies suggested that GTR does not significantly improve survival [64]. No survival benefit was observed in patients with low-grade glioma presenting with epilepsy who underwent upfront surgery compared to a watch-and-wait approach [65]. In contrast, other researchers have argued for a survival benefit associated with GTR for low-grade gliomas. McGirt et al. reported a 95% 5-year survival in the GTR group, compared to 70% 5-year survival in the STR group [51]. Jakola et al. compared the outcomes of upfront resection to a watch-and-wait strategy by studying two population-based parallel cohorts [66]. Median survival was significantly longer in patients treated with upfront surgery, and the 5-year survival rate was 74% in the surgical group. However, that study had a relatively smaller sample size. Our pooled estimates showed that mean OS was 6.68 years in the STR group and 10.65 years in the GTR group. These findings suggest that maximum safe resection prolongs survival in patients harboring low-grade gliomas.

Many studies have demonstrated the benefits of GTR to prolong PFS [17,57,60]. This is intuitive because of the reduced tumor burden associated with greater EOR. Our meta-analysis supports this point. Patients who underwent GTR had 2.08 years of PFS over those who underwent STR, with a RR of 1.78 for PFS at 5 years. These results suggest that maximum safe resection not only prolongs OS but delays the time to recurrence. Approximately 80% of patients with low-grade glioma present with seizures. Chang et al. reported 49% pharmacoresistance in patients with low-grade gliomas [34]. Intractable seizures and antiepileptic drug therapy negatively affect cognitive status and quality of life. Seizures also tend to occur in patients with low-grade glioma seated in a cortex or the insula, making GTR challenging [67]. Our results indicate that GTR was superior for improving seizure control in patients with low-grade gliomas compared to STR, with a pooled OR of 4.25 (95% CI 2.99–6.05; $P < 0.00001$). The mean seizure-free rate of patients with low-grade glioma was 68.7% (62.6–74.2) in patients undergoing resection of any extent, and was 54.2% (48.7–59.6) in the STR group and 81.0% (74.6–86.2) in the GTR group. Additionally, GTR was superior for reducing malignant transformation of low-grade gliomas compared to STR, with a pooled OR of 0.28 (95% CI 0.13–0.60; $P = 0.001$). The mean malignant transformation rate decreased from 46.5% (28.1–66.0) in patients undergoing resection of any extent and was 47.5% (30.3–65.4) in the STR group and 15.9% (4.2–44.7) in the GTR group. However, the mean mortality rate of patients with low-grade glioma was 1.0% (0.5–2.0) in patients undergoing resection of any extent, and was 2.3% (1.2–4.4) in the STR group and 3.1% (1.5–6.5) in the GTR group, whereas the mean mortality rate in patients with high-grade glioma was 2.1% (0.01–0.04) in those undergoing resection of any extent and was 2.8% (0.01–0.11) in the STR group and 1.5% (0.01–0.09) in the GTR group; the mean morbidity rate was 12.3% (0.09–0.17) in patients undergoing resection of any extent, and was 12.7% (0.07–0.22) in the STR group and 6.6% (0.03–0.16) in the GTR group.

5. Limitations and recommendations

Several limitations of the present analysis should be discussed. First, the retrospective nature of the studies included and lack of control over data collection may be a source of bias. Thirty-two studies were designed as retrospective studies, and 10 studies (23.8%) were designed as prospective studies. Certain variables, such as tumor residual volume, were not included in the prognostic analysis, as the data were not available for all patients. These factors appear to contribute to estimating prognosis. Another possible confounding factor was the heterogeneity in the patient population and the treatments. Sample sizes ranged from 11 to 508 patients. This large span may have led to some bias. However, to reach a sufficient sample size for our comprehensive analysis, we did not exclude small sample size studies. Finally, the prognosis of patients with tumors was influenced by multiple factors, such as age, adjuvant therapy, tumor size, and histological type, which

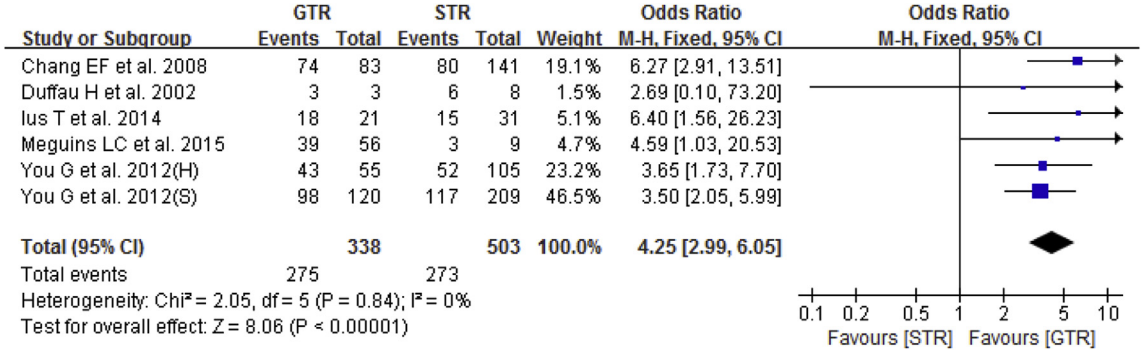

Fig. 7. The comparison between GTR and STR for low-grade glioma regarding seizure control rate.

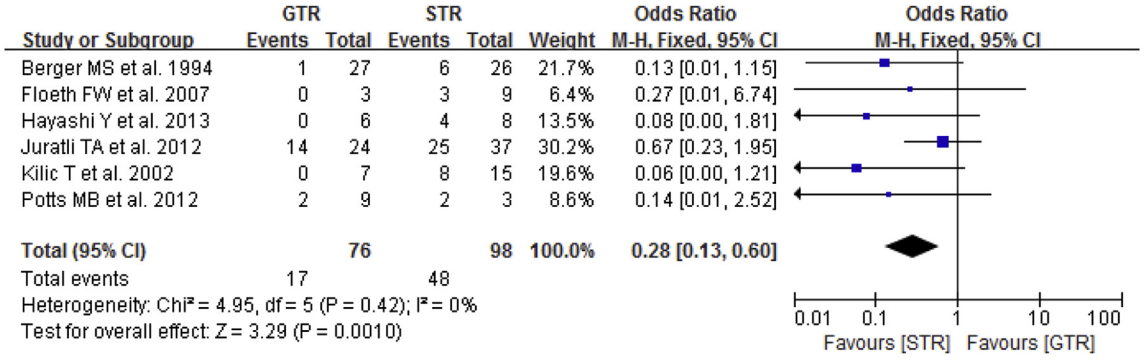

Fig. 8. The comparison between GTR and STR for low-grade glioma regarding malignant transformation.

should also be considered. Considering these limitations, more well-designed and bias-controlled prospective studies are needed.

The efficacy of GTR on survival is remarkable because it significantly improved OS, 5-year survival rate, and PFS of patients with gliomas. Functional outcomes were better in patients who received GTR than in those who received STR, given that GTR significantly improved seizure control of patients with gliomas. GTR also led to decreased tumor progression and malignant transformation. In conclusion, our meta-analysis supports the superior efficacy of GTR on survival, functional outcome, tumor progression, seizure control, malignant transformation, morbidity, and mortality for patients with gliomas.

Ethical approval

Ethical Approval is not applicable.

Author contribution

The authors on this paper all participated in study design. All authors have read and approved this version of the article, and due care has been taken to ensure the integrity of the work. The material of this article is original research and no part of this paper has been previously published. The material has also not been submitted for publication elsewhere while under consideration. No conflict of interest exits in the submission of this manuscript. All authors have the appropriate permissions and rights to the reported data.

Conflicts of interest

The authors declare no relevant conflict of interest.

Research registry number

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The material of this article is original research. All data in this manuscript is available and transparent for readers.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.02.004.

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