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REVIEW

The impact of intraoperative mapping during re-resection in recurrent gliomas: a systematic review

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Abstract

Purpose Previous evidence suggests that glioma re-resection can be effective in improving clinical outcomes. Furthermore, the use of mapping techniques during surgery has proven beneficial for newly diagnosed glioma patients. However, the effects of these mapping techniques during re-resection are not clear. This systematic review aimed to assess the evidence of using these techniques for recurrent glioma patients.

Methods A systematic search was performed to identify relevant studies. Articles were eligible if they included adult patients with recurrent gliomas (WHO grade 2–4) who underwent re-resection. Study characteristics, application of mapping, and surgical outcome data on survival, patient functioning, and complications were extracted.

Results The literature strategy identified 6372 articles, of which 125 were screened for eligibility. After full-text evaluation, 58 articles were included in this review, comprising 5311 patients with re-resection for glioma. Of these articles, 17% (10/58) reported the use of awake or asleep intraoperative mapping techniques during re-resection. Mapping was applied in 5% (280/5311) of all patients, and awake craniotomy was used in 3% (142/5311) of the patients.

Conclusion Mapping techniques can be used during re-resection, with some evidence that it is useful to improve clinical outcomes. However, there is a lack of high-quality support in the literature for using these techniques. The low number of studies reporting mapping techniques may, next to publication bias, reflect limited application in the recurrent setting. We advocate for future studies to determine their utility in reducing morbidity and increasing extent of resection, similar to their benefits in the primary setting.

Keywords Glioma · Recurrence · Re-resection · Intraoperative mapping · Survival

Introduction

Adult-type diffuse gliomas are the most common primary malignant brain tumors in adults [1]. Maximal safe resection to prolong survival is the mainstay of the treatment in the newly diagnosed setting, with extent of resection (EOR) and residual tumor volume as important prognostic factors [2, 3]. For tumors located in or near functional tissue, maximal safe resection can be challenging. Intraoperative mapping (i.e. electrophysiology) has the potential to achieve a maximal safe resection without causing neurological deterioration by locating important functions such as motor or language function [4, 5]. Compared to general anesthesia without mapping, intraoperative mapping has been demonstrated effective in glioma populations in terms of neurological, functional, cognitive, radiological, and survival outcomes [4, 6–8].

There is some controversy on the standard-of-care in the recurrent setting [9, 10]. Re-resection is one of the possibilities, as are (re-)challenge chemotherapy, (re-)irradiation, targeted therapy (e.g. vorasidenib [11] or dabrafenib/trametinib [12]), recruitment into clinical trials, or best supportive care [2]. Treatment decisions are influenced by several factors including overall performance (Karnofsky Performance Status (KPS) or World Health Organization

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(WHO) functioning scale), tumor location and size, and prior treatment [2]. For glioma WHO grade 2, there is little debate on the importance of maximal safe re-resection [13–15]. Likewise, patients with glioma WHO grade 4 might benefit from re-resection, albeit limited to selected patients on the favorable side of the spectrum [16–19].

Although the surgical goal for recurrent gliomas is often the same as for newly diagnosed tumors, the impact of intraoperative mapping in this recurrent setting is poorly understood. Studies on this topic either failed to stratify between glioma WHO grade 2 and 3–4 [20, 21], included grade 2 tumors that had progressed to grade 3 or 4 [22, 23] or failed to stratify between use/non-use of intraoperative mapping [24–26] This has resulted in mixed results that are hard to interpret. In the absence of solid evidence, it is likely that intraoperative mapping is currently omitted in potentially eligible cases or not seriously considered in some departments. Therefore, to maximize safe re-resection in patients with recurrent glioma WHO grade 2–4, the current lack of evidence and treatment recommendations must be addressed.

This systematic review aimed to investigate the impact of intraoperative mapping during re-resection on survival, neurological, functional and radiological outcomes in patients with recurrent glioma WHO grade 2–4. The results of this review may help neurosurgeons in the delicate process of surgical decision making in these patients.

Methods

Search strategy

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. A computer-aided search of PubMed, Embase, Web of Science, Medline (OvidSP), Cochrane and Google Scholar was performed with the help of the biomedical information specialist to identify relevant studies (*Supplemental S1*). The databases were searched up to August 2023. All identified abstracts were screened on title and abstract by two authors (YS and JKWG). Full-text screening of potentially relevant publications was performed according to predefined criteria (see Study selection). Any discrepancies were resolved by discussion. Reference lists of included articles were screened for additional references to be included.

Study selection

Inclusion criteria for eligible studies were (1) study population consisted of adult patients with recurrent gliomas WHO grade 2–4 who had undergone re-resection, (2) 15 or more participants, and (3) written in English. Exclusion criteria were (1) no stratification between gliomas WHO grade 2 and 3–4, (2) no stratification between awake and asleep craniotomy, (3) secondary malignant progression from WHO grade 2 to grade 3 or 4, and (4) book chapters, case reports, letters to editors, technical reports, review articles.

Quality assessment and risk of bias

The quality of the included articles was evaluated using the Newcastle–Ottawa scale for observational cohort studies [28] by one reviewer (MPvO) and verified by the senior authors (AJPEV, JKWG). The Newcastle–Ottawa score for cohort studies is divided in three domains: selection, comparability and outcome. The selection category consisted of four items: representativeness of the exposed cohort, selection of the non-exposed cohort, and ascertainment of exposure. The comparability category assessed the comparability of cohorts based on the design or analysis. Finally, the outcome category contained three scoring items: assessment of outcome, whether follow-up was long enough for outcomes to occur, and adequacy of follow-up for cohorts. According to this scale, studies were qualified as 'good quality' if they scored 3–4 points in the selection domain, 1–2 points in the comparability domain, and 2–3 points in the outcome/exposure domain. 'Fair quality' comprised studies that scored 2 points in the selection domain, 1–2 points in the comparability domain, and 2–3 points in outcome/exposure domain. Studies were qualified as 'poor quality' if they scored 0–1 point in the selection domain, 0 points in the comparability domain, or 0–1 point in outcome/exposure domain.

Data extraction

Study characteristics that were extracted included study design, number of patients undergoing re-resection, patient demographics, anesthesia technique (awake or asleep), application of intraoperative mapping, WHO classification, pre- and postoperative KPS, EOR, procedure-related complications, postoperative treatment, and survival. Survival was defined as the time between primary diagnosis and death of any cause (overall survival) and the time between re-resection and death of any cause (post-progression survival).

Statistical analysis

Categorical variables were reported as absolute numbers (n) and percentages of the total. Data was stratified for recurrent glioma WHO grade 2–4 and the intraoperative mapping techniques were compared. Medians or percentages for different outcomes were calculated based on the number of patients included in each study or treatment arm. Medians were weighted to control for different sample sizes. P-values of < 0.05 were considered statistically significant.

Results

Search results

The search strategy resulted in 6372 abstracts, of which 6369 remained after removing duplicates. Of these, 6244 articles were excluded during the initial screening based on title and abstract. Of the remaining 125 abstracts that were full-text screened, 58 articles were classified eligible according to the predefined criteria. See Fig. 1 for an overview of the selection process.

Study characteristics

A total of 5311 patients were included in this systematic review. Of the 58 included articles, six articles were of prospective design and 52 articles were of retrospective design. The year of publication ranged from 1981–2023, with the majority (46 [79%] of 58) of the studies published within the last 10 years. Two studies (2 [3%] of 58) included only patients with glioma WHO grade 2 (without progression to grade 3 or 4), 55 studies (55 [95%] of 58) included only patients with glioma WHO grade 3–4 and one study (1 [2%]

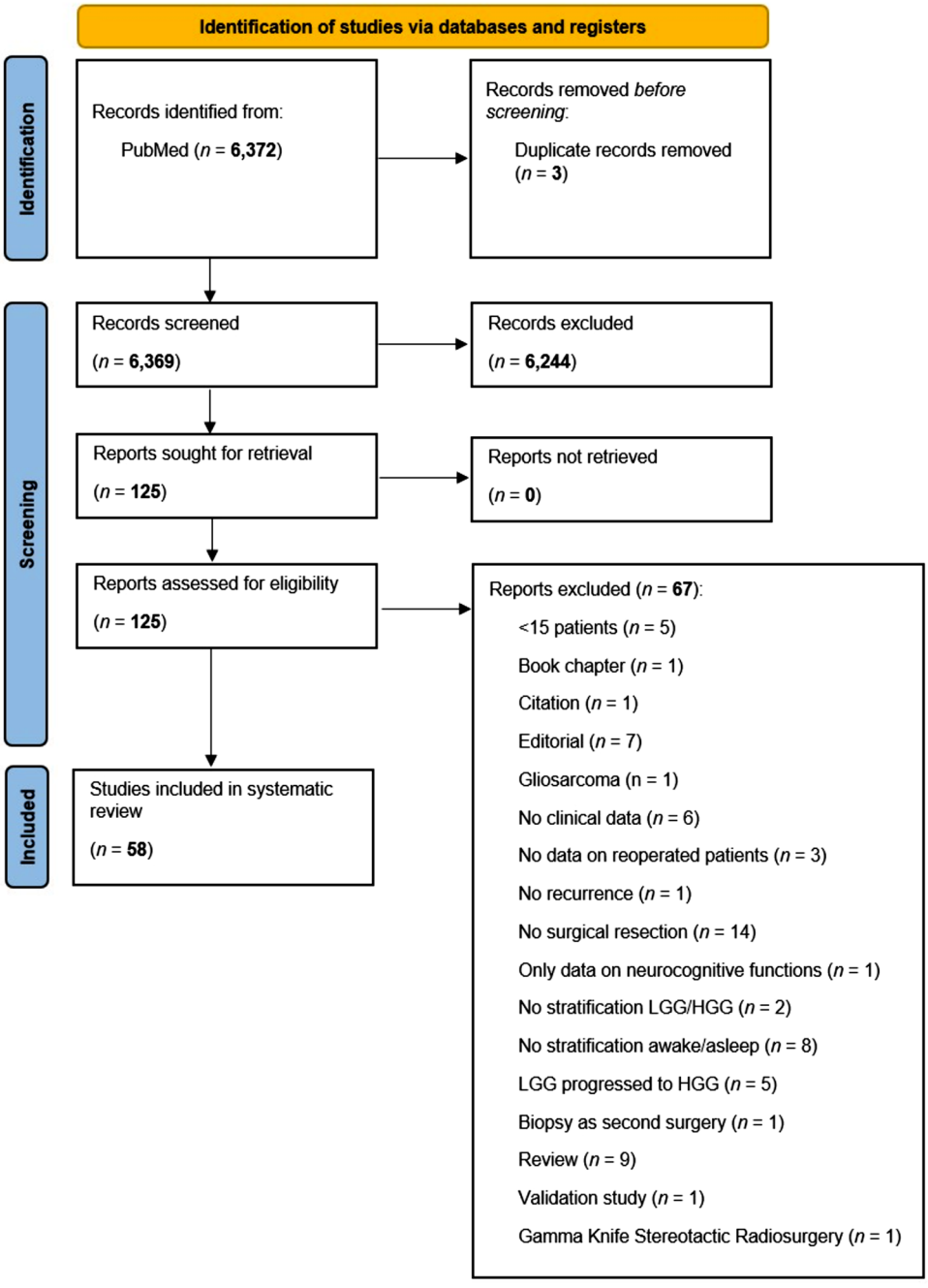

Fig. 1 Schematic breakdown of literature search results. *HGG* high-grade glioma WHO grade 3–4, *LGG* low-grade glioma WHO grade 2

of 58) included both gliomas WHO grade 2 and 3–4. The weighted median age of the patients was 56 years (range 45.5–72), for those studies that reported the median (33 [57%] of 58). The study characteristics of the included studies can be found in Table 1 (Supplemental S2).

General findings on mapping

The first main finding was that only 10 studies (10 [17%] of 58) mentioned whether re-resection had been performed under awake/asleep conditions and/or whether intraoperative mapping techniques had been used [20, 29–37]. All other articles did not provide details on awake/asleep craniotomy and/or mapping technique during re-resection [17, 38–84]. Regarding the anesthesia technique (awake/asleep) used in these 10 studies, two studies included re-resections in which awake craniotomy was used [31, 34], five studies described re-resection under general anesthesia [29, 30, 32, 36, 37], two studies included both awake and asleep re-resections (but did not stratify the outcomes by either awake or asleep) [20, 35], and one study did not specify any awake/asleep approach [33]. On a total of 58 studies, re-resection in an awake setting was performed in 3% (142/5311) of the patients. See Fig. 2 for a schematic overview of studies with information on awake/asleep craniotomy and intraoperative mapping.

The second main finding was that similar to information on awake/asleep conditions, additional information on the use of intraoperative mapping was not routinely included: only six studies described this [20, 31–34, 36]. Overall, out of a total of 58 studies, intraoperative mapping was applied to 5% (280/5311) of the patients. Intraoperative mapping techniques that were described included awake speech mapping, direct cortico-subcortical electrostimulation, and motor-evoked or somatosensory-evoked potentials.

Outcomes for recurrent glioma WHO grade 2

Intraoperative mapping during re-resection for glioma WHO grade 2 was described in three of the six studies, all under awake conditions (Fig. 2) [20, 31, 34]. Although survival outcomes were not reported in these studies, information on the extent of resection was available. The percentage of complete resections was reported in all three studies and ranged from 5% (1/20) in one study on recurrent insular glioma WHO grade 2 [34] to 21% (13/62) in one study that was not limited to tumors in specific locations [31]. The third study found a complete resection rate of 65% (17/26) after awake

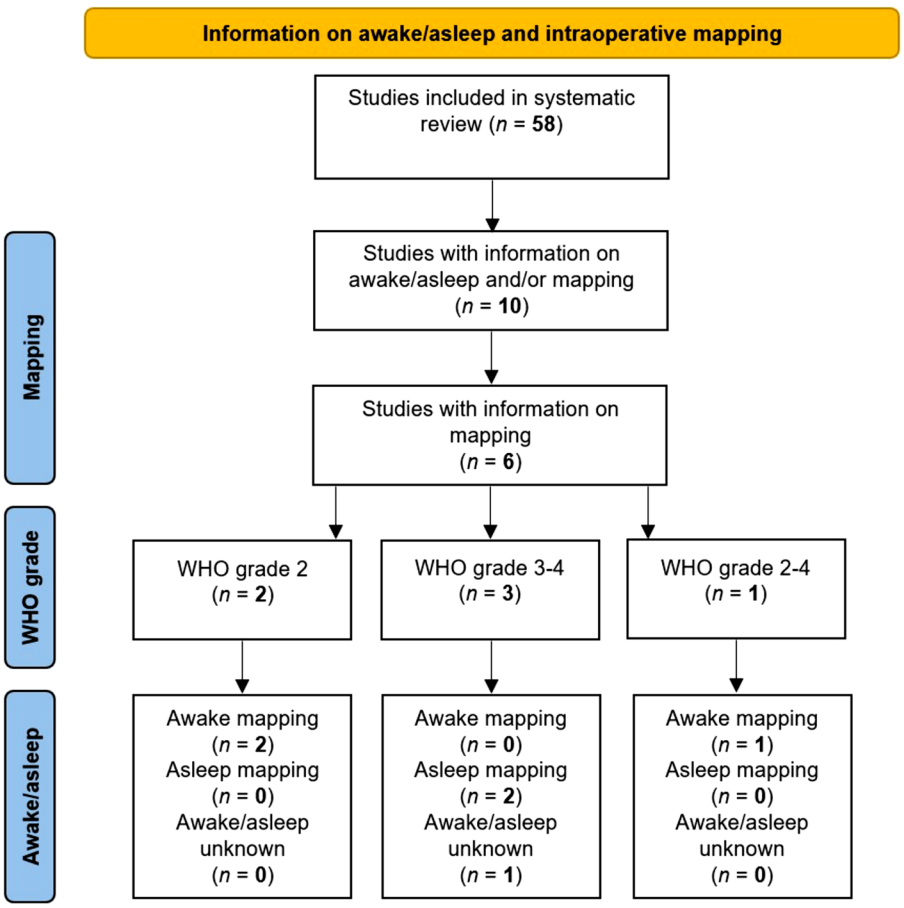

Fig. 2 Schematic breakdown of studies with information on intraoperative mapping

craniotomy with intraoperative mapping but did not stratify between recurrent gliomas WHO grade 2 and 3–4. [20] Only one study mentioned the treatment after mapping-guided re-resection, showing that 95% (59/62) of the patients did not receive postoperative treatment. [31]

Information on the safety of the procedure was available in all three studies. The percentage of perioperative complications (e.g. surgical-site infections or transient neurological deficits) ranged between 4 to 36%, although definitions of complications immediately after surgery differed among the included studies. Focusing on the clinical examination three months postoperatively, 89–100% of the patients recovered from initial postoperative worsening of their neurological condition [31, 34]. The third study, including both patients with recurrent gliomas WHO grade 2 and 3–4, also included a study arm with general anesthesia without intraoperative mapping [20]. This design allowed comparisons in neurological deficits after either awake or asleep craniotomy. One week after re-resection, significantly more neurological deficits were seen in the asleep group compared to the awake group (22% versus 4%, $p=0.032$), but three months postoperatively no significant difference was observed (12% versus 4%, $p=0.231$). [20]

Studies on re-resection for glioma WHO grade 2 using general anesthesia with or without intraoperative mapping were not included in the final selection of this review.

Outcomes for recurrent glioma WHO grade 3, astrocytoma grade 4, and glioblastoma

Intraoperative mapping was mentioned in four studies that focused on patients with recurrent glioma WHO grade 3–4, either during awake craniotomy [20], under general anesthesia [32, 36] or with unknown awake/asleep setting (Fig. 2). [33] Two studies reported the survival after mapping-guided re-resection. The results from both these studies did not show a significant benefit on post-progression survival (PPS) (10.3 months, 95% CI 7.6–10.4 [33], odds ratio 0.9, 95% CI 0.6–1.3 [36]). Complete resection, in this study defined as surgical resection of > 90% of the pre-operative tumor volume, was achieved in 75% (48/64) of the patients [33]. In the same study, new neurological deficits occurred in 13% (8/64) of the patients, but the timing of this observation was not described. Adjuvant treatment after mapping-guided re-resection was also reported by two studies, showing that 74–88% of the patients received postoperative treatment. [33, 36]

In two studies, patients with glioma WHO grade 3–4 were operated in an awake setting although the application of any type of intraoperative mapping was not mentioned [20, 35]. The association between awake/asleep re-resection and survival was investigated in one of these articles which showed no significant difference between awake and asleep re-resection for overall survival (OS) (hazard ratio 1.82, 95% confidence interval 0.99–3.34) or PPS (hazard ratio 1.02, 95% confidence interval 0.58–1.8) [35]. No details were reported in both these studies on the impact of awake craniotomy on postoperative KPS, perioperative complications or postoperative treatment. In contrast to awake craniotomy, the survival after re-resection under general anesthesia was detailed by several studies. When combining these studies, a weighted median OS of 16.9 months (range 16.7–31.0) [30, 32, 36, 37] and a weighted median PPS of 11.0 months (range 5.0–11.0) [29, 30, 36, 37] was observed, although mapping was not taken into account in this analysis. For those studies providing the endpoint GTR, this was achieved in 55% (302/551) of cases [29, 32, 36]. Perioperative complications were summarised for 599 patients, with events, regardless of grade, in 19% (111/599) of the patients. [29, 30, 32, 36, 37]

Quality assessment

The median quality assessment score of the 58 studies was 7 out of 9 with a range of 3–9. The mean score was 6.7 out of 9.0 with a standard deviation of 1.6. Thirty-six percent (21/58) of studies could be classified as 'good quality', 24% (14/58) as 'fair quality', and 40% (23/58) as 'poor quality'. Most studies failed on the representativeness of the exposed cohort (i.e., they selected re-resection candidates only without including a nonsurgical control arm, therefore increasing the risk of selection bias) and/or showed no sufficient comparability (i.e., they did not control for important factors such as age and/or EOR, KPS, time to recurrence, both within and between groups). An overview of the quality assessment per study is shown in Table 2 (Supplemental S3).

Discussion

This systematic review demonstrated that there is a very limited amount of evidence to assess the impact of intraoperative mapping during re-resection for patients with recurrent glioma WHO grade 2–4. A minority of the included articles (10 [17%] of 58) reported the use of awake/asleep craniotomy and/or mapping technique during re-resection, with awake re-resection described in only 3% (142/5311) of the patients. Intraoperative mapping in general was described in a mere 5% (280/5311) of the patients. A possible explanation for this limited number of studies reporting mapping in the recurrent setting could be that few surgeons apply mapping in this setting. Furthermore, factors such as publication bias and inconsistent reporting might play a role. The limited amount of evidence for these mapping techniques is in stark contrast with the situation for patients with newly diagnosed tumors. For these patients, these techniques already have proven to be effective for improving outcomes by increasing extent of resection, decreasing postoperative deficits, and consequently, prolonging survival [4, 6–8]. Although

some reports indicate that these techniques might have the same benefits in the recurrent setting, high-quality evidence is needed to assess this comprehensively.

A first reason for the lack of evidence for intraoperative mapping in the recurrent setting is the low number of cases that have been carried out using these techniques in the literature. We also observed that articles often did not differentiate between glioma WHO grade 2 and grade 3–4, or included patients with glioma WHO grade 2 that had progressed to WHO grade 3 or 4 at the time of re-resection. Moreover, almost all included studies lacked proper stratification: outcomes were not stratified by awake/sleep, use/non-use of intraoperative mapping, or WHO tumor grade. This made a comprehensive evaluation of the prognostic impact of mapping during re-resection difficult.

A second reason for the lack of evidence is the overall low quality of studies. As demonstrated in the quality assessment (Table 2), 17% (10/58) of the included studies did not show comparability of the cohorts on the basis of the design or analysis since they do not control for one or two important factors such as age and/or O6-methylguanine-DNA methyltransferase (MGMT) promotor methylation, EOR, KPS or time to recurrence. Studies also failed on the selection of the exposed cohort (45%, 26/58) since selection bias frequently led to the inclusion of optimal surgical candidates only, which is not representative of the average condition of patients with recurrent glioma WHO grade 2–4.

These limitations of the current evidence illustrate the need for carefully designed high-quality studies. This need is underlined by the fact that currently, international guidelines leave treatment decisions for recurrent glioma WHO grade 3–4 up to individual decision with little to no guidance [2, 85, 86]. As a result, treatment preferences for the use or non-use of intraoperative mapping differ between surgeons and centers, as does the indication for re-resection in general [87]. Importantly, since there is evidence that eloquent areas might have been reorganized at the time of re-resection, the possibility of this 'functional reshaping' may warrant the use of intraoperative mapping during re-resection to achieve maximal safe re-resection [88–90].

Studies should not only apply stratification between different patient subgroups, but factors such as predefined endpoints and adequate power analysis should be considered to generate high-quality evidence. Ideally, these studies are carried out prospectively. Examples are the ongoing RESURGE (NCT02394626) and RECSUR (NCT06283927) studies investigating re-resection versus best supportive care, and the RECMAP study (NCT06273176) investigating the impact of intraoperative mapping during re-resection. However, since a prospective design is not always feasible, retrospectively designed studies should control for selection bias and confounding with techniques such as propensity score matching with multivariate regression or stratification of subgroups and outcomes.

Limitations

This systematic review has some limitations. First, several outcome variables were not comparable between the articles included in this study. For instance, the definition of GTR varied and the KPS was either on a continuous scale or categorized, making comparisons difficult. Another limitation is the large percentage of retrospective studies and the small percentage of studies focusing on recurrent glioma WHO grade 2. Third, the included studies did often not explain their indication setting for using mapping techniques. The results, therefore, have to be interpreted with caution since we were not able to assess the presence of selection bias in our congregate results.

Conclusions

Previous studies indicate that re-resection of recurrent tumors may improve clinical outcomes for glioma patients. Furthermore, mapping techniques have been proven to be effective in increasing extent of resection while decreasing postoperative deficits in newly diagnosed tumors. In this systematic review, we investigated the effect of these mapping techniques when used during resection for recurrent tumors. We hypothesized that these mapping techniques can be beneficial as well in the recurrent setting to make the surgery safer and more extensive. However, there was insufficient evidence to adequately assess the comprehensive impact of these techniques during re-resection on neurological, functional, radiological and survival outcomes in recurrent glioma patients. This lack of high-quality evidence may have been caused by the relatively low number of surgeons currently using it, and the overall low quality of studies included in this review. We are concerned that the current lack of strong evidence for, and the reluctance to use these techniques in daily practice may cause a vicious circle, while their potential benefits remain unknown. We advocate, therefore, for well-designed studies to comprehensively determine their potential utility in reducing morbidity and increasing extent of resection, similar to their benefits in the primary setting. The results from these studies could improve the indication setting for these techniques and consequently, the clinical outcomes for recurrent glioma patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11060-024-04874-1.

Author contributions MPvO, YS, AJPEV and JKWG contributed to the study conception and design. Material preparation, data collection and analysis were performed by MPvO, YS, MED, AJPEV and JKWG. The first draft of the manuscript was written by MPvO and all authors commented on previous versions of the manuscript. Supervision was provided by AJPEV and JKWG. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflicts of interest The authors have not disclosed any competing interests.

References

1. Ostrom QT, Gittleman H, Liao P et al (2017) CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. Neuro Oncol 19(5):v1–v88
2. Weller M, van den Bent M, Preusser M et al (2021) EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol 18(3):170–186
3. Molinaro AM, Hervey-Jumper S, Morshed RA et al (2020) Association of maximal extent of resection of contrast-enhanced and non-contrast-enhanced tumor with survival within molecular subgroups of patients with newly diagnosed glioblastoma. JAMA Oncol 6(4):495–503
4. De Witt Hamer PC, Robles SG, Zwinderman AH et al (2012) Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol 30(20):2559–2565
5. Sanai N, Mirzadeh Z, Berger MS (2008) Functional outcome after language mapping for glioma resection. N Engl J Med 358(1):18–27
6. Saito T, Muragaki Y, Tamura M et al (2022) Awake craniotomy with transcortical motor evoked potential monitoring for resection of gliomas within or close to motor-related areas: validation of utility for predicting motor function. J Neurosurg 136(4):1052–1061
7. Bu LH, Zhang J, Lu JF et al (2021) Glioma surgery with awake language mapping versus generalized anesthesia: a systematic review. Neurosurg Rev 44(4):1997–2011
8. Gerritsen JKW, Zwarthoed RH, Kilgallon JL et al (2022) Effect of awake craniotomy in glioblastoma in eloquent areas (GLIOMAP): a propensity score-matched analysis of an international, multicentre, cohort study. Lancet Oncol 23(6):802–817
9. Vaz-Salgado MA, Villamayor M, Albarrán V et al (2023) Recurrent glioblastoma: a review of the treatment options. Cancers (Basel). https://doi.org/10.3390/cancers15174279
10. Nahed BV, Redjal N, Brat DJ et al (2015) Management of patients with recurrence of diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. J Neurooncol 125(3):609–630
11. Mellinghoff IK, van den Bent MJ, Blumenthal DT et al (2023) Vorasidenib in IDH1- or IDH2-mutant low-grade glioma. N Engl J Med 389(7):589–601
12. Habibi MA, Mirjani MS, Ahmadvand MH et al (2024) The safety and efficacy of dabrafenib and trametinib in patients with glioma: a systematic review and meta-analysis. Eur J Clin Pharmacol 80(5):639–656
13. Uppstrom TJ, Singh R, Hadjigeorgiou GF et al (2016) Repeat surgery for recurrent low-grade gliomas should be standard of care. Clin Neurol Neurosurg 151:18–23
14. Ramakrishna R, Hebb A, Barber J et al (2015) Outcomes in reoperated low-grade gliomas. Neurosurgery 77(2):175–184
15. Shofty B, Haim O, Costa M et al (2020) Impact of repeated operations for progressive low-grade gliomas. Eur J Surg Oncol 46(12):2331–2337
16. Lu VM, Jue TR, McDonald KL et al (2018) The survival effect of repeat surgery at glioblastoma recurrence and its trend: a systematic review and meta-analysis. World Neurosurg 115:453–9.e3
17. Ringel F, Pape H, Sabel M et al (2016) Clinical benefit from resection of recurrent glioblastomas: results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection. Neuro Oncol 18(1):96–104
18. Behling F, Rang J, Dangel E et al (2022) Complete and incomplete resection for progressive glioblastoma prolongs post-progression survival. Front Oncol 12:755430
19. Robin AM, Lee I, Kalkanis SN (2017) Reoperation for recurrent glioblastoma multiforme. Neurosurg Clin N Am 28(3):407–428
20. Li YC, Chiu HY, Wei KC et al (2021) Using cortical function mapping by awake craniotomy dealing with the patient with recurrent glioma in the eloquent cortex. Biomed J 44:S48-s53
21. Morshed RA, Young JS, Han SJ et al (2018) Perioperative outcomes following reoperation for recurrent insular gliomas. J Neurosurg 131(2):467–473
22. Kaspera W, Majchrzak K, Bobek-Billewicz B et al (2013) Reoperations of patients with low-grade gliomas in eloquent or near eloquent brain areas. Neurol Neurochir Pol 47(2):116–125
23. Hamdan N, Duffau H (2022) Extending the multistage surgical strategy for recurrent initially low-grade gliomas: functional and oncological outcomes in 31 consecutive patients who underwent a third resection under awake mapping. J Neurosurg 136(4):1035–1044
24. Mukherjee S, Wood J, Liaquat I et al (2020) Craniotomy for recurrent glioblastoma: Is it justified? A comparative cohort study with outcomes over 10 years. Clin Neurol Neurosurg 188:105568
25. Oppenlander ME, Wolf AB, Snyder LA et al (2014) An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. J Neurosurg 120(4):846–853
26. Yong RL, Wu T, Mihatov N et al (2014) Residual tumor volume and patient survival following reoperation for recurrent glioblastoma. J Neurosurg 121(4):802–809
27. Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62(10):1006–1012
28. Wells G SB, O'Connell D et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [Internet]. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Accessed 6 November 2023].
29. Karschnia P, Dono A, Young JS et al (2023) Prognostic evaluation of re-resection for recurrent glioblastoma using the novel RANO classification for extent of resection: a report of the RANO resect group. Neuro Oncol 25(9):1672–1685
30. Krivoshapkin A, Gaytan A, Abdullaev O et al (2021) Prospective comparative study of intraoperative balloon electronic

brachytherapy versus resection with multidisciplinary adjuvant therapy for recurrent glioblastoma. Surg Neurol Int 12:517
31. Ng S, Lemaitre AL, Moritz-Gasser S et al (2022) Recurrent low-grade gliomas: does reoperation affect neurocognitive functioning? Neurosurgery 90(2):221–232
32. Pala A, Schmitz AL, Knoll A et al (2018) Is MGMT promoter methylation to be considered in the decision making for recurrent surgery in glioblastoma patients? Clin Neurol Neurosurg 167:6–10
33. Pessina F, Navarria P, Cozzi L et al (2017) Role of surgical resection in recurrent glioblastoma: prognostic factors and outcome evaluation in an observational study. J Neurooncol 131(2):377–384
34. Ribeiro L, Ng S, Duffau H (2023) Recurrent insular low-grade gliomas: factors guiding the decision to reoperate. J Neurosurg 138(5):1216–1226
35. Voisin MR, Zuccato JA, Wang JZ et al (2022) Surgery for recurrent glioblastoma multiforme: a retrospective case control study. World Neurosurg 166:e624–e631
36. Woo PYM, Law THP, Lee KKY et al (2023) Repeat resection for recurrent glioblastoma in the temozolomide era: a real-world multi-centre study. Br J Neurosurg. https://doi.org/10.1080/02688697.2023.2167931
37. Yang K, Ellenbogen Y, Martyniuk A et al (2022) Reoperation in adult patients with recurrent glioblastoma: a matched cohort analysis. Neurooncol Adv. 4(1):115
38. Ammirati M, Galicich JH, Arbit E et al (1987) Reoperation in the treatment of recurrent intracranial malignant gliomas. Neurosurgery 21(5):607–614
39. Archavlis E, Tselis N, Birn G et al (2014) Salvage therapy for recurrent glioblastoma multiforme: a multimodal approach combining fluorescence-guided resurgery, interstitial irradiation, and chemotherapy. Neurol Res 36(12):1047–1055
40. Azoulay M, Santos F, Shenouda G et al (2017) Benefit of re-operation and salvage therapies for recurrent glioblastoma multiforme: results from a single institution. J Neurooncol 132(3):419–426
41. Bagley SJ, Schwab RD, Nelson E et al (2019) Histopathologic quantification of viable tumor versus treatment effect in surgically resected recurrent glioblastoma. J Neurooncol 141(2):421–429
42. Barker FG 2nd, Chang SM, Gutin PH et al (1998) Survival and functional status after resection of recurrent glioblastoma multiforme. Neurosurgery 42(4):709–720
43. Boiardi A, Eoli M, Pozzi A et al (1999) Locally delivered chemotherapy and repeated surgery can improve survival in glioblastoma patients. Ital J Neurol Sci 20(1):43–48
44. Brandes AA, Bartolotti M, Tosoni A et al (2016) Patient outcomes following second surgery for recurrent glioblastoma. Future Oncol 12(8):1039–1044
45. Brennan PM, Borchert R, Coulter C et al (2021) Second surgery for progressive glioblastoma: a multi-centre questionnaire and cohort-based review of clinical decision-making and patient outcomes in current practice. J Neurooncol 153(1):99–107
46. Chamberlain MC (2015) Salvage therapy with lomustine for temozolomide refractory recurrent anaplastic astrocytoma: a retrospective study. J Neurooncol 122(2):329–338
47. Chen YR, Sole J, Ugiliweneza B et al (2018) National trends for reoperation in older patients with glioblastoma. World Neurosurg 113:e179–e189
48. Clarke JL, Ennis MM, Yung WK et al (2011) Is surgery at progression a prognostic marker for improved 6-month progression-free survival or overall survival for patients with recurrent glioblastoma? Neuro Oncol 13(10):1118–1124
49. D'Amico RS, Cloney MB, Sonabend AM et al (2015) The safety of surgery in elderly patients with primary and recurrent glioblastoma. World Neurosurg 84(4):913–919
50. De Bonis P, Fiorentino A, Anile C et al (2013) The impact of repeated surgery and adjuvant therapy on survival for patients with recurrent glioblastoma. Clin Neurol Neurosurg 115(7):883–886
51. Delgado-Fernandez J, Garcia-Pallero M, Blasco G et al (2017) Usefulness of reintervention in recurrent glioblastoma: an indispensable weapon for increasing survival. World Neurosurg 108:610–617
52. Delgado-Fernández J, Frade-Porto N, Blasco G et al (2020) Does reintervention improve survival in recurrent glioblastoma? Facing a temporal bias in the literature. Acta Neurochir (Wien) 162(8):1967–1975
53. Ening G, Huynh MT, Schmieder K et al (2015) Repeat-surgery at glioblastoma recurrence, when and why to operate? Clin Neurol Neurosurg 136:89–94
54. Fariña Nuñez MT, Franco P, Cipriani D et al (2020) Resection of recurrent glioblastoma multiforme in elderly patients: a pseudo-randomized analysis revealed clinical benefit. J Neurooncol 146(2):381–387
55. Franceschi E, Bartolotti M, Tosoni A et al (2015) The effect of re-operation on survival in patients with recurrent glioblastoma. Anticancer Res 35(3):1743–1748
56. Furtak J, Kwiatkowski A, Śledzińska P et al (2022) Survival after reoperation for recurrent glioblastoma multiforme: a prospective study. Surg Oncol 42:101771
57. González V, Brell M, Fuster J et al (2022) Analyzing the role of reoperation in recurrent glioblastoma: a 15-year retrospective study in a single institution. World J Surg Oncol 20(1):384
58. Guyotat J, Signorelli F, Frappaz D et al (2000) Is reoperation for recurrence of glioblastoma justified? Oncol Rep 7(4):899–904
59. Hager J, Herrmann E, Kammerer S et al (2018) Impact of resection on overall survival of recurrent glioblastoma in elderly patients. Clin Neurol Neurosurg 174:21–25
60. Harsh GRT, Levin VA, Gutin PH et al (1987) Reoperation for recurrent glioblastoma and anaplastic astrocytoma. Neurosurgery 21(5):615–621
61. Hong B, Wiese B, Bremer M et al (2013) Multiple microsurgical resections for repeated recurrence of glioblastoma multiforme. Am J Clin Oncol 36(3):261–268
62. Huang R, Wang T, Liao Z et al (2021) A retrospective analysis of the risk factors affecting recurrence time in patients with recurrent glioblastoma. Ann Palliat Med 10(5):5391–5399
63. Kalita O, Kazda T, Reguli S et al (2023) Effects of reoperation timing on survival among recurrent glioblastoma patients: a retrospective multicentric descriptive study. Cancers (Basel). https://doi.org/10.3390/cancers15092530
64. Kim HR, Kim KH, Kong DS et al (2015) Outcome of salvage treatment for recurrent glioblastoma. J Clin Neurosci 22(3):468–473
65. McNamara MG, Lwin Z, Jiang H et al (2014) Factors impacting survival following second surgery in patients with glioblastoma in the temozolomide treatment era, incorporating neutrophil/lymphocyte ratio and time to first progression. J Neurooncol 117(1):147–152
66. Montemurro N, Fanelli GN, Scatena C et al (2021) Surgical outcome and molecular pattern characterization of recurrent glioblastoma multiforme: a single-center retrospective series. Clin Neurol Neurosurg 207:106735
67. Ortega A, Sarmiento JM, Ly D et al (2016) Multiple resections and survival of recurrent glioblastoma patients in the temozolomide era. J Clin Neurosci 24:105–111
68. Palmer JD, Siglin J, Yamoah K et al (2015) Re-resection for recurrent high-grade glioma in the setting of re-irradiation: more is not always better. J Neurooncol 124(2):215–221
69. Perrini P, Gambacciani C, Weiss A et al (2017) Survival outcomes following repeat surgery for recurrent

glioblastoma: a single-center retrospective analysis. J Neurooncol 131(3):585–591
70. Quick J, Gessler F, Dützmann S et al (2014) Benefit of tumor resection for recurrent glioblastoma. J Neurooncol 117(2):365–372
71. Rubin MC, Sagberg LM, Jakola AS et al (2022) Primary versus recurrent surgery for glioblastoma-a prospective cohort study. Acta Neurochir (Wien) 164(2):429–438
72. Sacko O, Lauwers-Cances V, Brauge D et al (2011) Awake craniotomy vs surgery under general anesthesia for resection of supratentorial lesions. Neurosurgery 68(5):1192–1198
73. Seyve A, Lozano-Sanchez F, Thomas A et al (2020) Initial surgical resection and long time to occurrence from initial diagnosis are independent prognostic factors in resected recurrent IDH wild-type glioblastoma. Clin Neurol Neurosurg 196:106006
74. Sipos L, Afra D (1997) Re-operations of supratentorial anaplastic astrocytomas. Acta Neurochir (Wien) 139(2):99–104
75. Suchorska B, Weller M, Tabatabai G et al (2016) Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma-results from the DIRECTOR trial. Neuro Oncol 18(4):549–556
76. Sughrue ME, Sheean T, Bonney PA et al (2015) Aggressive repeat surgery for focally recurrent primary glioblastoma: outcomes and theoretical framework. Neurosurg Focus 38(3):E11
77. Tully PA, Gogos AJ, Love C et al (2016) Reoperation for recurrent glioblastoma and its association with survival benefit. Neurosurgery 79(5):678–689
78. van Linde ME, Brahm CG, de Witt Hamer PC et al (2017) Treatment outcome of patients with recurrent glioblastoma multiforme: a retrospective multicenter analysis. J Neurooncol 135(1):183–192
79. Wallner KE, Galicich JH, Malkin MG et al (1989) Inability of computed tomography appearance of recurrent malignant astrocytoma to predict survival following reoperation. J Clin Oncol 7(10):1492–1496
80. Wann A, Tully PA, Barnes EH et al (2018) Outcomes after second surgery for recurrent glioblastoma: a retrospective case-control study. J Neurooncol 137(2):409–415
81. Woernle CM, Péus D, Hofer S et al (2015) Efficacy of surgery and further treatment of progressive glioblastoma. World Neurosurg 84(2):301–307
82. Xu JF, Fang J, Shen Y et al (2011) Should we reoperate for recurrent high-grade astrocytoma? J Neurooncol 105(2):291–299
83. Yamaguchi S, Motegi H, Ishi Y et al (2021) Clinical outcome of cytoreductive surgery prior to bevacizumab for patients with recurrent glioblastoma: a single-center retrospective analysis. Neurol Med Chir (Tokyo) 61(4):245–252
84. Young B, Oldfield EH, Markesbery WR et al (1981) Reoperation for glioblastoma. J Neurosurg 55(6):917–921
85. Stupp R, Brada M, van den Bent MJ et al (2014) High-grade glioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. https://doi.org/10.1093/annonc/mdu050
86. Mohile NA, Messersmith H, Gatson NT et al (2022) Therapy for diffuse astrocytic and oligodendroglial tumors in adults: ASCO-SNO guideline. J Clin Oncol 40(4):403–426
87. van Opijnen MP, de Vos FYF, Nabuurs RJA et al (2023) Practice variation in re-resection for recurrent glioblastoma: a nationwide survey among Dutch neuro-oncology specialists. Neurooncol Pract 10(4):360–369
88. Southwell DG, Hervey-Jumper SL, Perry DW et al (2016) Intraoperative mapping during repeat awake craniotomy reveals the functional plasticity of adult cortex. J Neurosurg 124(5):1460–1469
89. Picart T, Herbet G, Moritz-Gasser S et al (2019) Iterative surgical resections of diffuse glioma with awake mapping: how to deal with cortical plasticity and connectomal constraints? Neurosurgery 85(1):105–116
90. Duffau H (2022) Repeated awake surgical resection(s) for recurrent diffuse low-grade gliomas: why, when, and how to reoperate? Front Oncol 12:947933

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