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The role of lobectomy in glioblastoma management: A systematic review and meta-analysis

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ABSTRACT

Introduction: Lobectomy has recently been employed in the management of glioblastoma (GB). Compared to subtotal, gross total and supramarginal resection, lobectomy provides maximum cytoreduction and improves overall survival (OS).

Research question: The primary aim of this study is to compare lobectomy to other techniques for managing GB in terms of OS and progression-free survival (PFS). This study evaluated the association of the available surgical techniques for GB management with the reported relevant seizure outcome, operation time, length of stay, complication incidence, and Karnofsky performance status.

Materials and methods: A PRISMA-compliant systematic review and meta-analysis was performed. We searched PubMed, Scopus, and Web of Science from January 2013 until April 2023. Random-effects models were employed. The Newcastle-Ottawa scale (NOS) and the GRADE approach were used for estimating risk of bias and quality of evidence.

Results: We included six studies. Lobectomy demonstrated a mean OS of 25 months, compared to 13.72 months for gross total resection (GTR), and a PFS of 16.13 months, compared to 8.77 months for GTR. Comparing lobectomy to GTR, no statistically significant differences were observed regarding seizure management, length of stay, operation time, complications, and KPS due to limited amount of data.

Discussion and conclusion: Our analysis demonstrated that lobectomy compared to GTR has a tremendous impact on the OS and the PFS, which seems to be improved almost by a year. Lobectomy, while demanding from a technical standpoint, constitutes a safe surgical procedure but further studies should assess its exact role in the management of GB patients.

1. Introduction

Glioblastoma (GB) remains the most common and the most aggressive primary tumor of the central nervous system in adults, with median overall survival (OS) ranging from 14 to 20 months (Louis et al., 2016; Eyüpoglu et al., 2016; Wach et al., 2023; Jackson et al.). Its devastating prognosis, despite the cytoreductive surgical interventions and the adjuvant radio-chemotherapeutic choices, is attributed mainly to the inevitable local recurrence (De Bonis et al., 2013; Mampre et al., 2018). Recurrence occurs in the vast majority, at the site of the original tumor, while some authors suggest that it happens precisely within 2 cm from the border of the original lesion in 90–95% of cases (De Bonis et al., 2013; Teyateeti et al., 2020).

There are several parameters that affect the OS and cannot be modified, such as age, preoperative Karnofsky Performance Status (KPS), location of the tumor, tumor volume, molecular type, and ventricular ependymal infiltration (Esquenazi et al., 2017; Glenn et al., 2018; Pessina et al., 2017; Li et al., 2016; Tripathi et al., 2022). The only modifiable parameter that seems to improve OS is the extent of resection (EoR) (Baik et al., 2023; Figueroa et al., 2020). Through the years, it is made clear that gross-total resection (GTR) overcomes sub-total resection (STR) (Stummer et al., 2008; Ewelt et al., 2010; Kreth et al., 1993; Sharma et al., 2018). Recently, supramarginal resection (SMR), when

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Abbreviations

ATL	Anterior Temporal Lobectomy
CI	Confidence Interval
CrI	Credibility Interval
EoR	Extent of Resection
GB	Glioblastoma
GTR	Gross Total Resection
HR	Hazard Rate
KPS	Karnofsky Performance Status
NA	Not Available
NOS	Newcastle-Ottawa Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
OR	Odds Ratio
STR	Subtotal Resection
SUCRA	Surface Under The Cumulative Ranking Curve
OS	Overall Survival
PFS	Progression Free Survival
IRB	Institutional Review Board

feasible, has become the surgical management of choice for GB, as it is proven to improve OS, compared to GTR (Eyüpoglu et al., 2016; Mampre et al., 2018; Glenn et al., 2018; Pessina et al., 2017; Vivas-Buitrago et al., 2022). Lobectomy, even though it is not yet considered the standard of care in GB patients, could affect the OS, since it would provide the maximum cytoreductive option.

The primary aim of our current study is to compare lobectomy to other surgical techniques for managing GB in terms of OS and to identify potential favorable prognostic factors (Q1), as well as progression-free survival (PFS) (Q2). Our secondary aims were to compare the relevant seizure outcome (Q3), operation time (Q4), length of stay (Q5), incidence of complications (Q6), and functional status measured by KPS (Q7).

2. Methodology

2.1. General

Our current study includes three parts: a systematic literature search leading to the data extraction process, an evidence synthesis process, and a risk of bias assessment. The reporting of our results follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for network meta-analysis) guidelines (Hutton et al., 2015). No approval from the institutional review board (IRB) of our hospital was required.

2.2. Search strategy

We systematically searched PubMed/MEDLINE, Scopus, and Web of Science for comparative studies on lobectomy in managing GB patients from January 2013 to April 2023. We used the following terms and their variants: “glioma" OR “glioblastoma" OR “glial tumor" AND “lobectomy" OR “anatomical resection". In addition, we searched the reference list of the retrieved articles for any additional potentially relevant studies.

2.3. Study selection

The inclusion criteria of our study comprise of: 1) original data comparisons between lobectomy and any other surgical alternative for the management of GBs, 2) adult patients (>18 years), 3) studies including >5 patients, and 4) studies published in an English peer-reviewed journal, which have extractable quantitative data on OS, PFS, seizure outcome, and complications. On the contrary, we excluded studies reporting on 1) pediatric population, 2) low-grade gliomas, 3) single-arm and/or underpowered studies (<5 patients), and 4) studies with irrelevant design (Table 1).

2.4. Data extraction

Each study was identified by the name of the first author and the year of publication. For our meta-analysis, we extracted the following data: 1) baseline characteristics of each study, including the mean patient age, comparison arms along with the number of patients in each arm, reported outcome, and length of follow-up and, 2) quantitative data regarding the outcomes of interest (counts in discrete outcomes and mean values along with standard deviation for continuous measures). The outcomes of interest corresponded to the study queries including OS, PFS, performance status, seizure control, and complications after glioma surgery.

2.5. Risk of bias assessment

We used the Newcastle-Ottawa Scale (NOS) to identify potential sources of bias in the eligible studies regarding selection, response, follow-up, misclassification biases, and potential biases in the outcome assessment, outcome measurement, and data analysis (Stang, 2010). In addition, the quality of evidence of our output results was estimated using the GRADE approach. The GRADE approach takes into consideration the risk of bias in individual studies, inconsistency, indirectness, imprecision, and publication bias for stratifying the quality of the body of evidence as “high”, “moderate”, “low”, or “very low” (Brożek et al., 2009).

2.6. Evidence synthesis

We summarized our evidence for each query using a pairwise meta-analysis if only two comparators were available, or a network meta-analysis if otherwise. In the absence of quantitative data, we summarized our evidence using a narrative review. If less than two studies were available for a query, we proceeded with a narrative evidence synthesis. The meta-analysis estimates were reported in absolute and relative estimates, along with the 95% confidence interval (CI) for pairwise comparisons or the 95% credibility interval (CrI) for network meta-analysis, using random effects models. The pooled estimates were odds ratio (OR) for discrete parameters, hazard rate (HR) for time-to-event parameters, and mean difference for continuous outcomes. The results were visualized in absolute and comparison forest plots. In paired comparison, the publication bias was assessed by eyeballing the funnel plots. Additionally, we employed Egger’s regression test only if more than 10 studies available. To validate our findings, we performed a sensitivity analysis by re-running our analysis, having excluded low-quality studies (NOS<7). Finally, we estimated the rank probabilities for the best treatment using the probability curves of the surface under the cumulative ranking curve (SUCRA) values. All statistical analyses were executed using the R statistical environment.

3. Results

3.1. Literature search

According to the search strategy noted above, we found 443 results from PubMed, 243 results from Scopus, and 132 articles from the Web of Science (Fig. 1). After removing duplicates, we reviewed 534 articles for relevance of the study title, abstracts, and full texts and ultimately excluded 522 studies. The remaining five articles formed the basis of our meta-analysis. We included one additional article after searching the reference list for potentially relevant studies. The gathered studies provide quantitative data on OS (n = 4), PFS (n = 3), KPS (n = 3), seizure

Table 1
Our systematic search strategy based on the PICO criteria.

Frame	Keywords	Search	Inclusion criteria	Exclusion Criteria	Sources
Patients	# 1. "glioma" OR "glioblastoma" OR "glial tumor"	#1 AND #2	"RCTs" OR "observational studies" OR "case series" OR "propensity-score matched studies" about glioma type of resection and providing data on survival, progression free survival, seizures Published in peer-reviewed journals Case reports or case series with more than five patients English language Adults	Studies not reporting on glioma resection Studies on pediatric population Studies solely reporting on other types of CNS tumors (e.g., spinal trauma) Case reports or case series with less than five patients Non-English Irrelevant title or abstract Irrelevant full text Study design other than RCTs/ observational studies/case series, including editorials, reviews (included systematic reviews), letters to the Editor, meta-analyses, original studies, experimental non-human studies	Databases (PubMed, Scopus, Web of Science) Reference list of the retrieved records
Intervention	#2. "lobectomy" OR "anatomical resection"				
Comparator	Other techniques ("gross total resection", "supra total resection", "supramarginal resection", "subtotal resection", "biopsy"				
Outcome	"Overall survival", "progression free survival"				
Study design	"RCTs" OR "observational studies" OR "case series" OR "propensity-score matched studies"				
Time	Search period: From January 2013 to April 2023				

PICO, patients/intervention/comparator/outcome; KPS, Karnofsky Performance Status.

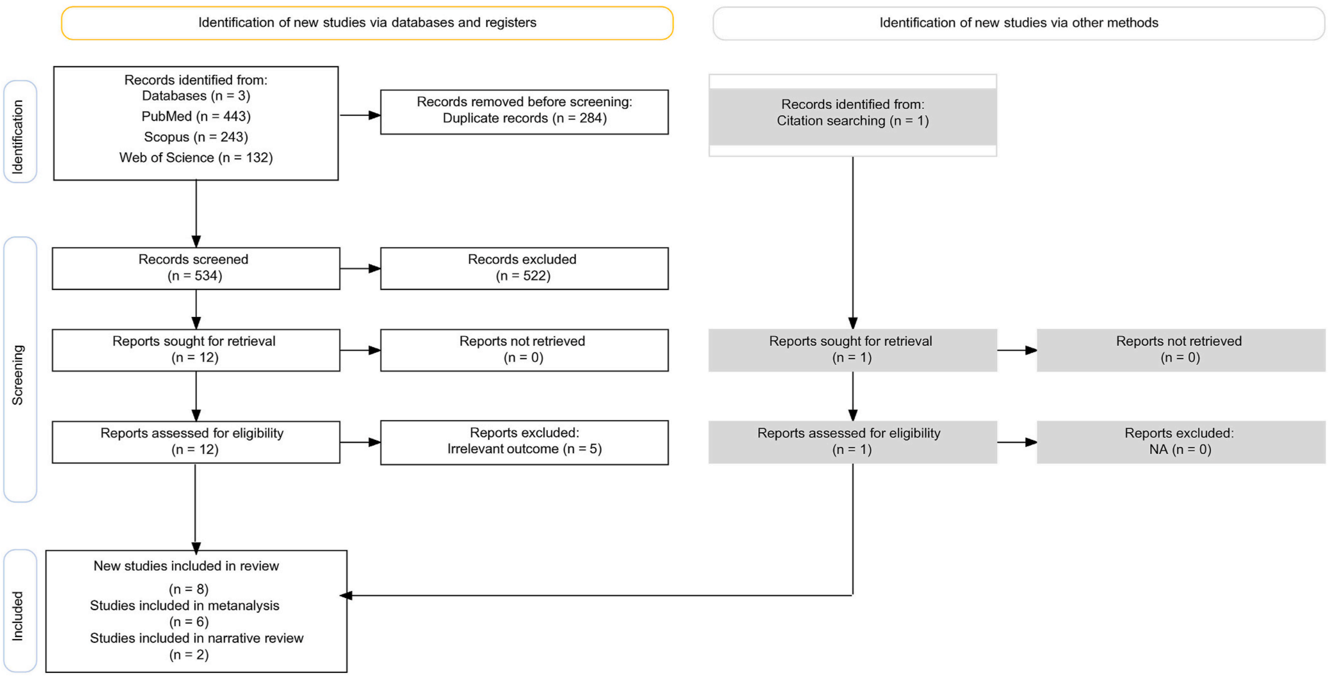

Fig. 1. Our current study's flowchart depicting that out of total of 818 articles, only six fulfilled our eligibility criteria and formed the basis of our meta-analysis.

Table 2
Basic characteristics of the eligible studies in our systematic review and meta-analysis.

	Country	Study design	Sample size	Age (Years)	Comparison	Outcome	Follow-up (months)
Hamada et al. (2016) (Hamada et al., 2016)	Egypt	PCoh	59	48 (±15)[a]	Lobectomy vs. GTR vs. STR vs. biopsy	OS	NR
Roh et al. *(2019)* (Roh et al., 2020)	Korea	RCoh	49	61.5 (34–75) *	Lobectomy vs. GTR	PFS, OS, and KPS	46
Schneider et al. (2019) (Schneider et al., 2019)	Germany	RCoh	38	68 (±8)[a]	Lobectomy vs. GTR	PFS and OS	12
Schneider et al. (2020) (Schneider et al., 2020)	Germany	RCoh	61	64 (54–73) *	Lobectomy vs. GTR	Complications, KPS, operation time, length of stay	NR
Shah et al. (2020) (Shah et al., 2020)	USA	RCoh	69	63 (±13)[a]	Lobectomy vs. GTR	PFS, OS, complications, seizure incidence and KPS	14
Borger et al. (2021) (Borger et al., 2021)	Germany	RCoh	33	59 (±14)[a]	Lobectomy vs. GTR	Seizure control	12

PCoh, prospective cohort study; RCoh, retrospective cohort study; GTR, gross total resection; PFS, progression free survival; OS, overall survival; KPS, Karnofsky performance status; STR, subtotal resection; NR, not reported.

[a] Values in mean and standard deviation; *, values in median and range.

control (n = 2), operation time (n = 1), and length of stay (n = 1). Our narrative review included two additional studies.

3.2. Eligible studies

Six studies fulfilled our eligibility criteria and were used in evidence synthesis (Table 2) (Hamada et al., 2016; Roh et al., 2020; Schneider et al., 2019, 2020; Shah et al., 2020; Borger et al., 2021). All studies were published between 2016 and 2021. Germany was the most productive country with three studies (Schneider et al., 2019, 2020; Borger et al., 2021), followed by Egypt (one study) (Hamada et al., 2016), Korea (one study) (Roh et al., 2020), and the USA (one study) (Shah et al., 2020). The sample size ranged between 33 and 69 patients, and their mean patient age ranged from 48 to 68 years. Lobectomy and GTR were the main comparators in all studies, whereas the study by Hamada and Abou-Zeid included two additional arms for STR and biopsy (Hamada et al., 2016). Finally, the follow-up time was reported in four studies and ranged from 12 to 46 months.

3.3. Risk of bias

The studies' quality in our meta-analysis ranged from 6 to 9 according to the NOS (Table 3). The study by Hamada and Abou-Zeid demonstrated the lowest score as it failed to ascertain the type of intervention and the comparability of the study groups (Hamada et al., 2016). Of note, we contacted by e-mail the authors of this study for clarification but received no response. Due to the low score, we excluded the study by Hamada and Abou-Zeid during the sensitivity analysis. The study by Schneider et al. did not provide direct information on the length of follow-up and scored 8/9 (Schneider et al., 2019). The remaining articles fulfilled all the criteria for proper reporting of cohort studies.

The quality of the available evidence was graded as "high-quality" for the OS, "moderate quality" for PFS, "low quality" for the operation time, length of stay, complication rate and performance status, and "very low quality" for seizure control (Table 4).

3.3.1. Overall survival (Q1)

Four studies with 194 patients reported on the OS regarding four interventions (lobectomy, GTR, STR, and biopsy) (Hamada et al., 2016; Roh et al., 2020; Schneider et al., 2019; Shah et al., 2020), and the relevant network is visualized in Fig. 2. The mean OS was 25 months (95%CI 15.43–34.57 months, $I^2 = 71\%$, N = 4) for lobectomy, 13.72 months (95%CI 10.36–17.08 months, $I^2 = 61\%$, N = 4) for GTR, 7.30 months (95%CI 5.79–8.81 months, I^2=NA, N = 1) for STR, and 4.70 months (95% CI 3.4–6.0 months, I^2=NA, N = 1) for biopsy (Fig. 3). Lobectomy resulted in a prolonged OS in comparison to GTR (10.99 months, 95% CrI: 2.79–19.19 months), STR (12.79 months, 95%CrI: 1.59–23.99 months), and biopsy (15.39 months, 95% CrI: 4.21–26.56 months) (Fig. 4). In other words, lobectomy had the highest probability to achieve maximal overall survival after surgery, followed by GTR, and STR (Fig. 5). According to the sensitivity analysis, and after excluding the study by Hamada and Abou-Zeid, our results were robust. Indeed, lobectomy achieved the longest survival (30.33 months; 95% CI 17.74–42.92 months, N = 3, $I^2 = 52\%$) in comparison to GTR (14.63 months; 95% CI 9.51–19.75, N = 3, $I^2 = 66\%$), with a mean difference of 14.7 months (95% CI 7–22.41 months, N = 3, $I^2 = 0\%$) (Table 5 and Suppl Figs. 1–3). Lastly, one study compared lobectomy to GTR using HR, showing, once again, prolonged survival among patients undergoing lobectomy (HR 0.079; 95% CI 0.014–0.447) (Roh et al., 2020). The impact of other factors such as patient's age, pre-operative KPS, tumor's molecular profiling, tumor's location, tumor's volume and post-resection cavity volumes, intra-operative administration of 5-aminolevulinic acid (5-ALA), operative time, and administration of adjuvant therapy was also examined in a few of the included studies. Our results are summarized in Table 6.

Table 3
Reporting clarity of the included studies using NOS.

Study	Selection				Comparability		Outcome			Total
	Representati- veness of the intervention cohort	Selection of the non -intervention cohort	Ascertainment of intervention	Demonstration that outcome of interest was not present at start of the study	Comparability of cohorts on the basis of the design or analysis	Additional factors	Assessment of outcome	Sufficient follow-up	Adequacy of follow-up	
Hamada et al. (2016) (Hamada et al., 2016)	*	*	0	*	0	0	*	*	*	6/9
Roh et al. *(2019)* (Roh et al., 2020)	*	*	*	*	*	*	*	*	*	9/9
Schneider et al. (2019) (Schneider et al., 2019)	*	*	*	*	*	*	*	0	*	8/9
Schneider et al. (2020) (Schneider et al., 2020)	*	*	*	*	*	*	*	*	*	9/9
Shah et al. (2020) (Shah et al., 2020)	*	*	*	*	*	*	*	*	*	9/9
Borger et al. (2021) (Borger et al., 2021)	*	*	*	*	*	*	*	*	*	9/9

Table 4
GRADE of the Evidence table.

Parameter	Starting Grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Magnitude of effect	Dose response	Confounding factors	Final grade	Quality of evidence
Overall survival	2	0	0	0	0	NA	+1	0	+1	4	⊕⊕⊕⊕
Progression-free survival	2	0	0	0	0	NA	+1	0	0	3	⊕⊕⊕
Seizure outcome	2	0	−1	0	0	NA	0	0	0	1	Å
Procedural duration	2	0	0	0	0	NA	0	0	0	2	ÅÅ
Length of stay	2	0	0	0	0	NA	0	0	0	2	ÅÅ
Complications	2	0	0	0	0	NA	0	0	0	2	ÅÅ
KPS	2	0	0	0	0	NA	0	0	0		ÅÅ

KPS, Karnofsky Performance Status.
NA, not available.
⊕⊕⊕⊕, high-quality evidence.
⊕⊕⊕, moderate-quality evidence.
ÅÅ, low-quality evidence.
Å, very low-quality evidence.

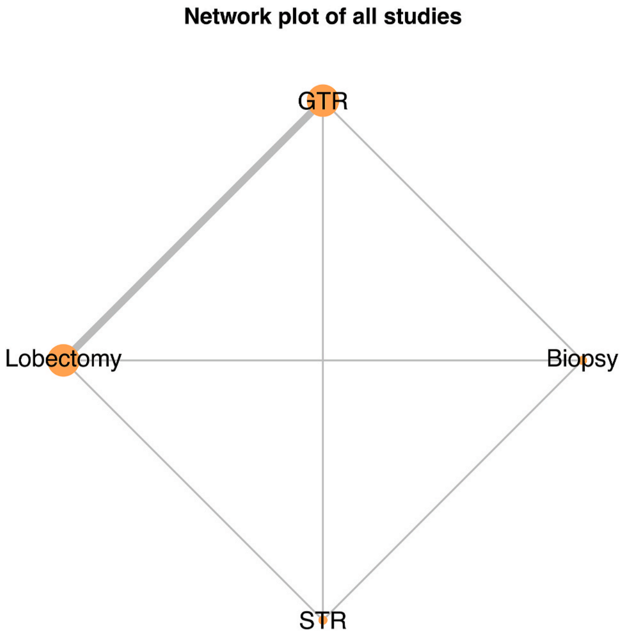

Fig. 2. Four studies provided data on OS comparing four different approaches: lobectomy, GTR, STR, and biopsy. This Network plot shows the interconnections between these four approaches, demonstrating that most of the data concerned comparison between lobectomy and GTR.

3.3.2. *Progression-free survival (Q2)*

Three studies compared lobectomy to GTR regarding PFS (Roh et al., 2020; Schneider et al., 2019; Shah et al., 2020). The mean PFS in lobectomy and GTR was 16.13 months (95% CI 10.84–21.42 months, $I^2 = 0\%$, $N = 3$) and 8.77 months (95% CI 6.41–11.13 months, $I^2 = 68\%$, $N = 3$), respectively (Figs. 6 and 7). A paired meta-analysis estimated the mean difference between the two treatment modalities to 8.77 months (95% CI 3.17–14.38 months, $I^2 = 20\%$) in favor of lobectomy (Fig. 8). The funnel plot of the meta-analysis is depicted in Fig. 9.

3.3.3. *Seizure outcome (Q3)*

Three studies with dissimilar data, compared lobectomy to GTR regarding seizure control with conflicting results (Schneider et al., 2020; Shah et al., 2020; Borger et al., 2021). Borger et al., reported that in series of 13 patients undergoing lobectomy, all patients achieved a favorable seizure outcome (ILAE I). On the other hand, from the 20 patients who underwent GTR, only 10 (50%) achieved a favorable seizure outcome (OR 27; 95% CI 1.4–515.9) (Borger et al., 2021). Notably, all tumors were in the temporal lobe, and there were no differences between the two study arms in terms of patients' age, gender, tumor location, and methylation status (Borger et al., 2021). On the contrary, Shah et al., after studying 32 patients with lobectomy and 37 patients undergoing GTR, reported no difference in seizure control rate (2.7% vs 3.1%, $p = 1.00$) (Shah et al., 2020).

3.3.4. *Operation time (Q4)*

One article compared the operative time required for ATL and GTR (Schneider et al., 2020). Due to the small number of available studies, we preferred to report our results narratively. According to Schneider et al., there was no difference ($p = 0.9$) in the operative time between ATL (270 min, ±97 min), and GTR (268 min, ±67 min) (Schneider et al., 2020).

3.3.5. *Length of stay (Q5)*

One article compared the length of stayin patients undergoing anterior temporal lobectomy (ATL) and GTR (Schneider et al., 2020). The mean hospital stay after ATL and GTR was 14 days (±7 days) and 15 days (±8 days) respectively, without any significant difference ($p = 0.6$) between the two (Schneider et al., 2020).

3.3.6. *Complications (Q6)*

Two studies reported on postoperative complications with similar results (Schneider et al., 2019; Shah et al., 2020). Due to the small number of studies, we prefer to report our results in a narrative review rather than performing a quantitative evidence synthesis. Shah et al. reported three postoperative complications after lobectomy (9.4%), including one case with postoperative meningitis, one case with postoperative seizures, and one case with cerebrospinal fluid leak (Shah et al., 2020). At the same time, the authors reported one patient with deep venous thrombosis and another one with postoperative seizures after GTR, with the complication rate reaching as high as 5.4% (Shah et al., 2020). However, the difference between the two surgical approaches in the complication rate was insignificant ($p = 0.657$) (Shah et al., 2020). Likewise, in another study, Schneider et al. reported the complication rates after ATL ($N = 20$) and GTR ($N = 41$) for temporal lobe GBs (Schneider et al., 2019). The authors identified no difference in the incidence of patient safety indicators (lobectomy 3 vs GTR 7, $p = 0.7$), hospital-acquired conditions (lobectomy 1 vs GTR 1, $p = 1.0$), and surgery-related complications (lobectomy 1 vs GTR 1, $p = 1.0$) (Schneider et al., 2019).

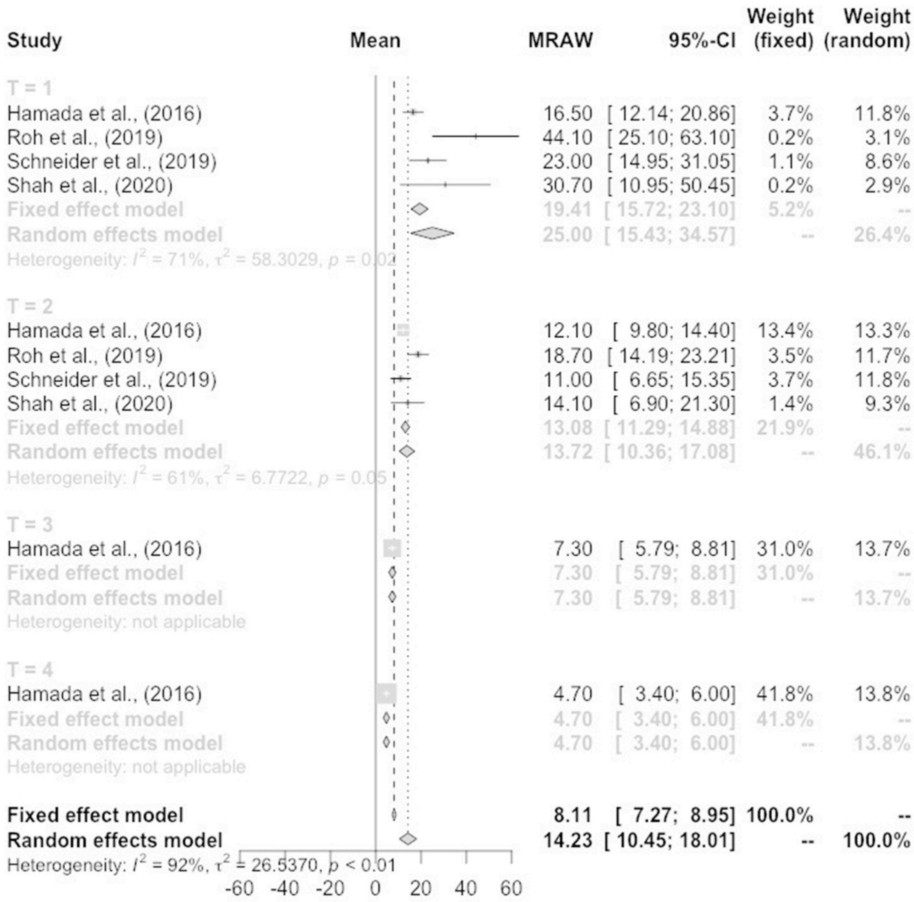

Fig. 3. In the four studies providing data regarding lobectomy and GTR, mean OS was 25 (95%CI 15.43–34.57) and 13.72 months (95%CI 10.36–17.08), respectively. One study provided data on STR, and biopsy, in which the mean OS achieved was 7.30 (95%CI 5.79–8.81) and 4.70 months (95%CI 3.4–6.0), respectively.

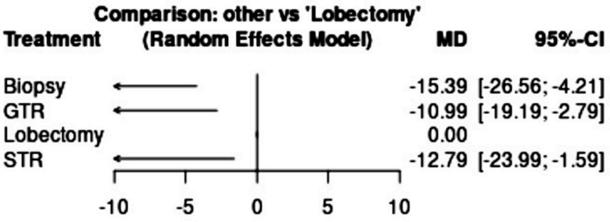

Fig. 4. When compared to other approaches, lobectomy prolongs OS by 10.99 months (95% CrI: 2.79–19.19) compared to GTR, 12.79 months (95% CrI: 1.59–23.99) compared to STR, and 15.39 months (95% CrI: 4.21–26.56), compared to biopsy.

3.3.7. KPS (Q7)

Three studies reported on the postoperative performance status (Roh et al., 2020; Schneider et al., 2020; Shah et al., 2020). Due to the small number of studies and inconsistent outcome reporting, we prefer to report our results narratively. Roh et al. compared the outcomes after lobectomy (20 patients) and GTR (20 patients) for GB patients in a retrospective cohort study (Roh et al., 2020). The functional status was similar in both groups, with a mean KPS of 80 (range 40–100) for lobectomy, and 80 (40–100) for GTR (Roh et al., 2020). In another study, Shah et al. found no difference between lobectomy and GTR at the last follow-up (mean KPS, 80 vs. 80, $p = 0.829$) (Shah et al., 2020). However, Schneider et al. compared 24 patients undergoing GTR to 14 patients after TL in terms of KPS. The authors reported that TL (KPS 80, 95% CI 60–90) was associated with a superior performance outcome ($p = 0.04$) to GTR (KPS 60, 95% 0–80) at the 12-months follow-up (26).

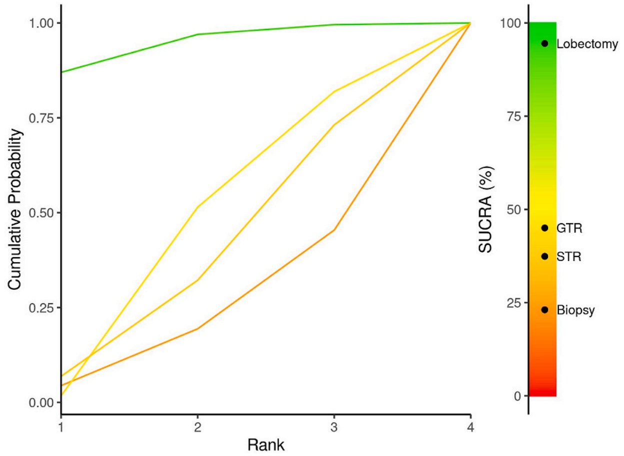

Fig. 5. Patients undergoing lobectomy have the highest probability to achieve maximal OS, followed by patients undergoing GTR, STR, and biopsy in decreasing order.

There are two more studies, which even though they were not included in our meta-analysis due to their heterogeneous data, they were included in our narrative review. Hollerhage et al. (1991), in a clinical series employing lobectomy in the management of GB patients, reported the possible benefit of a lobectomy in GB patients. Precisely, the median OS of patients undergoing total removal of the tumor along with a lobectomy was 10.4 months. On the other hand, the median OS of patients undergoing total tumor removal without a lobectomy was 8.6

Table 5
Summary of the evidence table on the comparison of lobectomy vs GTR in managing malignant GBs.

	GRADE	K	Lobectomy (N1)/ GTR (N2)	Pooled mean for lobectomy (95% CI)	Pooled mean for GTR (95% CI)	Mean difference (95% CI)	Heterogeneity (I^2, %)	Publication bias (Begg's test, p)
Overall survival (months)	⊕⊕⊕⊕	3	66/81	30.33 (17.74–42.92)	14.63 (9.51–19.75)	14.7 (7–22.41)[a]	0	NA#
Progression-free survival (months)	⊕⊕⊕	3	66/81	8.77 (6.41–11.13)	6.13 (10.84–21.42)	8.77 (3.17–14.38)[a]	0	NA#

MD, mean difference; NA, not applicable.
#, k >10.
[a] Statistical significant result.

months, in their series (Hollerhage et al., 1991). Likewise, Teyateeti et al., included in their series patients with grade II-IV temporal gliomas, undergoing either partial or complete temporal lobectomy. As partial temporal lobectomy was defined a wide tumor resection plus a tumor surrounding zone of normal appearing brain parenchyma, while total lobectomy included also the mesial temporal structures. The median PFS for complete temporal lobectomy and partial temporal lobectomy cohorts were 15.5 and 10.8 months, respectively. This difference in their study reached no statistical significance ($p = 0.627$). Respectively the median OS for complete and partial temporal lobectomy was 19.5 and 19.0 months ($p = 0.425$) (Teyateeti et al., 2020).

4. Discussion

Extent of resection and its impingement in GB patients is currently of great interest. So far bibliography agrees that maximal EoR is associated with increased OS and even more interestingly, that applies regardless of the GB's molecular subtype (Baik et al., 2023; Figueroa et al., 2020; Molinaro et al., 2020; Zheng et al., 2023). Moreover, frontal, temporal, and occipital GB cases constitute approximately 70–75% of the total number of GBs and are therefore potentially amenable to lobectomy (Bohn et al., 2018; Larjavaara et al., 2007). However, it has to be emphasized that not all patients with frontal, temporal, or occipital GB are candidates for undergoing lobectomy. There are additional factors affecting this choice, reducing significantly the final number of lobectomy candidates. Such factors include but are not limited to the anatomic location of the tumor in non-eloquent areas, the absence of subependymal infiltration, the confinement of the tumor to a single lobe, as well as the absence of tumor infiltration of the corpus callosum in the preoperative imaging studies. Moreover, the exact role of lobectomy in the cases of temporal and frontal lobe infiltration for decompressing purposes, relieving the increased intracranial pressure, and providing enough space for the upcoming adjuvant radiation therapy remains to be examined. Characteristically, Schneider et al., 2019, 2020, and Borger et al. (2021), performed temporal lobectomy only when the temporal GB was confined within a margin of 4–5 cm from the temporal pole in the dominant, and within 5–6 cm in the non-dominant hemisphere. Respectively, Roh et al. (2020), employed lobectomy only in patients with nondominant frontal and temporal GBs, while Shah et al. (2020), performed lobectomy only in GB cases of non-dominant frontal/temporal/occipital or dominant occipital lobes. The aim of this study is to compare lobectomy to other surgical approaches, regarding primarily OS and PFS and secondarily KPS, seizure outcome, operation time, length of stay, and complications.

In our meta-analysis, the mean OS was 25 months for lobectomy, and 13.72 months for GTR, while PFS in lobectomy and GTR was 16.13 months and 8.77 months, respectively. Our results are similar to the data of the current bibliography (Baik et al., 2023; Hamada et al., 2016; Roh et al., 2020; Schneider et al., 2020; Shah et al., 2020; Hollerhage et al., 1991). Schneider et al. report in their study an OS of 23 months, in their lobectomy group compared to the significant difference of 11 months in the GTR group (Schneider et al., 2019). Even more compelling are the results of Roh et al., who report that the lobectomy group had a median OS of 44.1 months, which was significantly longer than the 18.7 months of the GTR group (Roh et al., 2020). Interestingly, the first report of the advantage of lobectomy over less radical resections in OS was published by Hollerhage et al., back in 1991 (Hollerhage et al., 1991). The only study that does not report any significant differences between the partial temporal lobectomy group and the complete temporal lobectomy group, regarding OS and PFS is by Teyateeti et al. (2020). As mentioned before though, this study was not included in our meta-analysis, since they provided a quite heterogeneous study population, with mixed pathologies.

The reasoning for performing a lobectomy is supported by the theory that anatomical surgical resection offers the best possibility of survival, through maximal cytoreduction and brain decompression (Youngblood et al., 2021; Yool et al., 2020). Moreover, the EoR should surpass the radiological abnormalities, since there is evidence that infiltrative neoplastic cells extended 3.5–5 cm beyond the observed boundaries of the tumor on FLAIR images (Pc et al., 1988). However, even though cytoreduction has been considered the primary aim, there are studies supporting that tumor resection also induces tumor-promoting activation of the tumor microenvironment. It has been postulated that resection directly promotes GB stem cell propagation and through increased hypoxia in the postoperative microenvironment, potentially decreases the efficacy of adjuvant therapies, such as radiotherapy and chemotherapy (Waqar et al., 2022; Knudsen et al., 2021). In other words, the remaining tumor cells in and/or adjacently to the resection cavity, become rapidly reactive and lead to tumor recurrence (Knudsen et al., 2021). It is possible that a complete anatomical, subpial resection minimizes the number of remaining tumor cells, creates no resection cavity, and thus reduces this rapid tumor cell self-renewal. These findings of the potential role of reactive post-surgical microenvironment could dictate novel treatment strategies such as neoadjuvant therapies and more direct and targeted adjuvant therapies (Waqar et al., 2022).

Regarding secondary outcomes such as KPS, seizure incidence, operation time, length of stay, and complications, reports are scarce. Two of the three studies, which provided data on KPS pre- and post-operatively, agree that there are no significant differences between lobectomy and GTR (Roh et al., 2020; Shah et al., 2020). These results, agree with the pertinent literature, which supports that EoR does not affect postoperative KPS (Eyüpoglu et al., 2016; Esquenazi et al., 2017; Baik et al., 2023; Figueroa et al., 2020). However, Schneider et al. reported superior postoperative KPS on lobectomy patients comparing to GTR patients at 12 months follow-up (KPS 80 vs. KPS 60, $p = 0.04$) (Schneider et al., 2020). Regarding the occurrence of intraoperative or postoperative lobectomy complications in GB cases there are no solid data provided in the literature. However, temporal lobectomy has been employed in the management of patients with drug-resistant epilepsy for many decades, and there is a significant body of data provided by the pertinent literature. Although the difference in the underlying pathology may cause significant differences in the incidence of peri-procedural complications, the already described potential procedure associated complications need to be seriously taken into consideration. Notably, postoperative mortality after temporal lobectomy has been estimated to be as high as 1%, with postoperative cumulative morbidity reaching up to 17% (Brotis et al., 2019). Reported complications encompass infections, hematomas, hydrocephalus, hemiparesis, language deficits,

Table 6
Summary and comparison of prognostic factors in eligible studies in our meta-analysis.

	Age	KPS	Molecular profiling	Postoperative adjuvant therapy	Length of stay	Operative time	Mesial structures resection	Tumor's location	Tumor's volume and post-resection cavity volume	5-ALA administration
Hamada et al., 2016 (Hamada et al., 2016)	Median 48.57 ± 15.32	5 patients had KPS<70%	NR	NR	NR	NR	NR	NR	NR	NR
Roh et al., 2019 (Roh et al., 2020)	Median 61.5 years	Mean 75%–80%	MGMT, IDH	NR	NR	NR	Temporal lobectomy plus amygdalohippocampectomy	Non dominant frontal or temporal lobe	Yes	Yes
Schneider et al., 2019 (Schneider et al., 2019)	Median 63 ± 9 (for temporal GTR) and 68 ± 8 (for temporal lobectomy)	>70% for the majority of the patients	MGMT, IDH	Yes (chemotherapy and radiotherapy)	NR	NR	NR	Temporal lobe	Yes	NR
Schneider et al., 2020 (Schneider et al., 2020)	Median 61 ± 12 years (for temporal lobectomy) 63 ± 12 years (for temporal gross total resection)	>70% for the majority of the patients	MGMT, IDH	NR	14 ± 7 (for temporal lobectomy) 15 ± 8 (for temporal gross total resection)	270 ± 97 (for temporal lobectomy) 268 ± 67 (for temporal gross total resection)	Temporal lobectomy plus amygdalohippocampectomy	Temporal lobe	NR	NR
Shah et al., 2020 (Shah et al., 2020)	Median 64 years	80% for temporal lobectomy 90% for temporal gross total resection	MGMT, IDH	Postoperative chemoradiation with temozolomide	NR	NR	Temporal lobectomy plus amygdalohippocampectomy	Temporal and occipital lobes	NR	NR
Borger et al., 2021 (Borger et al., 2021)	Median 59 ± 14 years	Median score 90	MGMT, IDH	Adjuvant treatment consisting of radiotherapy, chemotherapy or combined radiochemotherapy	16 ± 10 (for patients with favorable seizure outcome) 11 ± 7 (for patients with unfavorable seizure outcome)	NR	Temporal lobectomy plus amygdalohippocampectomy	Temporal lobe	NR	Yes

Study	Weight (fixed)	Weight (random)	Mean IV, Fixed + Random, 95% CI
Roh et al., (2019)	4.0%	4.0%	30.70 [4.32; 57.08]
Schneider et al., (2019)	73.2%	73.2%	15.00 [8.82; 21.18]
Shah et al., (2020)	22.8%	22.8%	17.20 [6.11; 28.29]
Total (fixed effect, 95% CI)	**100.0%**	**--**	**16.13 [10.84; 21.42]**
Total (random effects, 95% CI)	**--**	**100.0%**	**16.13 [10.84; 21.42]**

Heterogeneity: Tau^2 = 0; Chi^2 = 1.34, df = 2 (P = 0.51); I^2 = 0%

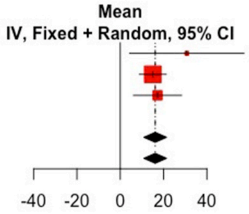

Fig. 6. Three of the examined studies provided data regarding PFS. Lobectomy patients achieved a mean PFS of 16.13 months (95% CI 10.84–21.42).

Study	Weight (fixed)	Weight (random)	Mean IV, Fixed + Random, 95% CI
Roh et al., (2019)	22.3%	29.9%	11.50 [8.80; 14.20]
Schneider et al., (2019)	26.0%	31.7%	7.00 [4.50; 9.50]
Shah et al., (2020)	51.7%	38.4%	8.10 [6.33; 9.87]
Total (fixed effect, 95% CI)	**100.0%**	**--**	**8.57 [7.30; 9.84]**
Total (random effects, 95% CI)	**--**	**100.0%**	**8.77 [6.41; 11.13]**

Heterogeneity: Tau^2 = 2.9621; Chi^2 = 6.31, df = 2 (P = 0.04); I^2 = 68%

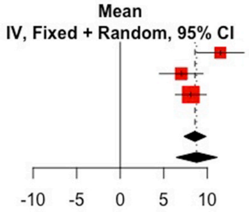

Fig. 7. Three of the overall studies provided data regarding PFS. GTR patients achieved a mean PFS of 8.77 months (95% CI 6.41–11.13).

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (fixed)	Weight (random)	Mean Difference IV, Fixed + Random, 95% CI
Roh et al., (2019)	30.70	60.2000	20	11.50	6.1600	20	4.5%	4.5%	19.20 [-7.32; 45.72]
Schneider et al., (2019)	15.00	11.8000	14	7.00	6.2400	24	70.6%	70.6%	8.00 [1.33; 14.67]
Shah et al., (2020)	17.20	32.0000	32	8.10	5.5000	37	24.9%	24.9%	9.10 [-2.13; 20.33]
Total (fixed effect, 95% CI)			**66**			**81**	**100.0%**	**--**	**8.77 [3.17; 14.38]**
Total (random effects, 95% CI)							**--**	**100.0%**	**8.77 [3.17; 14.38]**

Heterogeneity: Tau^2 = 0; Chi^2 = 0.65, df = 2 (P = 0.72); I^2 = 0%

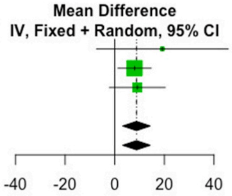

Fig. 8. A paired-meta-analysis was performed for comparing PFS between lobectomy and GTR. Mean difference in PFS between these approaches was 8.77 months (95% CI 3.17–14.38) in favor of lobectomy.

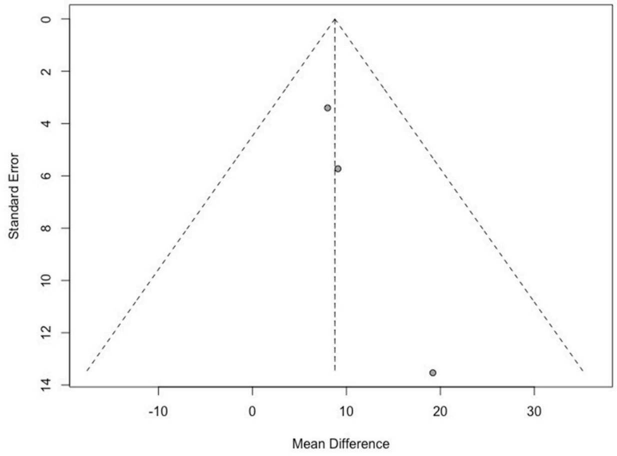

Fig. 9. Funnel plot of our paired meta-analysis. Due to the small number of the eligible studies, it was unclear to establish the presence of publication bias after eyeballing the funnel plot.

visual field defects, cranial nerve deficits, cognitive disorders, psychiatric disorders, and medical complications, such as deep venous thrombosis, pulmonary embolism, pneumonia etc (Brotis et al., 2019). Among the most prevalent complications following anterior temporal lobectomy (ATL) are postoperative cognitive (Popovic et al., 1995; Jayalakshmi et al., 2016; Wiebe et al., 2001) and psychological/-psychiatric disorders (Popovic et al., 1995; Jayalakshmi et al., 2016; Wiebe et al., 2001; Sindou et al., 2005; Grivas et al., 2006), with incidence reaching up to 5% and 7%, respectively. These neurocognitive and/or psychiatric manifestations may represent either novel or exacerbation of pre-existing conditions in epilepsy cases. In GB cases the neurocognitive impact of lobectomy would be of great interest. Additionally, serious complications such as hemiparesis and language disorders have been reported at rates as high as 4% (Popovic et al., 1995; Jayalakshmi et al., 2016; Falowski et al., 2012; Salanova et al., 2002), while symptomatic homonymous quadrantanopia may occur in up to 6% of cases (Engel, 2012; López-González et al., 2011). A meta-analysis conducted by Tebo et al. (2014) highlighted that the majority of postoperative complications included neurological deficits, infections, and hemorrhages, with reported proportions of 19%, 1.4%, and 1.3%, respectively. Other reported complications encompass cranial nerve deficits (especially trochlear nerve) (Jacobson et al., 1995), hydrocephalus and cerebrospinal fluid (CSF)-related disorders, and extra-axial fluid collections (Brotis et al., 2019). Noteworthy is the observed decrease in complication rates over time since early 80s', as indicated by studies conducted by Brotis et al. and Georgiadis et al. (Brotis et al., 2019; Georgiadis et al., 2013). The importance of reporting solid and frank data regarding the incidence of lobectomy-associated complications in GB patients cannot be overemphasized.

Anatomical subpial resection is well known to achieve excellent seizure outcome in patients undergoing epilepsy surgery (Esquenazi et al., 2017; Przybylowski et al., 2021; Hebb et al., 2011; Hussein et al., 2021; Wen et al., 2017). Therefore, it is reasonable to achieve better seizure control in GB patients that undergo lobectomy and subpial resection, compared to GTR. What also needs to be emphasized though, is the importance of resecting the mesial structures in the temporal lobectomy cases for two reasons: 1) minimizing the chance of any postoperative seizure activity, and 2) drastically decompressing the adjacent brainstem. This eliminates the chance of post-treatment uncal herniation, due to adjuvant treatment associated edema development. It has to be noted, that it is crucial for the surgeon to manage gently the exposed vessels (middle cerebral artery in temporal lesions, anterior cerebral and pericallosal arteries in frontal lesions). Maintenance of intact pia, whenever feasible, is of paramount importance for mitigating the chance of vasospasm development postoperatively. In our study, seizure control was only mentioned in three of the included studies. Even though Borger et al. (2021) report that from their 13 patients undergoing lobectomy, all achieved a favorable seizure outcome (ILAE I), whereas from the 20 patients who underwent GTR, only 10 (50%) achieved a favorable seizure outcome, Shah et al. report no significant changes between their two respective groups.

Schneider et al. and Shah et al. were again the only two studies reporting complication data, and they both had similar results between the compared groups. These data also align with the current bibliography, which suggests that the EoR does not play a significant role in the incidence of postoperative complications (Wach et al., 2023; Jackson et al.; Glenn et al., 2018; Hollerhage et al., 1991).

The limited amount of data that we have regarding KPS, length of stay, operation time, and complications depict the need for newer and more complete studies, which will also address these very important matters, that highly affect patient's quality of life. At the same time, there are more issues, which require immediate address such as operative blood loss, incidence of postoperative hematomas in the formed large space after the lobectomy, incidence of postoperative CSF fistulas, hydrocephalus secondary to temporal or frontal horn opening, and feasibility of lobectomy in all GB molecular subtypes. However, the most complex matter to be addressed is the neurocognitive outcome of these patients, and to what extent this radical resection affects it. Therefore, it is imperative that these patients undergo neurocognitive evaluation pre- and postoperatively. After having all these information, surgeons could make an integrated decision on whether lobectomy and its OS is worthwhile.

Additionally, it has to be emphasized that, lobectomy is a highly demanding operation from a technical standpoint, and not all neurosurgeons are properly trained for performing such procedures. Profound anatomical knowledge of the involved areas, mastering of subpial resection technique, and employment of specific instruments such as CUSA are of paramount importance. Therefore, lobectomy cannot be considered as a panacea for GBs and has certain indications, which need to be precisely outlined in the near future. Most of the studies included on our meta-analysis describe their surgical technique for performing a lobectomy. Borger et al. reported that the temporal lobe was removed up to a maximum of 4.5 cm from the temporal pole in the dominant, and 6.5 cm in the non-dominant hemisphere (Borger et al., 2021). Removal of the uncus and the amygdala was performed using a subpial resection technique via Cavitron Ultrasonic Surgical Aspirator (CUSA) or a Penfield dissector (Borger et al., 2021). Then they opened the temporal horn using again a Penfield dissector, and resection of the head and the anterior part of the body of the hippocampus was performed (Borger et al., 2021). Roh et al. described their technique in frontal lobectomy (Roh et al., 2020). Firstly, they removed the tumor under navigation guidance, and subsequently they performed frontal pole resection (Roh et al., 2020). Then, a subpial dissection/resection was performed at the medial, lateral, and inferior surfaces of the frontal lobe, while the surrounding vascular structures and the ipsilateral olfactory nerve were preserved (Roh et al., 2020). The authors stressed out their effort to avoid opening of the ipsilateral frontal horn (Roh et al., 2020). Similarly, Shah et al. described a frontal corticectomy to the anterior skull base and then a subpial dissection laterally to the level of the sylvian fissure and the falx (Shah et al., 2020). They also pointed out their effort to stay rostral to the corpus callosum and to avoid entering the frontal horn. In cases of temporal lobectomy, a similar technique was used with the superior and posterior aspects of the dissection guided by the tumor boundaries (Shah et al., 2020).

4.1. Limitations

The current study has some important limitations. Firstly, the number of the included studies and the reported patients is limited. Secondly, the quality of the available evidence is mostly of low quality. Thirdly, we frequently used a narrative evidence synthesis due to non-comparable data. Fourthly, due to the small number of studies, we were not able to assess the impact of publication bias in our review. Fifthly, the studies that are included in our meta-analysis provide heterogenous data. With future studies, there is a high probability that our current findings might change.

5. Conclusion

Lobectomy for carefully selected GB cases is a current very promising, neuro-oncological surgical strategy, which seems to improve OS almost by a year. However, data regarding the secondary outcome of lobectomy in GBs remain scarce. Further prospective, meticulous, extensive studies, analyzing not only OS and PFS but also parameters such as neurocognitive outcome, seizure incidence, postoperative complications, procedure duration and other procedure-related parameters need to be addressed for defining the exact role of lobectomy in the management of GB patients.

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Declaration of competing interest

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bas.2024.102823.

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