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TOPIC REVIEW

A systematic review and meta-analysis of supratotal versus gross total resection for glioblastoma

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Abstract

Purpose Due to the infiltrative nature of glioblastoma (GBM) outside of the contrast-enhancing region on MRI, there is interest in exploring supratotal resections (SpTR) that extend beyond the contrast-enhancing portion of the tumor. However, there is currently no consensus on the potential survival benefit of SpTR in GBM compared to gross total resection (GTR). In this study, we compare the impact of SpTR versus GTR on overall survival (OS) of GBM patients.

Methods We performed a systematic review and meta-analysis of literature published on PubMed, Embase, The Cochrane Library, Web of Science, Scopus, and ClinicalTrials.gov, from inception to August 16, 2018, to identify articles comparing OS after SpTR versus GTR.

Results We identified 8902 unique citations, of which 11 articles met study inclusion criteria. 810 patients underwent SpTR out of a total of 2056 patients. 9 of 11 studies demonstrated improved outcomes with SpTR compared to GTR (median improvement in OS of 10.5 months), with no significant difference in postoperative complication rate. Overall study quality was variable, with ten studies presenting level IV evidence and one study presenting level IIIb evidence. Subgroup meta-analysis based on SpTR definition demonstrated a statistically significant 35% lower risk of mortality in patients who underwent anatomical SpTR compared to patients who underwent GTR (Hazard ratio = 0.65, 95% CI 0.47- 0.91, p = 0.003).

Conclusion Our systematic review indicates SpTR may be associated with improved OS compared to GTR for GBM, especially with anatomical SpTR. However, this is limited by variable study design and significant clinical and methodological heterogeneity among studies. There is need for prospective clinical data to further guide parameters regarding the use of SpTR in GBM.

Keywords Extent of resection · EOR · Glioblastoma · GBM · Supratotal resection · T2 FLAIR

Introduction

Glioblastoma (GBM) is the most common and aggressive primary central nervous system malignancy in adults with a median overall survival (OS) of 20 months despite surgical resection, radiation, and chemotherapy [1, 2]. While surgical resection plays a critical role in the multimodal treatment schema of GBM, there has historically been variability in the extent of resection (EOR) goals of surgery—ranging from minimally invasive biopsies to gross total resections (GTR) [3, 4].

Several systematic reviews and meta-analyses have reported a significant decrease in mortality and disease progression for patients undergoing GTR compared with subtotal resection (STR) or biopsies for GBM [3, 5]. The comprehensive work of Sanai et al. demonstrated that increasing EOR > 78% of contrast-enhancing tumor for newly diagnosed GBM corresponded to a survival benefit, further expanding the threshold for improved survival beyond previous work demonstrating a threshold of 98% [6]. This study and others have posited that a lower residual tumor burden

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allowed more effective tumor response to chemoradiation [5–7].

Despite these trends favoring aggressive cytoreductive surgery, tumor recurrence is inevitable, and patients uniformly succumb to their disease [8]. Historically, GTR has been defined as resection of the contrast-enhancing portion of the tumor on magnetic resonance imaging (MRI). However, due to the infiltrative nature of GBM, contrast enhancement has limitations in delineating the tumor margin with tumor cells often found outside of the contrast-enhancing region in the peritumoral zone [9, 10]. These glioma cells are thought to be represented in part by T2 fluid-attenuated inversion recovery (FLAIR) regions on MRI [11]. Importantly, these peritumoral cells are thought to drive tumor recurrence and progression [12, 13]. With these findings and the development of surgical adjuncts such as intra-operative MRI and fluorescence labeling with 5-aminolevulinic acid (5-ALA), there has been a movement to extend the edge of surgical resection beyond the contrast-enhancing portion of the tumor, thereby resulting in supratotal resection (SpTR). However, while the T2 FLAIR region in low-grade gliomas consist mainly of tumor cells without associated enhancement, the T2 FLAIR region in GBM can also result in false positive signals secondary to cerebral edema, demyelination, and surgical injuries [14]. Therefore, complete resection of T2 FLAIR regions in GBM offers additional risks relative to such resections in low-grade gliomas with concern for increased iatrogenic risk of neurological injury from removal of critical cortical and subcortical tissue [7, 15]. As such, there is currently no consensus on the potential overall risks versus benefits from extending GBM resection beyond contrast enhancement into T2 FLAIR regions.

In this context, there have been two recent systematic reviews examining the role of SpTR in gliomas, though they either did not focus specifically on GBM nor include more recent studies [16, 17]. Previous systematic reviews are limited due to a narrow criteria of SpTR that focused mainly on imaging characteristics. Given the lack of clearly delineated tumor margins in GBM, we sought to provide a more comprehensive review of the pertinent literature that comprised of multiple definitions of SpTR to better capture the effects of resection beyond GTR on GBM outcomes. Therefore, in this systematic review, we expanded upon the current literature by examining the most recent studies on the impact of SpTR—defined in our review as resection beyond contrast-enhancing regions of tumor on MRI including any amount of T2 FLAIR signal and any anatomical resection beyond the region of contrast-enhancing tumor—upon OS and PFS in GBM specifically.

Methods

The methodologies for this systematic review were carried out using PRISMA formatting and guidelines under the supervision of an expert librarian (C.P.) with special training in evidence-based literature [18, 19].

Search strategy

A comprehensive literature search was performed in six databases including PubMed via PubMed.gov, Excerpta Medica Database (Embase) via Embase.com, The Cochrane Library via Wiley, Web of Science via Clarivate, Scopus via Elsevier, and ClinicalTrials.gov from their inception through August 16, 2018. Three main concepts were utilized to obtain articles related to SpTR in GBM. With input from an information specialist (C.P.), a search was created with the concepts of "glioblastoma", "supratotal", and "resection". An effort was made to account for synonyms, acronyms, plurals, and variations in spelling. We utilized a combination of controlled vocabulary terms (i.e. MeSH terms in PubMed and Emtree in Embase) as well as key words. The comprehensive search terms used for each database are listed in Appendix 1 (see Appendix, Supplemental Digital Content).

Initial screening using eligibility criteria

Manual review of all articles and trials identified through the above electronic databases was carried out for relevance within Covidence Systematic Review Software (Melbourne, Australia) [20]. Duplicated articles were screened for and consolidated on initial review. Manuscript titles identified from each of the above database searches were then evaluated by one reviewer (C.J.) and eligible articles, predicated on criteria listed below, were selected for full systematic review (Fig. 1).

Inclusion criteria

The following inclusion criteria were used: (1) manuscripts involving human subjects; (2) manuscripts including data on at least five patients; (3) manuscripts reporting primary data; and (4) manuscripts providing survival or complication data on GTR versus SpTR of GBM, with SpTR defined as any resection beyond the contrast-enhancing portion of disease on MRI.

Exclusion criteria

After the exclusion of duplicate articles, individual citations were reviewed to exclude off topic citations, editorials, and

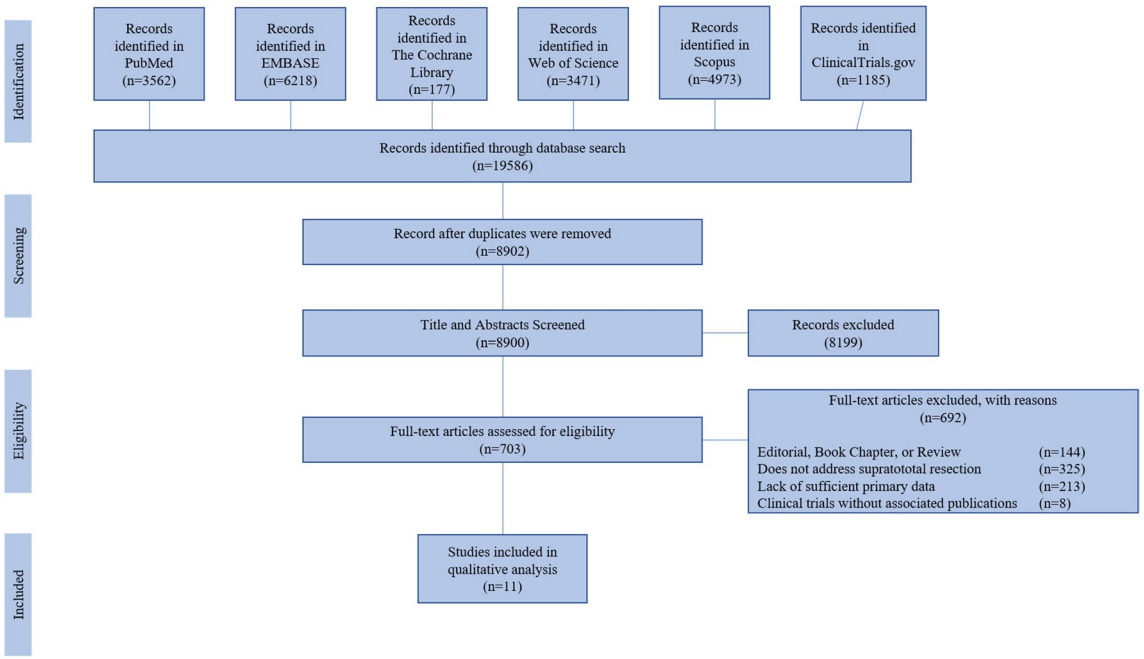

Fig. 1 PRISMA flow diagram

review articles. Case reports and series including less than five patients were also excluded. Additionally, articles that primarily included pediatric patient populations and those not written in English were excluded. Articles that represented greater than 50% of tumor types outside of GBM were excluded. Full-text review of the remaining 703 articles excluded studies that discussed EOR without including comparison groups or specific survival outcome data. Studies were also excluded if EOR did not include SpTR or resections beyond the T1 contrast-enhancing region.

Data Extraction and Analysis

Each of the studies that were selected for inclusion were mined for the following data: year of publication, number of patients treated within each cohort, study design, level of evidence, and major findings within each article. All studies selected for final inclusion were independently reviewed for inclusion by two reviewers (C.J. and D.M.). One reviewer (C.J.) extracted data from each manuscript into a standardized evidence table, while another reviewer (D.M.) independently assessed this table for accuracy and completeness.

Levels of evidence

Each article was graded according to guidelines set forth by the 2011 Oxford Centre for Evidence-Based Medicine [21]. Within this schema, level Ib evidence included individual randomized controlled trials. Level IIb evidence included individual, prospective cohort studies. Level IIIb evidence was derived from individual case–control studies. Level IV data was derived from either case series or retrospective analyses (see Supplemental Table 1, Supplemental Digital Content). The quality of evidence was rated by two independent reviewers (C.J and J.C) with discrepancies mediated by a third reviewer (D.M.).

Analysis

Qualitative synthesis

We included a narrative synthesis of our review. We described (1) the clinical and methodological characteristic of the included studies, (2) the strengths and limitations of individual studies and patterns across studies, (3) how weaknesses in studies' design could bias results, (4) the relationships between characteristics of the different studies and their reported findings, and (5) the relevance of individual studies to the populations, exposures, settings, and outcomes of interest.

Assessment of heterogeneity

We assessed study heterogeneity across three domains: clinical (i.e. differences in patient populations or exposure categories), methodological (i.e. differences in study type), and statistical.

Meta-analysis

We collected or calculated hazard ratios (HRs) with a 95% confidence interval (CI) for the SpTR and GTR cohorts using the reported data in the included studies. HRs were either calculated using NCSS (Statistical Software Inc., Kaysville, Utah, USA) or extracted and calculated from survival curves using construction techniques and data extrapolation methods described in the systemic review literature [22, 23]. Due to the substantial heterogeneity across all domains mentioned previously, we used the random-effects meta-analysis model instead of the fixed-effects model to provide a reliable interpretation of the weighted statistics. Data is presented in forest plots using Review Manager (RevMan Version 5.3.5, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity is identified and quantified in RevMan using chi-square tests and I^2 [24]. A p value < 0.05 was used to determine statistical significance. An observed value of 75% to 100% in I^2 was interpreted as considerable heterogeneity.

Results

Search results

Utilizing the search strategy noted above, we found 3562 citations from PubMed, 6218 from Embase, 177 from Cochrane, 3471 from Web of Science, 4973 from Scopus, and 1185 from ClinicalTrials.gov. After removal of duplicate records, a total of 8902 citations were subsequently reviewed. Review of titles excluded 8199 citations based upon failure to meet basic inclusion and exclusion criteria. 703 citations were deemed potentially suitable for inclusion and were assessed via full-text review. Of these, 144 were excluded for being editorials and review articles, and eight were excluded for being clinical trials without associated publications. An additional 213 citations were excluded for lacking sufficient primary data and 325 were found to not provide data on SpTR vs GTR. We additionally eliminated two abstracts due to lack of sufficient primary data. Following this process, 11 articles were included for final review and data extraction. The search process and results are outlined in Fig. 1.

Broad characteristics of included studies are presented in Table 1. Our search did not result in any level Ib or IIb studies. All of the identified studies were single-institution studies. We included one level IIIb study that involved secondary analysis of prospectively collected patient and control groups. The remainder of the manuscripts were categorized as level IV evidence. Study populations ranged from 32 to 876 patients [5, 25]. The included studies consisted of a total of 2056 patients; of these, 810 patients underwent SpTR of their tumor beyond the contrast-enhancing border of the tumor. All studies were published between 2013 and 2018 with patient treatments spanning from 1993 to 2015. The 11 articles included studies from the United States (5) [7, 25–28], Italy (2) [29, 30], Egypt (1) [31], Germany (1)

Table 1 Summary of included studies

Study	Level of evidence	Study design	Number of patients	Supratotal Resection	Gross total resection	Age	% Male	Duration of follow up
Extent of T2 FLAIR resection								
M Grabowski et al. [27] (2014)	IV	Retrospective	128	NS	NS	60 (median)	NS	NS
Y Li et al. [7] (2016)	IV	Retrospective	876	643	233	55.7 (mean)	61.6%	19.9 months
F Pessina et al. [30] (2017)	IV	Retrospective	282	21	60	61 (median)	62.7%	13.8 months
R Grossman et al. [34] (2017)	IV	Retrospective	103	103	NS	59.6 (mean)	64%	NS
D Mampre et al. [28] (2018)	IV	Retrospective	245	11	84	59.8 (mean)	61%	12.1 months
Extended anatomical resection								
P De Bonis et al. [29] (2012)	IV	Retrospective	88	36	52	57.5 (mean)	53.4%	NS
S Hamada et al. [31] (2016)	IV	Retrospective	59	20	21	48.57 (mean)	72.8%	NS
Y Esquenazi et al. [26] (2017)	IV	Retrospective	86	25	13	56 (mean)	66.3%	17.8 months
C Glenn et al. [25] (2018)	IV	Retrospective	32	7	9	54.9 (mean)	78%	NS
Intra-operative fluorescence-guided resection								
G Aldave et al. [33] (2013)	IV	Retrospective	52	25	27	NS	NS	NS
I Eyupoglu et al. [32] (2017)	IIIb	Prospective Cohort	105	30	75	63 (median)	57.1%	NS

NS not specified

[32], Spain (1) [33], and Israel (1) [34]. The studies had significant heterogeneity in patient characteristics including medical comorbidities, tumor molecular status, tumor focality, adjuvant treatment, and performance status. Only one study reported patient comorbidities that ranged from diabetes to gastrointestinal disease [32]. Pre-operative KPS ranged from 30–100 and adjuvant therapy included standard chemoradiation, BCNU wafers, and immunotherapy. Tumor locations included in the studies ranged from temporal location only to spanning all supratentorial locations.

Types of exposure

Our exposure was categorized and defined differently in various studies. Four studies defined SpTR or supramaximal resection as resection extending beyond the T1 contrast-enhancing margin on postoperative MRI [5, 7, 28, 30]. In two studies, instead of categorizing the patients into (1) a group of GTR of the T1 contrast-enhancing tumor and (2) a group with resection beyond the T1 contrast-enhancing tumor, patients were instead categorized by the association of postoperative residual contrast enhancement and residual T2/FLAIR volume with survival outcomes [27, 34]. Four studies used extended anatomical resection of non-eloquent adjacent areas beyond gross tumor and contrast-enhancing regions as a measure of SpTR [25, 26, 29, 31]. An additional two studies involved the use of fluorescence-guided surgery to extend resection beyond gross tumor visualization [32, 33].

Outcomes

We considered two main outcomes: progression-free survival (PFS) and OS. All 11 studies reported rates of OS, while only four studies reported recurrence rates [25, 28–30]. Methods for ascertainment of patient mortality (autopsy report, national death file, etc.) were not well-described in 8 of the 11 studies. Eight out of the 11 studies reported a hazard ratio (HR) as their summary measure for patient mortality. Two studies reported Kaplan Meier (KM) survival outcomes as their measure of survival [29, 31].

Nine of the 11 studies demonstrated a survival benefit with increased EOR beyond the contrast-enhancing region of the tumor with a median OS of 12–54 months in the SpTR group compared to 11–17.5 months in the GTR group [7, 8, 25, 26, 29–31, 33, 34]. Of the 6 studies that reported PFS, three studies demonstrated a benefit of SpTR in PFS (12–24.5 months) compared to GTR (7–11.9 months) [25, 29, 30]. While the study by Grabowski et al. demonstrated a survival advantage for SpTR with T2 FLAIR resection but did not directly compare outcomes to contrast-enhancing GTR, and the study by Mampre et al. failed to demonstrate a survival advantage to SpTR compared to GTR [27, 28].

Comprehensive summary and analysis of each study are further detailed in Table 2 and Appendix 2 (see Appendix, Supplemental Digital Content).

Risk of biases of included studies

Selection bias

All included reports are single-center studies and are from single countries. The extent to which such cohorts truly represent the more diverse GBM population is unknown, and the degree to which their findings can be generalizable is unclear. Furthermore, the selection of patients depended upon how SpTR was defined in each study. For studies where SpTR was defined as an anatomical resection including the surrounding gyri, only patients with tumors outside of eloquent regions were included [25, 26, 29, 31]. Furthermore, for the majority of studies, there was a pre-selection bias toward patients who had tumors that were conducive to surgical resection, specifically GTR. Additionally, while several studies attempted to account for factors such as tumor location and proximity to eloquent regions, there is a risk of selection bias between patients who underwent SpTR compared to patients who had GTR. These biases could affect PFS and OS of the cohorts identified and may not be representative of the overall heterogeneity of patients with GBM. We therefore considered these studies to be broadly at high risk of bias based on PRISMA criteria [18].

Comparability

The majority of studies were observational, with the exception of the study by Eyupoglu et al. where patients were enrolled prospectively into two exposure groups [32]. No patients were randomized and no studies chose to match between groups, possibly leading to significant differences in clinical characteristics, ethnicity, and comorbidities between groups. Furthermore, only a limited number of studies had an internal control group—namely, patients who underwent GTR of the contrast-enhancing region of tumor—to serve as a direct comparison in outcomes to the SpTR group [7, 25, 29–33]. The other studies used historical controls, which limited the authors' ability to accurately compare outcomes between the current SpTR patient cohort and historical controls given likely differences in patient characteristics, timing and types of treatment, and availability of intra-operative adjuncts between these two groups.

Outcomes

We assessed two domains for risk of bias as related to outcomes: (1) overall assessment of outcomes and (2) follow-up adequacy. In general, the description of how studies assessed

Table 2 Summary of survival analysis

Study	Number of patients	Definition of supratotal resection (SpTR)	Comparative Groups	Overall survival				Progression free survival			Post-Operative Complications	Limitations
				SpTR (months)	GTR (months)	p value	Hazard ratio	SpTR (months)	GTR (months)	p value		
Extent of T2 FLAIR resection												
M Grabowski et al. [27] (2014)	128	Resection of T2 FLAIR abnormalities	T2 FLAIR residual tumor volume vs CE residual tumor volume	12	16	n/a	1.01 (p = 0.10)					Significant variability due to measurer experience
Y Li et al. [7] (2016)	876	Resection of > 53.2% of T2 FLAIR abnormalities	T2 FLAIR resection ≥ 53.21% vs T2 FLAIR resection < 53.21%	20.7	15.5**	< 0.001					Patients with ≥ 53.21% FLAIR resection had fewer overall complications, but no difference in neurologic sequalae	No subset analysis on MGMT methylation and IDH mutation (mt) status
F Pessina et al. [30] (2017)	282	Resection of T2 FLAIR abnormalities	SpTR with 100% CE and T2 FLAIR regions vs GTR with 90–100% CE	29	16	0.001		24.5	11.9	0.001	Lower rates of post-operative neurological complications in SpTR (4.8%) compared to GTR (13.3%)	Operator differences
R Grossman et al. [34] (2017)	103	< 19.3 cm^3 T2 FLAIR volume 3 months postoperative	3 month postoperative T2 FLAIR volume ≤ 19.3 cm^3 vs T2 FLAIR volume < 19.3 cm^3	26.7	13.4***	< 0.001						Possibility of pseudoprogression, selection bias, limited sample size
D Mampre et al. [28] (2018)	245	Resection of T2 FLAIR abnormalities	No comparative controls				1.022* (p = 0.46)			0.968 (p = 0.47)		Unable to factor in MGMT methylation or IDH mt status

Table 2 (continued)

Study	Number of patients	Definition of supratotal resection (SpTR)	Comparative Groups	Overall survival				Progression free survival			Post-Operative Complications	Limitations
				SpTR (months)	GTR (months)	p value	Hazard ratio	SpTR (months)	GTR (months)	p value		
Extended anatomical resection												
P De Bonis et al. [29] (2012)	88	Gross resection 1–2 cm beyond tumor margin	SpTR with extended anatomical resection vs border resection of CE tumor margins	19	17	0.15		12	9			No multivariate analysis
S Hamada et al. [31] (2016)	59	Gross resection into involved noneloquent gyri or lobe	SpTR of adjacent normal tissue vs GTR of CE region vs STR vs surgical debulking	16.5	12.09	0.002						Lack of multivariate analysis for age, KPS, MGMT methylation or IDH mt status, tumor burden, eloquent areas
Y Esquenazi et al. [26] (2017)	86	Subpial resection beyond contrast enhancement	SpTR with extended anatomical resection vs historical controls	54	16.5 (HC)	< 0.01					Neurological deficits and complications from subpial resection were comparable to other resection series	Lack of internal controls, no account for MGMT methylation or IDH mt status
C Glenn et al. [25] (2018)	32	Lobectomy	SpTR beyond CE vs GTR of CE region	24	11	0.004		15	7	0.003	No differences in overall postoperative or neurological complications	Insufficient power due to small sample size

Table 2 (continued)

Study	Number of patients	Definition of supratotal resection (SpTR)	Comparative Groups	Overall survival				Progression free survival			Post-Operative Complications	Limitations
				SpTR (months)	GTR (months)	p value	Hazard ratio	SpTR (months)	GTR (months)	p value		
Intra-operative fluorescence-guided resection												
G Aldave et al. [33] (2013)	52	Resection of 5-ALA residual fluorescent regions	SpTR with no residual fluorescence in surgical field vs resection with residual fluorescence after surgery	27	17.5	0.015	2.5 (p = 0.041)				Increased neurological complications in SpTR (18.5%) compared to patients with residual fluorescence (8%)	Low number of patients and variable treatment regimens
I Eyupoglu et al. [32] (2017)	105	DiVA with intraoperative MRI and 5-ALA	SpTR with complete resection of 5-ALA + intraoperative CE vs GTR with intraoperative residual CE alone	18.5	14	0.004	0.449 (95% CI 0.289–0.696)				No significant differences in neurological complications	Use of a retrospective control arm

SpTR supratotal resection, *GTR* gross total resection,

[*] HR calculated to time of death for supratotal resection,

[**] < 53.21% of T2 FLAIR abnormalities resected, *HC* Historical controls,

[***] > 19.3 cm^3 of residual T2 FLAIR volume at 3 months postoperative scans, mt = mutant

OS outcome was good, though not all studies reported PFS or time to recurrence. Patient mortality was clearly defined across studies. However, seven studies did not clearly delineate patient follow-up time and, among the studies that did, median follow-up time varied significantly from 12.1 to 19.9 months [7, 28, 30, 33]. Moreover, only 4 studies described any loss to follow-up [26, 27, 29, 34]. In general, follow-up adequacy was poorly reported across all studies, as defined by PRISMA guidelines [18].

Assessment of heterogeneity

Clinical and methodological heterogeneity

There was significant clinical and methodological heterogeneity in our systematic review. This was evidenced by a wide range of study locations as well as differences in the number of patients, types of patient comorbidities, and range of adjuvant therapies employed, including BCNU wafers, irinotecan, and immunotherapy. Moreover, length of follow-up was significantly different among studies (12.1 months to 19.9 months), as was the range of PFS and OS (PFS: 7–24.5 months, OS: 11–54 months). While studies attempted to control for confounding factors, they generally controlled for different covariates in their multivariable models with inconsistent availability of confounding variable data. Nine studies included multivariable analysis with some studies accounting for only age and KPS, while others accounted for eloquence of tumor location, tumor volume, prior treatment, and molecular characteristics [7, 25–30, 33, 34]. There is a lack of consistent reporting of molecular characteristics such as O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation and isocitrate dehydrogenase (IDH) mutation status, which have both been shown to be independently correlated with response to chemotherapy and OS [35–38]. Five studies reported patients' MGMT promoter methylation status, and 3 studies reported patients' IDH mutation status, yet only 4 studies included those variables in the multivariable analysis [25, 30, 32–34]. Additionally, while one study was a prospective cohort study [32], the remainder were retrospective in nature and therefore are subject to the inherent limitations of such analyses. Finally, the 11 studies lacked a uniformed definition for SpTR, with criteria ranging from extended anatomical resection to T2 FLAIR based resections.

Statistical heterogeneity

We encountered minimal statistical heterogeneity among the studies reviewed. While potential confounding variables differed among the studies, 8 out of the 11 studies performed multivariate analysis to evaluate the association between SpTR and OS. The remaining 3 studies compared OS between the SpTR and GTR groups using unadjusted Kaplan Meier survival analysis [29, 31, 32].

Subgroup analyses

Due to the differing definitions of SpTR featured in the studies of this review, we examined each definition separately to minimize heterogeneity and determine if each SpTR subgroup was associated with a similar impact upon OS. Specifically, we divided studies into three subgroups that examined SpTR by extent of T2 FLAIR resection [7, 27, 28, 30, 34]], extended anatomical resection [25, 26, 29, 31], or intra-operative fluorescence-guided resection [32, 33]. Overall, we found there was improved comparability among studies within each subgroup.

Within the subgroup that defined SpTR via T2 FLAIR resection, patients' clinical characteristics, including mean or median age (55.7–60 years old), sex (61–67% male), median KPS (80 or 90), and post-surgical treatment regimen involving the Stupp protocol, were similar. All 5 studies accounted for tumor eloquence and found that eloquence was not significantly associated with improved survival in either univariate or multivariate analysis. However, consistency in accounting for tumor molecular status was lacking with only two of the five studies accounting for either MGMT methylation or IDH mutation status in multivariate analysis [30, 34]. Four out of the five studies demonstrated a significant association between the amount of T2 FLAIR resection and OS [7, 27, 30, 34]. Three of those studies featured direct comparisons between OS in GTR and SpTR cohorts with multivariate analyses adjusting for age, sex, location of the tumor, pre-operative tumor volume, and KPS status [7, 27, 30]. While the comparability of studies could have allowed for integration of patient cohorts across studies, there was inconsistency in hazard or odds ratio reporting.

Among the manuscripts that defined SpTR as extended anatomical resection of the surrounding gyrus and normal white matter, we found a similar improvement in comparability between studies, with the exception of one study that included patients treated with local BCNU wafers [26] and one study that only focused on resection of temporal lobe GBM [25]. Notably, all four study populations were limited to patients with tumors in non-eloquent locations, suggestive of an inherent selection bias for this mode of SpTR compared to others. All 4 studies found a survival advantage in patients who underwent SpTR anatomical resection (SpTR 16.5–54 months versus GTR 11–17 months).

Lastly, two studies defined SpTR via intra-operative fluorescence-guided resection [32, 33]. While these studies also reported longer OS in patients who had greater resection of fluorescent tissue (SpTR 18.5–27 months versus GTR 14–17.5 months), there was more heterogeneity between these two studies than within other subgroups. These studies

differed in evidence grade, with the study by Eyupoglu et al. [32] utilizing a prospectively collected cohort (level IIIb) with intra-operative MRI in addition to 5-ALA-guided resection, while the study by Aldave et al. [33] was a retrospective series (level IV) in which all patients received dendritic cell vaccine immunotherapy in addition to standard Stupp protocol [32, 33]. Due to the significant heterogeneity between these two studies, we elected not to perform a meta-analysis for this subgroup.

Meta-analyses

Given the improvement in comparability across the studies after stratifying them based on the definition of SpTR, we intended to perform subgroup meta-analyses on the impact of SpTR on survival within each subgroup. However, when comparing HRs across studies within the T2 FLAIR resection and fluorescence-guided resection groups, there was not enough data provided to perform robust meta-analyses. Therefore, our subgroup meta-analysis included four studies comparing HRs of SpTR versus GTR within the anatomical resection group [25, 26, 29, 31]. Our meta-analysis demonstrated a statistically significant 35% lower risk of mortality in the SpTR versus the GTR cohorts of 88 versus 95 GBM patients, respectively (HR = 0.65, 95% CI 0.47–0.91; p = 0.003; $I^2 = 79\%$, Fig. 2).

Discussion

Historically, the literature demonstrates a trend toward favoring GTR over STR, as exemplified by findings that demonstrated increased EOR associated with improved outcomes in GBM [3, 5]. In 2018, de Leeuw et al. conducted a systematic review of the benefit of SpTRs with two studies focusing on GBM. While their analysis indicated that SpTR correlated with improved OS and PFS, the sparsity of reports, small sample size, and the lack of comparative cohorts undergoing GTR limited the conclusions that could be drawn [16]. Recently, Incekara et al. aimed to more specifically address SpTR for GBM through a systematic review and meta-analysis [17]. They analyzed 6 of the 11 studies we identified and noted significant heterogeneity between studies, including differences in defining SpTR and varying patient clinical characteristics. While the study's meta-analysis demonstrated that SpTR for GBM was associated with a 6.4-month longer median OS and 53% lower risk of mortality relative to GTR, the authors urged the readers to interpret their analysis with caution due to limitations of the included studies.

Expanding upon the studies conducted by de Leeuw et al. and Incekara et al., we performed the largest systematic review to date examining 11 studies from 2013 to 2018 to compare the impact of SpTR and GTR on OS and/or PFS in GBM patients with rigorous assessment of the quality of existing evidence. In particular, we included additional studies that examined anatomical approaches for SpTR. We believe the inclusion of these additional studies is clinically relevant, as not all institutions have the availability to perform intra-operative imaging or 5-ALA guided SpTR, while others simply choose to perform anatomically based SpTR when feasible.

While our qualitative synthesis identified large clinical and methodologic differences, 9 of the 11 studies demonstrated increased OS and/or PFS in patients who underwent resection beyond the contrast-enhancing portion of tumor [14, 25, 26, 30–33] with one additional study demonstrating a significant association between T2 FLAIR resection and OS, though it lacked direct comparison to GTR. Five of the six studies that included postoperative complication rates demonstrated no increase in neurological complications for SpTR compared to GTR [7, 11, 25, 26, 30] (Table 2).

As we performed our systematic analysis of the 11 studies, 3 different definitions of SpTR emerged: resection of T2 FLAIR signal, extended anatomical resection, and fluorescence-guided SpTR. To determine if these three methods of SpTR independently conferred any difference in survival benefit, we performed additional review of studies within each subgroup. Subgroup analysis led to decreased heterogeneity and improved comparability within each subgroup. SpTR was associated with improved OS compared to GTR irrespective of SpTR method. OS appeared to be greatest in

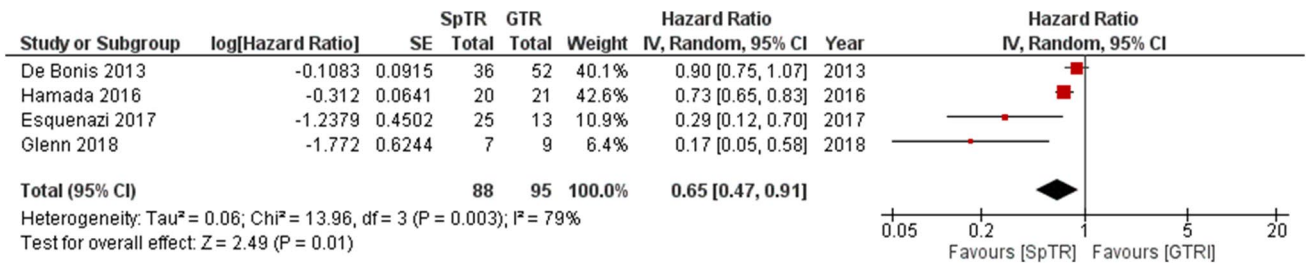

Fig. 2 Meta-analysis of SpTR versus GTR within extended anatomical resection subgroup

the anatomical resection subgroup (16.5–54 months) relative to the T2-FLAIR resection (12–26.7 months) and fluorescence-guided resection (18.5–27 months) subgroups. However, this trend toward improved survival in the anatomical resection subgroup may have been influenced by inherently favorable factors, including non-eloquent anatomic location or advantageous molecular markers.

As discussed more expansively in our sections highlighting risk of biases as well as our assessment of heterogeneity, our systematic review has several limitations, including the small number of single center retrospective studies of SpTR in GBM as well as the small number of total patients who underwent SpTR. The patient samples are heterogenous and many studies lacked comparable clinical and molecular characteristics, secondarily limiting the generalizability of overall study findings. One of the most important limitations across these studies was the lack of IDH mutation and MGMT promoter methylation status in multivariate analyses. As multiple studies have demonstrated the prognosticating values of these molecular markers in GBM survival, the results of the studies can be significantly confounded by the exclusion of these factors. Furthermore, these molecular correlates are of particular importance in the context of our systematic review in light of recent studies that have established relationships between the resectability of glioma and their tumor genotype, including IHD1 status [39]. It should be noted however that in the studies accounting for MGMT and IDH status, there were still significant differences between patients receiving SpTR vs GTR for survival outcomes [25, 30, 32–34].

Another potential confounder to the results is the eligibility of a tumor for SpTR resection. Our subgroup analysis made this potential selection bias apparent with the selection of only non-eloquent tumors in the extended anatomical resection subgroup possibly contributing to this subgroup's longer reported OS. While studies in the T2 FLAIR and fluorescence-guided resection subgroups showed a trend toward improved survival following SpTR even after accounting for tumor eloquence, there is still a need to address other potential eligibility confounders, such as tumor focality and depth, in future studies. In addition, the safety of SpTR has not yet been well established in the literature. In our series of 11 studies, only 6 reported post-operative complications rates between patients who underwent SpTR and GTR [14, 25, 26, 30, 32, 33]. While five out of the six studies reported no significant differences in post-operative neurological complication rates between the two resection groups, there was significant heterogeneity in the specific neurological sequelae and timing of complications reported between studies.

Given the clinical and methodological heterogeneity of the current literature, future prospective studies including randomized multi-institutional clinical trials would be beneficial to establishing more rigorous guidelines regarding the true utility of SpTR over GTR for GBM. As the molecular characteristics of GBMs become more granular in stratifying survival, it is imperative for future studies to account for these factors in outcome analysis. Intrinsic to this process would include the utilization of a uniformed definition of SpTR and standardized outcome measures to allow for more effective analysis of potential benefit of SpTR.

Despite these limitations, our review connotes a cautious optimism in approaching SpTRs, with the majority of studies indicating a positive correlation between OS and SpTR in GBM. Though SpTR should be approached carefully with appropriate selection of patients, surgical techniques, and utilization of intra-operative adjuncts, it remains imperative to minimize post-operative neurological complications that may negate any potential survival benefit. Until further prospective studies are performed, we must rely on this available data and our best clinical judgement to select those patients who may benefit most from SpTR in the management of GBM.

Declarations

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Compliance with ethical standards

Conflict of interest C.B. is a consultant for Depuy-Synthes and M.L. is a consult for Tocagen, SQ Technologies, Stryker, and Baxter.

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