Association Between Supratotal Glioblastoma Resection and Patient Survival: A Systematic Review and Meta-Analysis

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INTRODUCTION

Patients with glioblastoma (GBM) have a poor prognosis with a median overall survival of 15 months, despite safe and maximal surgical resection, followed by chemotherapy and/or radiotherapy.[1] GBM will typically appear on contrast-enhanced magnetic resonance imaging (MRI) studies as a contrast enhancing (CE) tumor with central necrosis. Maximal and safe surgical resection or gross total resection (GTR) of the CE area is currently the main goal of GBM surgery. Both the

■ BACKGROUND: Gross total resection (GTR) of the contrast enhancing (CE) area will improve the survival of patients with glioblastoma (GBM). However, GBM can infiltrate into the brain parenchyma, beyond the CE margins. It remains unclear whether resection beyond the CE area (supratotal resection [SPTR]) can improve survival without causing additional neurological deficits. The aim of the present meta-analysis was to study the association between SPTR and overall survival of patients of GBM.

■ METHODS: Embase, PubMed, and other literature databases were searched for eligible studies until August 2018. Studies involving patients with GBM that had compared SPTR with GTR were included in the present study. The main outcome was overall survival, presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and median overall survival differences with the 95% CIs.

■ RESULTS: The meta-analysis, which included 6 studies and 1168 unique patients with GBM, showed that compared with GTR, SPTR of GBM resulted in a 53% lower risk of mortality at any time during follow-up (HR, 0.47; 95% CI, 0.31—0.72; *P* = 0.0005). The median overall survival of the SPTR group was 6.4 months (95% CI, 3.2—9.7) longer than the GTR group (*P* = 0.0001). Reports on postoperative deficits were limited, and the quality of evidence was moderate to very low.

■ CONCLUSIONS: Compared with GTR, SPTR of GBM resulted in a lower risk of mortality and longer median overall survival. However, the quality of evidence of the available studies was poor. Therefore, it remains unclear whether SPTR is safe and actually improves the survival of patients with GBM. Future prospective trials and a standardized definition of SPTR are needed.

survival benefits of GTR and the optimal method to achieve this have been extensively debated in neurosurgical studies.

Brown et al.[1] showed, in a systematic review and meta-analysis of 37 studies and 41,117 unique patients, that compared with subtotal resection, GTR of the CE area will decrease the risk of mortality, with 28% at 1 year and 16% at 2 years (P < 0.001). Jenkinson et al.[2] recently showed in a Cochrane review that resection with 5-aminolevulinic acid (5-ALA) fluorescence guidance or intraoperative MRI guidance can increase the extent of GBM resection.

However, GBM is known to infiltrate far beyond the CE margins as seen on MRI into the surrounding edematous T2-weighted

fluid-attenuated inversion recovery (FLAIR) hyperintense region.[3] This raises the question of whether GTR of the CE portion will constitute "total" resection or whether surgical resection should also include a part of the hyperintense T2-weighted FLAIR region to improve survival. It has been suggested that 5-ALA fluorescence accumulates in cancer cells and not only corresponds to the CE portion on MRI but also exceeds this area as vague fluorescence, which corresponds with the portions of GBM often infiltrating into an eloquent brain area.[4]

This concept of so-called supramarginal or supratotal resection (SPTR), is already known in the field of low-grade glioma surgery,[5,6] because low-grade gliomas

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.
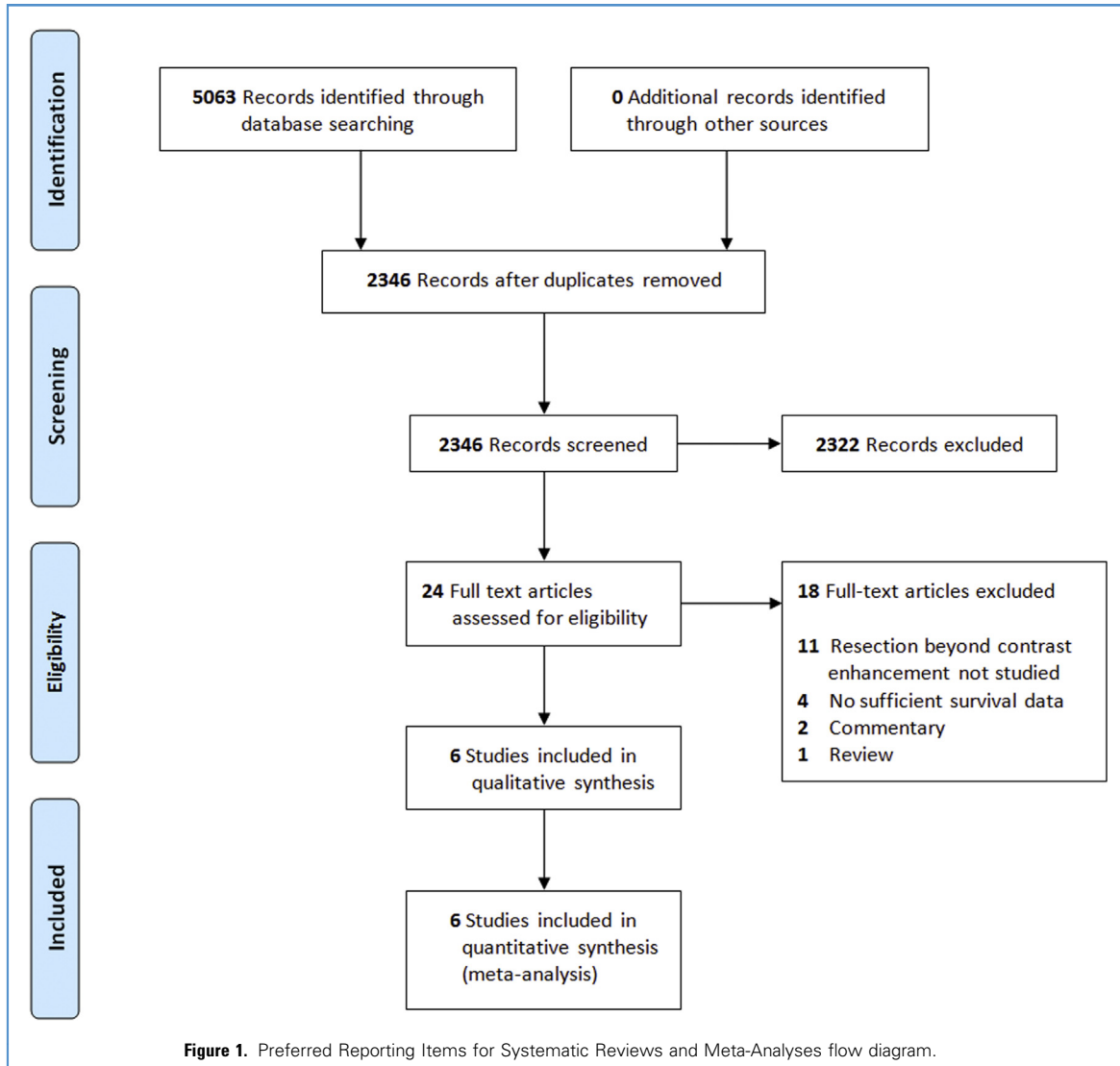
commonly do not enhance and, therefore, lack the CE target for surgical resection. However, SPTR of GBM has been less extensively investigated, and, to the best of our knowledge, no quantitative data analysis has been performed to clarify the association of survival with SPTR versus GTR for patients with GBM and the postoperative neurological complications.

The aim of the present study was to investigate the association between SPTR and survival in patients with GBM using a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7]

METHODS

Systematic Review

We searched for studies that had included patients with GBM who had undergone surgical resection and had pre- and postoperative MRI studies available. Letters, editorials, abstracts, and non-English citations were excluded. The search query was designed with an expert librarian at the Erasmus University Medical Center, Medical Library, to capture all citations reported until August 2018 within PubMed [[(Glioblastoma/ OR (glioblastom* OR (maligna* ADJ3 glioma*) OR (high* ADJ3 grade* ADJ3 glioma*) OR ((grade-iv OR

grade-4) ADJ3 glioma*) OR gbm).ab,-ti,kw.) AND (Surgical Procedures, Operative/ OR exp Neurosurgery/ OR Neurosurgical Procedures/ OR exp Brain Neoplasms/su OR (surg* OR neurosurg* OR resect*).ab,ti,kw.) AND (Margins of Excision/ OR (flair OR (Fluid ADJ3 attenuat* ADJ3 invers* ADJ3 recover*) OR t2 OR t-2 OR gross-total OR ((exten* OR Supratotal* OR Supramaxim*) ADJ3 (resect* OR remov*)) OR ((surg* OR excis* OR resect*) ADJ3 margin*) OR ((beyond OR additional*) ADJ6 (contrast OR boundar*))).ab,ti,kw.) NOT (letter* OR news OR comment* OR editorial* OR congres* OR abstract* OR book* OR

Table 1. Study Demographics

Investigator	Country	Definition of GTR	Definition of SPTR	HR Group Comparison*	HR Multivariate Analysis†	Quality of Evidence (GRADE)‡
Aldave et al.,[12] 2013	Spain	100% of CE area	100% of CE + total resection of fluorescing tumor	Yes	Yes	3
Li et al.,[8] 2016	USA	100% of CE area	100% of CE + >0%—100% FLAIR	Yes	Yes	2
Eyüpoglu et al.,[19] 2016	Germany	100% of CE area	100% of CE + total resection of fluorescing tumor	Yes	No	3
Pessina et al.,[28] 2017	Italy	100% of CE area	100% of CE + 100% of FLAIR	Yes	Yes	3
Esquenazi et al.,[18] 2017	USA	95%—100% of CE area	>100% of CE	Yes	Yes	3
Glenn et al.,[21] 2018	USA	100% of CE area	100% of CE + >1 cm of surrounding brain tissue	Yes	Yes	4

GTR, gross total resection; SPTR, supratotal resection; HR, hazard ratio; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; CE, contrast enhancing; FLAIR, fluid-attenuated inversion recovery.

*"Yes" indicates the HR should be interpreted as a between group comparison; "no" indicates the HR should be interpreted as per unit of residual T2-weighted FLAIR volume.

†Included prognostic factors in the model such as age, tumor volume, tumor location, Karnofsky performance scale, methylguanine-DNA methyltransferase methylation status, and adjuvant therapy (Supplemental Table 2).

‡Quality of evidence levels: 1, high; 2, moderate; 3, low; 4, very low (Supplemental Table 1).

chapter* OR dissertation abstract*).pt.] Embase, Web of Science, Cochrane Central, and Google Scholar (search queries for these sources are listed in the Supplemental Materials).

After removing duplicate reports, 2 independent reviewers (F.I. and S.K.) screened the studies by title and abstract and removed off-topic citations. The full text of the remaining reports were independently read by the reviewers (F.I., S.K.) to determine whether they were eligible for final inclusion. Studies of solely pediatric or non-GBM cases, recurrent GBM, nonoperative or surgery of the enhancing tumor portion alone, or biopsy only and studies without survival data were excluded. The present study was performed and presented in accordance with the PRISMA guidelines.[7]

Data Collection

The main outcome of interest was overall survival, presented as hazard ratios (HRs) with 95% confidence intervals (CIs), and median overall survival with 95% CIs of the GTR and SPTR groups. These data were collected from the included studies, calculated from other available data, or extracted based on data points created using a pixel-by-pixel method from the survival curves. GTR and SPTR were defined by the authors

of the studies included in our meta-analysis. We categorized GTR as 100% resection of the CE area, and SPTR as every effort to resect beyond GTR of the CE portion, which had been qualitatively or quantitatively defined by the authors of the included studies. Li et al.[8] presented their data on survival and neurological outcomes mainly by categorizing the resection as <53% FLAIR and ≥53% FLAIR. However, after e-mail correspondence with the senior author, we received additional survival data on the GTR and SPTR groups to perform our meta-analysis.[8] When available, data on postoperative new neurological deficits, surgical complications, and/or quality of life after surgery were collected to assess the safety of both SPTR and GTR.

Meta-Analysis

The HRs with 95% CIs and median overall survival with 95% CIs for the SPTR and GTR groups were collected or calculated for each study using the available data and the random effects model and presented in forest plots using Review Manager (RevMan, version 5.3 [Cochrane Collaboration, London, United Kingdom]). The random effects model was used instead of the fixed effects model because of the heterogeneity among the studies to provide a more conservative and clinically

reliable interpretation of the summarized statistics and 95% CIs. The HRs had been corrected by the authors of the individual studies for several prognostic factors across the studies such as age, Karnofsky performance scale (KPS), adjuvant therapy, tumor volume and location, and methylguanine-DNA methyltransferase (MGMT) methylation and isocitrate dehydrogenase (IDH) mutation status. A P value of < 0.05 was considered to indicate statistical significance. Heterogeneity was calculated and interpreted using the χ^2 test and I^2 values with Review Manager (Cochrane Collaboration).

Quality of Evidence

The quality of evidence obtained from the reports included in the present study was graded using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system[9] (Supplemental Table 1). Within the GRADE system, 4 levels of quality rating can be assigned to studies: high, often given to randomized controlled trials; moderate or low, often given to observational studies; and very low. The quality of evidence was rated by 1 of us (F.I.) and was determined from the methodological quality, risk of biases (using the ROBINS-I [risk of bias in non-randomized studies—of interventions]

tool),[10] heterogeneity, and precision of effect estimates.

RESULTS

We identified 1796 citations from Embase, 1503 from PubMed, 1424 from Web of Science, 140 from Cochrane Central, and 200 from Google Scholar. Removal of the duplicate reports resulted in 2346 unique citations that were screened by title and abstract. A total of 2322 off-topic studies were excluded, leaving 24 that were read in full.[6,8,11-32] After reading, 18 reports were excluded owing to the absence of SPTR (n = 11), absence of sufficient survival data (n = 4), and article type (n = 3; 2 commentaries and 1 review). This resulted in a final total of 6 studies[8,12,18,19,21,28] that were included in our systematic review and meta-analysis. The process of study inclusion is presented in the PRISMA flow diagram in Figure 1, and demographics of the included studies are presented in Table 1.

Meta-Analysis

Our meta-analysis included 6 studies comparing SPTR and GTR,[8,12,18,19,21,28] with 1168 unique patients with GBM. Our meta-analysis resulted showed that compared with GTR, SPTR of GBM resulted in a 53% lower risk of mortality at any time during the follow-up period (HR, 0.47; 95% CI, 0.31–0.72; P = 0.0005; I², 68%; Figure 2).

The median overall survival for the GTR and SPTR groups was 15.0 months (95% CI, 2.9–26.1) and 28.3 months (95% CI, 12.5–

44.1), respectively (P < 0.0001). The survival benefit with SPTR was 13.3 months (95% CI, 3.6–23.1) compared with GTR (P = 0.007). However, the findings from Esquenazi et al.,[18] in particular, influenced the heterogeneity (I²) of the median overall survival analysis, possibly owing to the much greater median overall survival for the SPTR group of 54 months within their study. The exclusion of their study in an additional median overall survival analysis showed a decrease of I² from 96% to 50%. Compared with GTR, SPTR of GBM resulted in a longer median overall survival of 6.4 months (95% CI, 3.2–9.7; P = 0.0001; Figure 3).

Quality of Evidence

No randomized controlled trials were available for inclusion in the present meta-analysis. All the studies were retrospective with a nonrandomized treatment assignment. Using the GRADE guidelines, the studies were assigned to the low-level[12,18,19,28] quality evidence and then possibly upgraded to a moderate level[8] or downgraded to a very low level[21] (Table 1) using previously stated mainly methodological factors such as study design, internal validity, risk of biases, and precision (Supplemental Table 1).

Postoperative New Neurological Deficits

In 3 studies, the incidence rates of postoperative new neurological deficits for both SPTR (range, 0%–19%) and GTR (range, 0%–8%) groups were reported. However, in the other 3 studies, these data either were not clearly presented or were absent (Table 2).
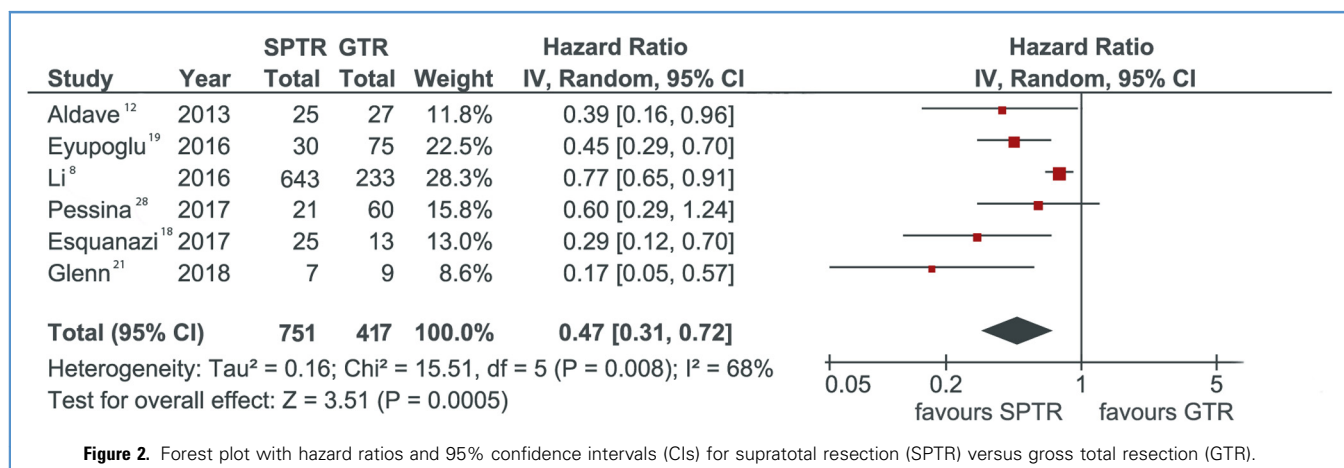
Overall, the reports were limited; thus, the difference in postoperative neurological outcomes between SPTR versus GTR could not clearly be analyzed.

DISCUSSION

The present PRISMA guided systematic review and meta-analysis studied the association between SPTR and survival in patients with GBM. Our analysis included 6 studies and 1168 unique patients and showed that compared with GTR, SPTR of GBM resulted in a 53% lower risk of mortality at any time during the follow-up period and a 6.4-month longer median overall survival duration. The quality of evidence for the available studies, however, was moderate to very low. Furthermore, the incidence rates of postoperative new neurological deficits was minimally and only qualitatively reported. Finally, data on the patients' quality of life were not reported in any of the included studies. It, therefore, remains unclear whether SPTR can be achieved as safely as GTR.
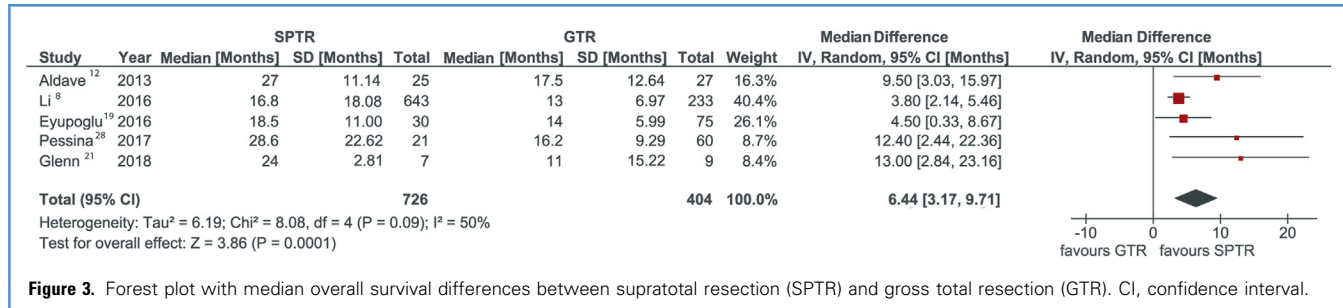
Defining SPTR

A multitude of definitions have been used for SPTR. The term was first used by Yordanova and Duffau[33] in 2011 to explain the procedure of low-grade glioma resection guided by functional boundaries, defined by the area of T2-weighted FLAIR hyperintensity during awake surgery, instead of the classic neuronavigation using preoperative MRI contrast-enhanced scans. Yordanova and Duffau[33] showed

Study	Year	SPTR Total	GTR Total	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Aldave[12]	2013	25	27	11.8%	0.39 [0.16, 0.96]	
Eyupoglu[19]	2016	30	75	22.5%	0.45 [0.29, 0.70]	
Li[8]	2016	643	233	28.3%	0.77 [0.65, 0.91]	
Pessina[28]	2017	21	60	15.8%	0.60 [0.29, 1.24]	
Esquanazi[18]	2017	25	13	13.0%	0.29 [0.12, 0.70]	
Glenn[21]	2018	7	9	8.6%	0.17 [0.05, 0.57]	
Total (95% CI)		**751**	**417**	**100.0%**	**0.47 [0.31, 0.72]**	

Heterogeneity: Tau² = 0.16; Chi² = 15.51, df = 5 (P = 0.008); I² = 68%
Test for overall effect: Z = 3.51 (P = 0.0005)

0.05   0.2   1   5
favours SPTR   favours GTR

Figure 2. Forest plot with hazard ratios and 95% confidence intervals (CIs) for supratotal resection (SPTR) versus gross total resection (GTR).

Study	Year	SPTR Median [Months]	SPTR SD [Months]	SPTR Total	GTR Median [Months]	GTR SD [Months]	GTR Total	Weight	Median Difference IV, Random, 95% CI [Months]	Median Difference IV, Random, 95% CI [Months]
Aldave [12]	2013	27	11.14	25	17.5	12.64	27	16.3%	9.50 [3.03, 15.97]	
Li [8]	2016	16.8	18.08	643	13	6.97	233	40.4%	3.80 [2.14, 5.46]	
Eyupoglu [19]	2016	18.5	11.00	30	14	5.99	75	26.1%	4.50 [0.33, 8.67]	
Pessina [28]	2017	28.6	22.62	21	16.2	9.29	60	8.7%	12.40 [2.44, 22.36]	
Glenn [21]	2018	24	2.81	7	11	15.22	9	8.4%	13.00 [2.84, 23.16]	
Total (95% CI)				**726**			**404**	**100.0%**	**6.44 [3.17, 9.71]**	

Heterogeneity: Tau² = 6.19; Chi² = 8.08, df = 4 (P = 0.09); I² = 50%
Test for overall effect: Z = 3.86 (P = 0.0001)

favours GTR   favours SPTR
-10   0   10   20

Figure 3. Forest plot with median overall survival differences between supratotal resection (SPTR) and gross total resection (GTR). CI, confidence interval.

that SPTR of low-grade glioma resulted in a significant delay of anaplastic degeneration (P = 0.037) without causing permanent neurological deficits.

With SPTR of GBM, the classically used CE boundaries of the tumor will be exceeded to include the nonenhancing hyperintense T2-weighted FLAIR region during resection, presumed to represent edematous, tumor-infiltrated tissue. This region can infiltrate deep into eloquent brain areas.[3] For our analysis, we considered any effort of resection beyond GTR of the CE areas as SPTR, irrespective of the procedure used to achieve the resection. Some studies used a relatively conservative SPTR procedure such as resection of additional residual 5-ALA—fluorescent tissue[12,19] or resection of an additional rim (>1 cm) after GTR of the CE area.[21] However, Li et al.[8] and Pessina et al.[28] defined SPTR as additional

resection of FLAIR abnormalities (range, >0%—100%) and 100% resection of T2-weighted FLAIR hyperintense volumes in addition to GTR of the CE areas, respectively. Additionally, a very recent study defined SPTR as GTR plus frontal or temporal lobectomy, without any volumetric analysis on the T2-weighted FLAIR volumes or functionally defined borders during awake surgery.[34] Therefore, based on the reported data, SPTR can only broadly be defined as every effort of resection after GTR of the CE portion of GBM. No standardized definition of SPTR exists; thus, SPTR needs to be defined in a prospective setting.

Li et al.[8] highlighted that compared with GTR the relatively low rates of postoperative new neurological deficits in the SPTR group could probably be explained by the increased use of awake surgery with

neurophysiological monitoring, cortical and/or subcortical mapping, and imaging guidance such as intraoperative MRI, functional MRI, and diffusion tensor imaging navigation.[2,8] Although Jenkinson et al.[2] showed in a recent Cochrane review that intraoperative MRI or 5-ALA fluorescent-guided surgery can help to increase the extent of GBM resection, the reports on adverse events were incomplete and the studies had very low quality evidence. Because portions of the hyperintense T2-weighted FLAIR area could represent both tumor-infiltrated edematous and solely edematous portions, additional methods to delineate non-CE tumor infiltration are important to obtain a target for SPTR. Resection of the former might contribute to better patient survival, although the impact of the latter on survival will be limited, but could also pose an unnecessary risk of

Table 2. Reported Incidence Rates of Postoperative Neurological Deficits

Investigator	GTR	SPTR	P Value	Comment
Aldave et al.,[12] 2013	2 (8)	4 (18.5)	0.27	No details on deficits reported
Li et al.,[8] 2016	NA	120 (19)	NA	Motor deficits and speech and visual impairments were the most commonly reported 30-day postoperative neurological complications
Glenn et al.,[21] 2018	0 (0)	1 (11.1)	0.66	One patient with dysphasia
Pessina et al.,[28] 2017	0 (0)	0 (0)	NA	No patient developed postoperative new neurological deficits in either group
Eyüpoglu et al.,[19] 2016	NA	NA	0.47—1.0	Rates on postoperative new neurological deficits between groups not clearly collectable; overall, no significant worsening of motor, visual, speech, or cognitive deficits or seizures reported in either group
Esquenazi et al.,[18] 2017	NA	NA	NA	Of 38 patients, 3 (7.9%) had transient and 2 (5.3%) had permanent neurological deficits; group-specific data not reported
GTR, gross total resection; SPTR, supratotal resection; NA, not applicable.				

complications. In addition to 5-ALA, physiological preoperative MRI such as positron emission tomography MRI might help to identify tumor-infiltrated, highly metabolic portions outside the CE areas of GBM as a specific target during surgery.[35]

Study Limitations

Overall, the results of our analysis should be interpreted with caution because of several limitations. First, the between-study heterogeneity ($I^2 = 68\%$) across the analyzed studies, which possibly arose from several factors, included the differences in defining SPTR, the heterogeneous or limited sizes of the small study populations across the studies, and their retrospective design and nonrandomized treatment assignment. As stated previously, the different definitions of SPTR across the studies, which were often retrospectively defined and varied between additional resection of fluorescing tumor tissue to total resection of T2-weighted FLAIR hyperintensity in addition to GTR of the CE area, made it challenging to draw clear conclusions that would benefit the clinical practice of neurosurgeons. Second, because the survival benefit and safety of resecting T2-weighted FLAIR hyperintense regions remains unclear, no clinical equipoise was found to randomize patients with GBM into SPTR or GTR groups. Therefore, SPTR was probably performed for only a selected group of patients, because extending the limits of GBM resection beyond the CE area was often not the main goal of the surgery, especially not for tumors located in eloquent brain areas.

Finally, a heterogeneous patient population with different prognostic factors such as age, KPS score, adjuvant therapy, IDH mutation and MGMT methylation status, and tumor volume and location were present across the 6 studies (Supplemental Table 2). Although corrections for some of these factors were applied in the multivariate analyses across the studies, the real effect of these factors for achieving SPTR and survival were difficult to determine owing to the retrospective nature of the studies. GBM location and the nearness of the tumor to eloquent areas is a known important prognostic factor. A very recent study suggested that GBMs located in noneloquent areas such as the frontal or temporal pole could possibly undergo safe SPTR with total lobectomy.[34] However, no clear comparison with GBMs located in eloquent areas was available. In the reports we included in our study, only limited correction for GBM eloquence was performed (Supplemental Table 2). Furthermore, some of these factors, such as genetic mutations and location and tumor size, are intercorrelated; thus, their influence on survival would be difficult to investigate retrospectively. Patients with GBM with an IDH mutation (and MGMT methylation) will have significantly better survival, although, at the same time, these tumors have more often been located in the frontal pole and have had a larger size.[36]

These limitations introduced biases such as confounding by indication, available information, and selection biases in the analyzed studies, which, consequently, negatively influenced the internal validity and quality of the studies. Because the quality of evidence of the analyzed studies were only moderate to very low, the benefit of SPTR of GBM on survival and its safety remains unclear and, thus, should not yet be considered as a main goal of GBM surgery.

With consideration of these limitations, we used a random effects model to provide a conservative, but clinically more reliable and meaningful, interpretation of the treatment effect of SPTR.[37] The random effects model summary results of a HR of 0.47 (95% CI, 0.31–0.72) and median overall survival benefit of 6.4 months (95% CI, 3.2%–9.7%) provides a more reliable average estimate effect because it considers the real differences in the SPTR versus GTR effect in each study and provides greater uncertainty around the estimate compared with the fixed effects model summary results of a HR of 0.67 (95% CI, 0.58–0.78) and a median overall survival benefit of 4.6 months (95% CI, 3.9–6.0).

In addition, SPTR should not be attempted at any cost. As always, the aim of GBM surgery should be to maximize the extent of GBM resection without causing new neurological deficits and maintaining a good quality of life for patients. Any potential benefits of prolonged survival by extending the tumor resection could be considered by exploring the functional boundaries during awake surgery and additional imaging adjuncts such intraoperative MRI, ultrasound, and 5-ALA guidance. This potential benefit should be weighed, together with the patient, against the risk of extending the boundaries of GBM resection and its effect on postoperative neurological functioning and quality of life.

In our study, the incidence of postoperative new neurological deficits was not well reported across the different studies. Postoperative neurological status was reported only descriptively, without the use of validated tests and quantitative outcome measures. Additionally, no data on patient quality of life were reported across the studies. The safety of the procedure, therefore, could not be established.

Future Directions

Future, well-designed, prospective, randomized controlled trials are needed to investigate both the safety and the survival benefit of SPTR of GBM. These trials should include prospective and clearly defined volumetric SPTR measures to standardize the definition of SPTR. Such a standardized definition of SPTR would be expected to improve comparability between studies and improve the quality of evidence of studies investigating SPTR of GBM. Advanced physiological imaging techniques could also be used to identify non−CE-infiltrating, residual tumor beyond the CE margins. Finally, validated measures for postoperative neurological outcomes and quality of life assessments (i.e., European Organization for Research and Treatment of Cancer core quality of life questionnaire and/or brain cancer module) that have been corrected for important prognostic factors such as age, KPS score, use of adjuvant therapy, and IDH mutation and MGMT methylation status should be used to study the benefit of SPTR of GBM on patient survival and safety.[38]

CONCLUSIONS

To the best of our knowledge, we have performed the first meta-analysis of SPTR for GBM. Our results suggest that compared with GTR, SPTR of GBM results in a lower risk of mortality at any time during the follow-up period and longer overall median survival. These results should, however, be interpreted with caution, because the quality of the available evidence was only moderate to very

low. In addition, no consensus has been reached on the definition of SPTR, and no reliable information on the safety of SPTR was available. Therefore, from the current available data, the benefit of SPTR of GBM on survival and its safety remains unclear and should not yet be considered as the standard of care for GBM surgery. Our findings, however, should encourage further investigation in well-designed, prospective, randomized trials to clarify whether SPTR can be achieved safely to improve the survival of patients with GBM.

ACKNOWLEDGMENTS

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SUPPLEMENTAL MATERIALS

Search Queries for Several Literature Sources

Embase.com. ('glioblastoma'/exp OR (glioblastom* OR (maligna* NEAR/3 glioma*) OR (high* NEAR/3 grade* NEAR/3 glioma*) OR ((grade-iv OR grade-4) NEAR/3 glioma*) OR gbm):ab,ti,kw) AND ('surgery'/de OR 'neurosurgery'/exp OR 'cancer surgery'/exp OR 'brain surgery'/exp OR 'brain tumor'/exp/dm_su OR 'surgical technique'/de OR (surg* OR neurosurg* OR resect*):ab,ti,kw) AND ('extent of resection'/de OR 'surgical margin'/exp OR 'fluid attenuated inversion recovery'/de OR 'fluid attenuated inversion recovery imaging'/de OR 'gross total resection'/de OR (flair OR (Fluid NEAR/3 attenuat* NEAR/3 invers* NEAR/3 recover*) OR t2 OR t-2 OR gross-total OR ((exten* OR Supratotal* OR Supramaxim*) NEAR/3 (resect* OR remov*)) OR ((surg* OR excis* OR resect*) NEAR/3 margin*) OR ((beyond OR additional*) NEAR/6 (contrast OR boundar*))):ab,ti,kw) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim)

Web of Science. ((glioblastom* OR (maligna* NEAR/3 glioma*) OR (high* NEAR/3 grade* NEAR/3 glioma*) OR ((grade-iv OR grade-4) NEAR/3 glioma*) OR gbm):ab,ti,kw) AND ((surg* OR neurosurg* OR resect*):ab,ti,kw) AND ((flair OR (Fluid NEAR/3 attenuat* NEAR/3 invers* NEAR/3 recover*) OR t2 OR t-2 OR gross-total OR ((exten* OR Supratotal* OR Supramaxim*) NEAR/3 (resect* OR remov*)) OR ((surg* OR excis* OR resect*) NEAR/3 margin*) OR ((beyond OR additional*) NEAR/6 (contrast OR boundar*))):ab,ti,kw)

Cochrane CENTRAL. ((glioblastom* OR (maligna* NEAR/3 glioma*) OR (high* NEAR/3 grade* NEAR/3 glioma*) OR ((grade-iv OR grade-4) NEAR/3 glioma*) OR gbm):ab,ti,kw) AND ((surg* OR neurosurg* OR resect*):ab,ti,kw) AND ((flair OR (Fluid NEAR/3 attenuat* NEAR/3 invers* NEAR/3 recover*) OR t2 OR "t 2" OR "gross total" OR ((exten* OR Supratotal* OR Supramaxim*) NEAR/3 (resect* OR remov*)) OR ((surg* OR excis* OR resect*) NEAR/3 margin*) OR ((beyond OR additional*) NEAR/6 (contrast OR boundar*))):ab,ti,kw)

Google Scholar. glioblastoma|"malignant glioma"|"high grade glioma" flair|"Fluid attenuating inverse"|"gross total"-|"Supratotal|Supramaximal resection"|"extent of resection"

Supplemental Table 1. Grades of Recommendation, Assessment, Development, and Evaluation Quality Ranking				
Investigator	**Quality Level***	**Underlying Study Method**	**Risk of Bias†**	**Precision**
Aldave et al.,[12] 2013	3	Nonrandom treatment allocation, retrospective	Moderate	Low patient numbers; wide 95% CIs
Li et al.,[8] 2016	2	Nonrandom treatment allocation retrospective	Moderate	High patient numbers, narrow 95% CIs
Eyüpoglu et al.,[19] 2016	3	Nonrandom treatment allocation retrospective	Moderate	Moderate patient numbers and 95% CIs
Pessina et al.,[28] 2017	3	Nonrandom treatment allocation retrospective	Moderate	Moderate patient numbers and 95% CIs
Esquenazi et al.,[18] 2017	3	Nonrandom treatment allocation retrospective	Moderate	Low patient numbers, wide 95% CIs
Glenn et al.,[21] 2018	4	Nonrandom treatment allocation, retrospective	Serious	Low patient numbers, wide 95% CIs

CI, confidence interval.

*Quality of evidence levels (Grades of Recommendation, Assessment, Development, and Evaluation Quality): 1, high; 2, moderate; 3, low; 4, very low.

†ROBINS-I (risk of bias in nonrandomized studies — of interventions) tool, based on risks of selection, information, and confounding biases, with summarized judgments that include moderate, serious, and critical risks of bias or no information.

Supplemental Table 2. Overview of Multivariate Analyses Across Studies with Adjustment for Prognostics Factors

Investigator	Multivariate Analysis	Prognostic Factors as Variables
Aldave et al.,[12] 2013	Yes	Age, KPS score, MGMT methylation status, tumor eloquent location, preoperative tumor volume, adjuvant therapy
Li et al.,[8] 2016	Yes	Unclear, at least treatment history
Eyüpoglu et al.,[19] 2016	No	Not performed
Pessina et al.,[28] 2017	Yes	Age, extent of CE resection, tumor location
Esquenazi et al.,[18] 2017	Yes	Age, tumor volume, KPS score, intraoperative mapping, BCNU wafer
Glenn et al.,[21] 2018	Yes	MGMT methylation status, tumor laterality

KPS, Karnofsky performance scale; MGMT, methylguanine-DNA methyltransferase; CE, contrast enhancing; BCNU, bis-chloroethylnitrosourea (or carmustine).