



## Recurrent glioblastoma in the era of molecular diagnostics: practice variation and practical implications

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# **PART I**

# **Practice variation**



# Chapter 2

## **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 6,372 articles, of which 125 were screened for eligibility. After full-text evaluation, 58 articles were included in this review, comprising 5,311 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% (280/5,311) of all patients, and awake craniotomy was used in 3% (142/5,311) 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.<sup>1</sup> 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.<sup>2,3</sup> 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, in case of awake mapping, language function.<sup>4,5</sup> 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.<sup>4,6-8</sup>

There is some controversy on standard-of-care in the recurrent setting.<sup>9,10</sup> Re-resection is one of the possibilities, as are (re-)challenge chemotherapy, (re-)irradiation, targeted therapy (e.g. vorasidenib<sup>11</sup> or dabrafenib/trametinib<sup>12</sup>), recruitment into clinical trials, or best supportive care.<sup>2</sup> Treatment decisions are influenced by several factors including overall performance (Karnofsky Performance Status (KPS) or World Health Organization (WHO) functioning scale), tumor location and size, and prior treatment.<sup>2</sup> For glioma WHO grade 2, there is little debate on the importance of maximal safe re-resection.<sup>13-15</sup> Also, patients with glioma WHO grade 4 might benefit from re-resection, albeit limited to selected patients on the favorable side of the spectrum.<sup>16-19</sup>

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 either failed to stratify between glioma WHO grade 2 and 3-4<sup>20,21</sup>, included grade 2 tumors that had progressed to grade 3 or 4<sup>22,23</sup> or failed to stratify between use/non-use of intraoperative mapping<sup>24-26</sup>, resulting in mixed results that are hard to interpret. In the absence of solid evidence, it is likely that intraoperative mapping is currently omitted in most of the cases or not seriously considered in many departments. Therefore, to maximize safe re-resection in patients with recurrent glioma WHO grade 2-4, the current lack of evidence and treatment recommendations needs to be solved.

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.<sup>27</sup> 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<sup>28</sup> 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 had 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 which had 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 had 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 divided in the time between primary diagnosis and death (overall survival) and the time between re-resection and death (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**

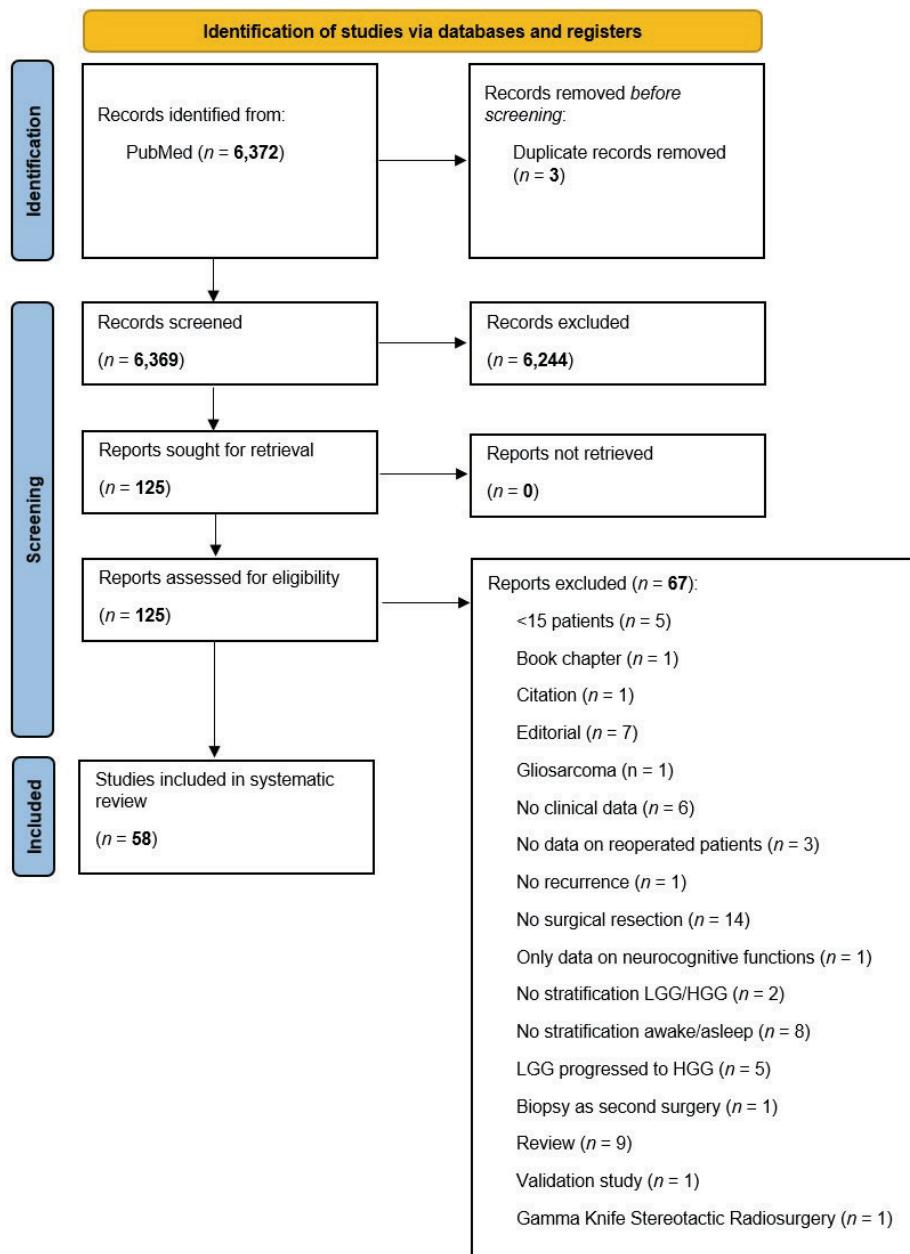
### **Search results**

The search strategy resulted in 6,372 abstracts, of which 6,369 remained after removing duplicates. Of these, 6,244 articles were excluded during the initial screening round 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 *Figure 1* for an overview of the selection process.

### **Study characteristics**

A total of 5,311 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%] 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)*.

**Figure 1.** Schematic breakdown of literature search results.

Abbreviations: HGG: high-grade glioma WHO grade 3-4, LGG: low-grade glioma WHO grade 2.

## General findings on mapping

The first main finding was that only 10 studies (10 [17%] of 58) mentioned whether the re-resection was performed under awake/asleep conditions and/or whether intraoperative mapping techniques were used.<sup>20, 29-37</sup> All other articles did not provide details on awake/asleep craniotomy and/or mapping technique during re-resection.<sup>17, 38-84</sup> Regarding the anesthesia technique (awake/asleep) used in the 10 studies, two studies included re-resections in which awake craniotomy was applied<sup>31, 34</sup>, five studies described re-resection under general anesthesia<sup>29, 30, 32, 36, 37</sup>, two studies included both awake and asleep re-resections (but did not stratify the outcomes by either awake or asleep)<sup>20, 35</sup>, and one study did not specify awake/asleep approach.<sup>33</sup> On a total of 58 studies, re-resection in an awake setting was performed in 3% (142/5,311) of the patients. See *Figure 2* for a schematic overview of studies with information on awake/asleep craniotomy and intraoperative mapping.

The second main finding was that, next to information on awake/asleep conditions, additional information on the use of intraoperative mapping was not routinely included: only six studies described this.<sup>20, 31-34, 36</sup> In general, out of a total of 58 studies, intraoperative mapping was applied in 5% (280/5,311) of the patients. Intraoperative electrophysiology techniques that were described included awake speech mapping, direct cortico-subcortical electrostimulation, and motor-evoked or somatosensory-evoked potentials.

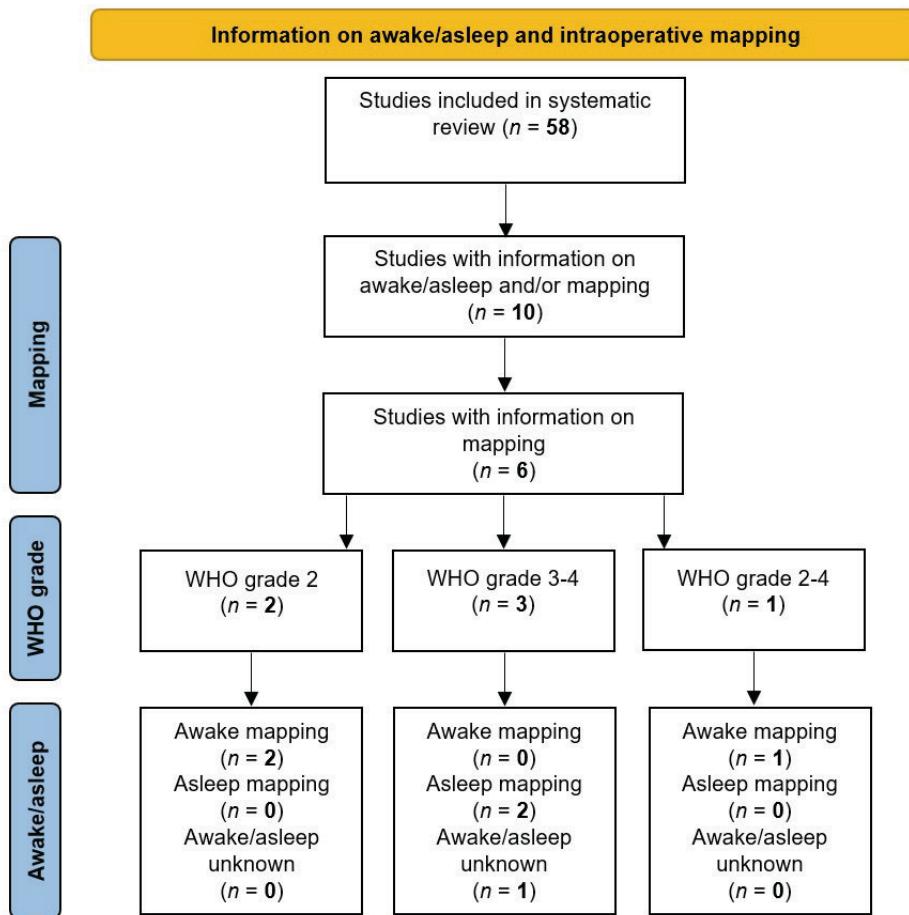
## Outcomes for recurrent glioma WHO grade 2

Intraoperative mapping during re-resection for glioma WHO grade 2 was described in three of the six studies, all under awake conditions (*Figure 2*).<sup>20, 31, 34</sup> 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<sup>34</sup> to 21% (13/62) in one study that was not limited to tumors in specific locations.<sup>31</sup> The third study found a complete resection rate of 65% (17/26) after awake craniotomy with intraoperative mapping but did not stratify between recurrent gliomas WHO grade 2 and 3-4.<sup>20</sup> Only one study mentioned the treatment after mapping-guided re-resection, showing that 95% (59/62) of the patients did not receive postoperative treatment.<sup>31</sup>

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.<sup>31, 34</sup> 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.<sup>20</sup> This 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%,  $p=0.231$ ).<sup>20</sup>

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.

**Figure 2.** Schematic breakdown of studies with information on intraoperative mapping.

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

Intraoperative mapping was mentioned in four studies on patients with recurrent glioma WHO grade 3-4, either during awake craniotomy<sup>20</sup>, under general anesthesia<sup>32, 36</sup> or with unknown awake/asleep setting (Figure 2).<sup>33</sup> Two studies reported the survival after mapping-guided re-resection. The results from both these studies indicated that mapping was associated with non-inferior post-progression survival (PPS) (10.3 months, 95% CI 7.6-10.4<sup>33</sup>, odds ratio 0.9, 95% CI 0.6-1.3<sup>36</sup>). 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.<sup>33</sup> 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.<sup>33, 36</sup>

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.<sup>20, 35</sup> The association between awake/asleep re-resection and survival was investigated in one of these articles using Cox proportional hazard models, 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).<sup>35</sup> 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. Taking these studies together, a weighted median OS of 16.9 months (range 16.7-31.0)<sup>30, 32, 36, 37</sup> and a weighted median PPS of 11.0 months (range 5.0-11.0)<sup>29, 30, 36, 37</sup> was observed, although mapping was not taken into account in this analysis. For those studies providing the endpoint GTR, GTR was achieved in 55% (302/551).<sup>29, 32, 36</sup> Perioperative complications were detailed for 599 patients, with events, regardless of grade, in 19% (111/599) of the patients.<sup>29, 30, 32, 36, 37</sup>

### 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 displayed in *Table 2 (Supplemental S3)*.

### DISCUSSION

This systematic review showed that there is a 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 on awake/asleep craniotomy and/or mapping technique during re-resection, with awake re-resection described in only 3% (142/5,311) of the patients. Intraoperative mapping in general was described in a mere 5% (280/5,311) 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, next to factors like publication bias and inconsistent reporting. 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 have proven to be effective for improving outcomes by increasing extent of resection, decreasing postoperative deficits, and consequently, prolonging survival.<sup>4, 6-8</sup> 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 in the recurrent setting is the low number of cases that have been carried out using intraoperative mapping 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.<sup>2, 85, 86</sup> 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.<sup>87</sup> 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.<sup>88-90</sup>

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 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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The authors have not disclosed any funding.

## **DATA AVAILABILITY**

No datasets were generated or analysed during the current study.

## **CONFLICTS OF INTEREST**

The authors have not disclosed any competing interests.

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