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Review Article

Efficacy and safety of awake craniotomy versus general anesthesia for glioma resection: A systematic review

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ABSTRACT

Background: Gliomas frequently arise in eloquent cortical regions, where achieving maximal resection while preserving neurological function poses a major challenge. Awake craniotomy (AC) with intraoperative mapping is increasingly employed for this purpose, but its comparative effectiveness against general anesthesia (GA) remains unclear.

Methods: This systematic review conducted under Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered in PROSPERO, searched PubMed, Embase, Cochrane Library, and Scopus for English-language studies published from 2015 to 2025. Eligible studies compared AC and GA in adults with supratentorial gliomas and reported outcomes on extent of resection, neurological preservation, survival, safety, quality of life, or cost-effectiveness. Data extraction was performed independently by three reviewers, and study quality was assessed with Risk of Bias 2, Newcastle-Ottawa Scale, or AMSTAR 2. Due to heterogeneity, findings were synthesized narratively.

Results: Six studies were included (4 primary, 2 reviews); only two directly compared approaches. Extent of resection ($P = 0.657$, $P = 0.17$), overall survival (adjusted hazard ratio [HR] 0.84, $P = 0.48$), and progression-free survival (adjusted HR 0.9, $P = 0.66$) showed no significant differences. AC cost $2,175 more per case ($P < 0.001$). Neurocognitive function was generally preserved; psychomotor speed declined most.

Conclusion: Neither approach demonstrated superiority. AC enables functional monitoring but offers no survival benefit and increases costs. Surgical decisions should be individualized. High-quality randomized trials are needed.

Keywords: Awake craniotomy, General anesthesia, Glioma, Neurological complications, Surgical outcomes

INTRODUCTION

Gliomas are the most common primary malignant tumors of the central nervous system, accounting for nearly 80% of adult brain malignancies.[7] This group of neoplasms is heterogeneous, defined by distinct histopathological and molecular characteristics. Frequent localization in eloquent cortical regions or adjacent to language areas of the dominant hemisphere such as Broca's and Wernicke's areas makes surgical resection particularly challenging.[3] Gliomas are the most prevalent primary malignant brain tumors, contributing to the majority of cases within an annual incidence of approximately 7/100,000 individuals.[25] Among these, glioblastoma is the most aggressive subtype, despite standard multimodal therapy, the median survival for glioblastoma multiforme (GBM) remains approximately 15 months.[2,21,28]

Complete resection of high-grade gliomas remains unachievable due to their infiltrative growth pattern. Surgical efforts therefore focus on maximizing removal of the magnetic resonance imaging-defined lesion, as survival outcomes are closely linked to the extent of resection.[30] Gross total resection has been associated with prolonged survival in selected patients, although with an increased risk of morbidity. Thus, the extent of resection represents a critical prognostic determinant for both overall survival and preserving quality of life. To achieve the dual goal of extensive resection and neurological safety, awake mapping strategies have become central to neurosurgical practice.

Direct electrical stimulation as used in awake craniotomy (AC) was initially introduced for localization of the sensorimotor cortex in epilepsy surgery, and in the 1940s, Lu *et al*. extended its application to the identification of language areas.[15] AC with intraoperative language mapping now employs this technique to delineate and preserve cortical and subcortical regions critical for speech.

AC is increasingly used to maximize the extent of tumor resection.[1] However, evidence remains conflicting regarding its impact on extent of resection, neurological outcomes, quality of life, complications, and cost-effectiveness. Although general anesthesia (GA) is conventionally employed for glioma resections, its use in tumors located within or near eloquent regions can limit intraoperative functional assessment. The asleep–awake–asleep (AA) technique offers the advantage of real-time language and motor mapping, yet there remains a paucity of evidence directly comparing surgical outcomes between AA and GA.[7] In adult glioma, it remains uncertain whether AC provides superior surgical outcomes, neurological preservation, and patient safety compared with GA. This systematic review aims to evaluate and synthesize the current evidence on this comparison.

MATERIALS AND METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered on PROSPERO (ID: 1084478).

Data sources

A comprehensive literature search was conducted using databases such as PubMed, Cochrane Library, Embase, and Scopus. The search targeted all relevant English-language articles from 2015 to 2025 of each database. Ongoing trials were searched through the ClinicalTrials.gov website.

Search strategy

The search strategy incorporated both Medical Subject Headings (MeSH) and non-MeSH terms pertinent to AC, GA, and gliomas. Detailed search strategies for each database are provided in Supplementary File 1. In addition, manual search techniques, including snowballing through references of relevant literature, were used to identify additional articles.

Eligibility criteria

The Population, Intervention, Comparison, and Outcome (PICO) question for this study was defined as follows:

- P: Adult patients (≥18 years) with supratentorial gliomas (World Health Organization [WHO] grades I–IV, eloquent or non-eloquent areas).
- I: AC with or without intraoperative brain mapping.
- C: Craniotomy under GA with or without neuromonitoring.
- O: Surgical, neurological, survival, safety, and quality-of-life outcomes.

Inclusion criteria

Eligible studies were randomized controlled trials, cohort studies, or case–control studies with a minimum of ten patients per group, comparing AC and GA in adult patients with supratentorial gliomas. Only articles published in English from 2015 onward and providing sufficient outcome data were included.

Exclusion criteria

Studies were excluded if they were case reports, small case series with fewer than ten patients per group, reviews, abstracts, editorials, or commentaries. Research involving pediatric patients (<18 years), non-glioma tumors, or procedures restricted to biopsy, stereotactic, endoscopic, robotic, or other experimental approaches was also excluded. In addition, non-English publications and preclinical studies were not considered.

Study outcomes

We evaluated surgical, neurological, survival, and safety outcomes as defined by each study. The outcomes assessed included extent of resection, reported as gross total, near-total, or subtotal resection rates, percentage of tumor volume removed, and residual tumor volume. Neurological outcomes were evaluated in terms of immediate, transient, and permanent postoperative deficits, as well as preservation of language, motor, and cognitive functions using standardized clinical or neuropsychological assessments where available. Additional measures included overall and progression-free survival, perioperative complications, morbidity, mortality, cost-effectiveness indicators such as healthcare utilization, and patient satisfaction.

Article screening and selection

The identified articles were imported to Zotero for duplicate removal, followed by screening 137 using Rayyan software. Three independent reviewers (EA, M, and CK) assessed the titles, abstracts, and full text of the articles based on predefined eligibility criteria. Any disagreements between reviewers were resolved by a third reviewer (CK).

Data extraction

Data from eligible studies were extracted by three authors (EA, M, and CK). Extracted variables included study characteristics (author, year of publication, country of origin, study design, and sample size), patient characteristics (age, sex, tumor grade, and location), details of intervention and comparator (AC techniques and GA techniques), and reported outcomes (extent of resection, neurological deficits, functional preservation, survival, perioperative complications, and quality of life measures). Two authors independently reviewed and verified the extracted data. The finalized dataset was organized and processed using Google Sheets for further analysis.

Risk of bias (RoB) assessment

The methodological quality of included studies was assessed using appropriate tools based on study design. Randomized controlled trials (RCTs) were evaluated with the Cochrane RoB 2 tool, while non-randomized and observational cohort studies were assessed using the Newcastle-Ottawa Scale (NOS). For systematic reviews, the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) checklist was applied Figures 1 and 2. RoB was independently assessed by two reviewers, with discrepancies resolved through discussion or consultation with a third reviewer. Methodological quality assessment is detailed in Table 1.

Statistical analysis

Due to heterogeneity in study designs, patient populations, interventions, and reported outcomes, no formal meta-analysis was conducted. Instead, a narrative synthesis of the evidence was performed.

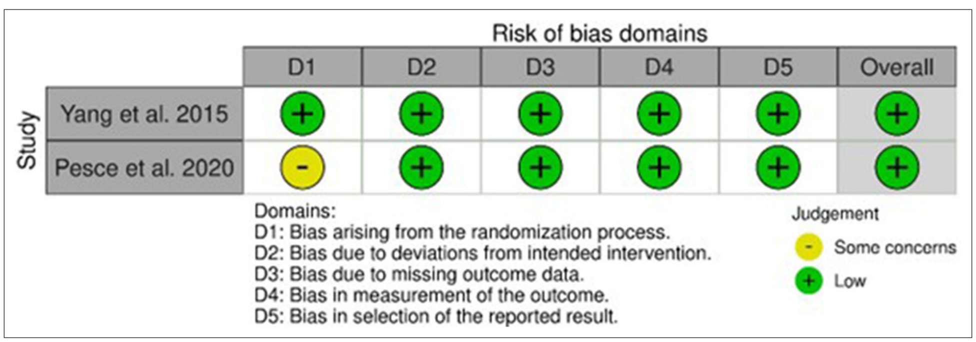

Figure 1: Risk of bias summary for the randomized trials included in the review. Each study is evaluated across five core domains, with judgments indicating the level of methodological rigor. Overall ratings reflect low risk or some concerns.

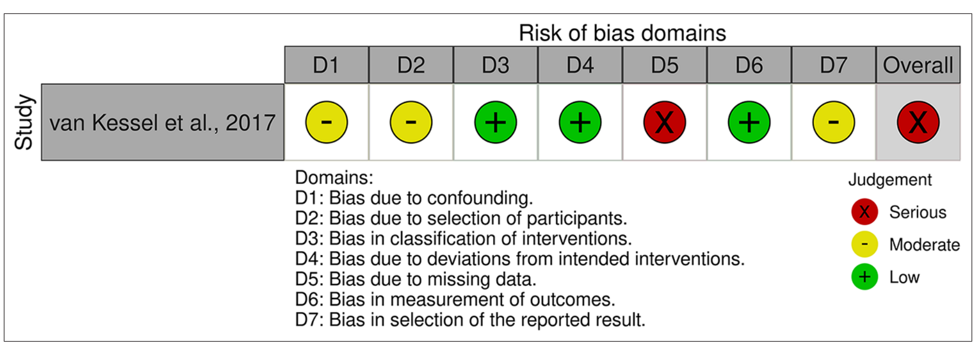

Figure 2: Risk of bias assessment for the included observational study, presenting judgments across seven relevant bias domains. The figure highlights areas of low, moderate, and serious risk contributing to the overall appraisal.

Study characteristics and results were summarized descriptively, with particular attention to extent of resection, neurological outcomes, survival measures, and perioperative complications. Where possible, findings were grouped by surgical approach (AC vs. GA) and stratified according to glioma grade, eloquence of tumor location, and patient demographics to identify consistent patterns and differences across studies.

Table 1: Quality assessment and risk of bias.

Study	Study design	Newcastle-Ottawa Scale Score	Risk of bias assessment	Main strengths	Main limitations
van Kessel *et al*., 2017[27]	Retrospective Cohort	7/9	Serious overall risk	Large sample, extensive neurocognitive data	Single-group study, >70% received adjuvant therapy
Pesce *et al*., 2020[22]	Non-randomized cohort	7/9	Some concerns	Direct comparison, focused analysis	Small sample (*n*=15), non-randomized
Yang *et al*., 2015[29]	RCT	8/9	Low risk	RCT design, blinded outcome assessment	No direct AC versus GA comparison
Sarikonda *et al*., 2025[24]	Retrospective cohort	7/9	Some concerns	Large sample, cost analysis, survival data	Single-institution, retrospective
Collée *et al*., 2022[6]	Systemic Review	AMSTAR-2 applied	NR	Comprehensive language outcome analysis	Heterogeneous studies
Kurian *et al*., 2022[12]	Systemic Review	AMSTAR-2 applied	NR	Large patient population	Limited direct comparisons

Risk of bias assessed using RoB 2 for RCTs, Newcastle-Ottawa Scale for cohort studies, and AMSTAR-2 for systematic reviews. AC: Awake craniotomy, GA: General anesthesia, NR: Not reported, RCT: Randomized controlled trials

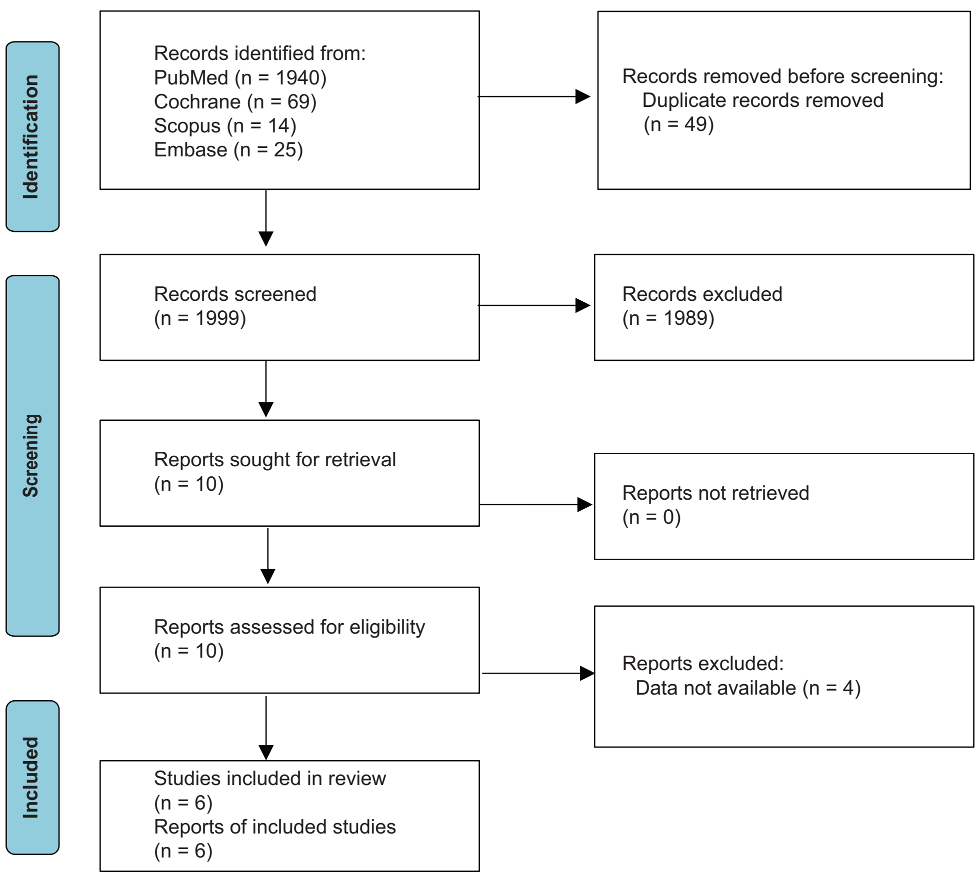

Figure 3: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart diagram.

RESULTS

A total of six studies were included in the final analysis as shown in the PRISMA flow diagram Figure 3. Four of the studies were primary studies (three cohort studies and one randomized controlled trial), and two were systematic reviews that had a publication range of 2015 to 2025. The primary studies were conducted in different regions including, the Netherlands (*n* = 2), Italy (*n* = 1), China (*n* = 1), and the USA (*n* = 2). Detailed study characteristics including study design, sample size, anesthetic groups, patient demographics, tumor grades, and primary outcomes assessed are presented in Table 2.

Patient and tumor characteristics

There was considerable variation in patient demographics and tumor characteristics among studies as shown in Table 3. Mean ages, when reported, ranged

Table 2: Study characteristics.

Author, Year	Country	Study design	Study period	Sample size (Total)	AC group	GA group	Mean age (AC/GA)	Male/ Female	Tumor grade	Primary outcomes assessed
van Kessel *et al.*, 2017[27]	Netherlands	Retrospective Cohort	2010–2016	168	168	N/A	N/A	N/A	WHO II–IV	Neurocognitive function
Pesce *et al.*, 2020[22]	Italy	Non-Randomized Cohort	2017–2019	15	6	9	52.1/54.3	NR	WHO II–IV (GBM 66.7%)	EOR, safety, operative time
Yang *et al.*, 2015[30]	China	Randomized Controlled Trial	NR	30	N/A	30	50.4±4.9/ 49.2±4.1	17/13	Glioma (NR)	AQP4/AQP9 expression
Sarikonda *et al.*, 2025[24]	USA	Retrospective Cohort	2017–2022	365	67	298	NR	NR	Glioma (NR)	Survival, cost-effectiveness
Collée *et al.*, 2022[6]	Netherlands	Systemic Review	Until July 2020	631 studies	N/A	N/A	N/A	N/A	WHO II–IV	Language outcomes
Kurian *et al.*, 2022[12]	USA	Systemic Review	1999–2020	1932 patients	N/A	N/A	N/A	N/A	NR	Motor mapping outcomes

AC: Awake craniotomy, EOR: Extent of resection, GA: General anesthesia, GBM: Glioblastoma multiforme, N/A: Not Applicable, NR: Not reported, WHO: World Health Organization

Table 3: Patient and tumor characteristics.

Study	Tumor location	Eloquent area involvement	Pre-op neurological deficits	WHO grade distribution	Molecular markers	KPS/ECOG score
van Kessel *et al.*, 2017[27]	Various (frontal, temporal, parietal, thalamic, insula)	NR	NR	II-IV diffuse gliomas	IDH mutation, 1p19q deletion	MR
Pesce *et al.*, 2020[22]	Temporal (60%), Frontal (20%), Other (20%)	Temporal eloquent: AC 67% versus GA 44%	Language impairments (47%), hemiparesis (13%)	GBM (67%), Grade II (33%)	IDH1/2, MGMT, 1p19q, EGFR	NR
Yang *et al.*, 2015[30]	NR	NR	NR	Glioma (grade NR)	NR	NR
Sarikonda *et al.*, 2025[24]	NR	NR	NR	No difference between groups (P=0.55)	NR	NR
Collée *et al.*, 2022[6]	All cortical regions	Language areas	Language deficits, anomia	WHO II–IV	NR	NR
Kurian *et al.*, 2022[12]	NR	Motor eloquent areas	NR	NR	NR	NR

AC: Awake craniotomy, GA: General anesthesia, GBM: Glioblastoma multiforme, NR: Not reported, WHO: World Health Organization, IDH1/2: Isocitrate dehydrogenase 1 and 2, MGMT: O6-Methylguanine-DNA Methyltransferase, 1p19q: Co-deletion of Chromosomal Arms 1p and 19q, EGFR: Epidermal growth factor receptor, KPS:Karnofsky performance status, ECOG: Eastern cooperative oncology group.

from 49.2 to 54.3 years, with all studies reporting a male-to-female distribution that was roughly equally distributed. Studies reported WHO tumor grades II–IV when specified, and the histology was primarily GBM when listed (66.7% in Pesce *et al.*).[22] Molecular markers of interest (isocitrate dehydrogenase [IDH] mutation status, 1p19q deletion, and O6-Methylguanine-DNA methyltransferase [MGMT] methylation) were also reported in one or more studies but were inconsistently reported across the cohort.[28]

Primary outcome analysis

Only two of the six included studies directly compared AC and GA for glioma resection: Pesce *et al*. (6 AC vs. 9 GA patients, $n = 15$ total) and Sarikonda *et al*. (67 AC vs. 298 GA patients, $n = 365$ total).[22,24] Van Kessel *et al*. examined AC exclusively ($n = 168$) without a GA comparison group, while Yang *et al*. compared propofol versus sevoflurane, both under GA, with no AC group.[24,27,30] The two systematic reviews by Collée *et al*. and Kurian *et al*. focused on language outcomes and motor mapping, respectively, with limited direct AC versus GA comparative data.[6,12]

Extent of resection showed no significant differences between surgical approaches, as detailed in Table 4. Pesce *et al*. reported gross total resection in 87% of patients (13/15) with no significant difference between AC and GA groups ($P = 0.657$).[22] Sarikonda *et al*. similarly found no difference in extent of resection ($P = 0.17$),[24] although specific resection percentages were not provided. Kurian *et al*.'s[12] systematic review reported higher rates of >90% resection with GA (74%) compared to awake surgery (57%), which the authors attributed to selection bias, as surgically challenging cases in eloquent regions were preferentially managed with awake techniques.

Operative times varied considerably across studies. Pesce *et al*. found that hypnosis-assisted AC required significantly longer operative duration compared to standard awake surgery (425.8 ± 105.5 vs. 223.3 ± 38.7 min, $P < 0.001$).[22] In contrast, Yang *et al*. reported comparable operative times between propofol-based TIVA and sevoflurane-based GA (94.7 ± 6.1 vs. 96.7 ± 10.1 min, $P > 0.05$).[30] Intraoperative complications were infrequently reported; Pesce *et al.*[22] documented one intraoperative seizure in the standard awake surgery group, with none in the hypnosis-assisted group. No studies reported conversions from AC to GA, and blood loss was not quantified in any included study.

Secondary outcome analysis

Neurological and functional outcomes are summarized in Table 5. Pesce *et al*. observed worsened neurological function in 4 of 15 patients (27%) during the immediate postoperative period (one in hypnosis-assisted AC and three in standard awake surgery).[22] However, substantial recovery occurred, with only 2 patients (13%; 1/group) demonstrating meaningful deficits at 30-day follow-up, representing 87% stability or improvement in neurological function.

Van Kessel *et al*. conducted comprehensive neurocognitive assessment, demonstrating preservation of most cognitive domains at 3–6 months following AC.[27]

Psychomotor speed emerged as the most vulnerable cognitive domain. Thalamic tumor involvement and IDH-wildtype status were identified as predictors of cognitive decline during follow-up. Collée *et al*.'s[6]

Table 4: Surgical outcomes.

Study	Extent of resection	Operative time (min)	Blood loss (mL)	Intraoperative complications	Conversion AC→GA
van Kessel *et al*., 2017[27]	NR	NR	NR	NR	NR
Pesce *et al*., 2020[22]	GTR: 87% (13/15), STR: 13% (2/15), P=0.657	AC: 425.8±105.5 versus GA: 223.3±38.7 (P<0.001)	NR	Seizure: 1 in GA group	None
Yang *et al*., 2015[30]	GTR mentioned but not quantified	Propofol: 94.7±6.1 versus Sevoflurane: 96.7±10.1	NR	NR	N/A
Sarikonda *et al*., 2025[24]	No difference (P=0.17)	NR	NR	NR	NR
Collée *et al*., 2022[6]	NR	NR	NR	Language errors during mapping	NR
Kurian *et al*., 2022[12]	>90% resection: Asleep 74% versus Awake 57%	NR	NR	Higher in asleep group	NR

AC-GA: Awake craniotomy to general anesthesia, GTR: Gross total resection, N/A: Not applicable, NR: Not reported, STR: Subtotal resection

Table 5: Neurological and functional outcomes.

Study	Immediate post-op deficits	Permanent neurological deficits	Language outcomes	Motor outcomes	Cognitive outcomes
van Kessel *et al.*, 2017[27]	Domain-based neurocognitive change at 3-6 months	NR	NR	NR	Most domains preserved; psychomotor speed most vulnerable
Pesce *et al.*, 2020[22]	4/15 worsened immediately	2/15 at 30 days (1/group)	Assessed with BADA test	Motor mapping performed	NR
Yang *et al.*, 2015[30]	NR	NR	NR	NR	NR
Sarikonda *et al.*, 2025[24]	NR	NR	NR	NR	NR
Collée *et al.*, 2022[6]	Language deficits, anomia	Pre-op deficits predict post-op deficits	Production deficits, anomia, speech arrest	N/A	NR
Kurian *et al.*, 2022[12]	Similar transient deficits both groups	Higher permanent deficits in awake group	N/A	Comparable motor outcomes	NR

N/A: Not applicable, NR: Not reported

Table 6: Survival and long-term outcomes.

Study	Overall survival	Progression free survival	Follow-up duration	Quality of life	Cost analysis
van Kessel *et al.*, 2017[27]	NR	NR	3–6 months	NR	NR
Pesce *et al.*, 2020[22]	NR	NR	30 days	NR	NR
Yang *et al.*, 2015[30]	NR	NR	NR	NR	NR
Sarikonda *et al.*, 2025[24]	Unadjusted: AC better (*P*=0.011) Adjusted: No difference (HR 0.84, *P*=0.48)	Unadjusted: No difference (*P*=0.106) Adjusted: No difference (HR 0.9, *P*=0.66)	NR	NR	AC $2,175 more expensive (*P*<0.001)
Collée *et al.*, 2022[6]	NR	NR	NR	Mentioned as outcome	NR
Kurian *et al.*, 2022[12]	NR	NR	NR	NR	NR

AC: Awake craniotomy, HR: Hazard ratio, NR: Not reported

systematic review identified pre-operative language deficits, intraoperative anomia, and intraoperative production errors (including speech arrest, semantic errors, and phonemic errors) as significant predictors of postoperative language decline. Kurian *et al.*'s[12] systematic review indicated comparable rates of transient neurological deficits between awake and asleep motor mapping techniques, though permanent deficits were slightly higher with awake motor mapping procedures.

Survival outcomes and economic data are presented in Table 6. Sarikonda *et al.*[24] provided the only comparative survival analysis between AC and GA approaches. Unadjusted analysis revealed better overall survival with AC compared to GA (P = 0.011), while progression-free survival showed no significant difference (P = 0.106). However, multivariate Cox proportional hazards modeling eliminated these differences, with neither overall survival (adjusted hazard ratio [HR] 0.84, P = 0.48) nor progression-free survival (adjusted HR 0.9, P = 0.66) demonstrating significant differences between approaches. The absence of survival benefit after confounder adjustment suggests patient selection rather than surgical technique accounted for unadjusted differences.

Sarikonda *et al.*[24] conducted the only economic analysis, demonstrating that AC resulted in significantly higher intraoperative costs compared to GA (additional $2,175/case, P < 0.001). This cost increase occurred without corresponding survival advantage after adjustment for confounding factors. Postoperative complications beyond neurological deficits were minimally reported. Pesce *et al.*[22] identified one surgical cavity hematoma in the hypnosis-assisted awake cohort, with no other major postoperative complications documented in any treatment group.

DISCUSSION

This systematic review synthesized evidence from six studies to compare AC with GA for glioma resection. The key finding is that current evidence does not demonstrate clear superiority of either surgical approach across all measured outcomes. While AC offers theoretical advantages for real-time functional assessment, only limited high-quality comparative data exist, and the available evidence presents a nuanced picture that challenges simplistic assumptions about optimal surgical technique selection.

Evidence base and clinical practice disconnect

It would seem that the selection of surgical options today is predominantly predicated on the theoretical benefits of awake surgery around functional preservation and improvement, rather than independent evidence that awake surgery has better clinical outcomes.[13] Nonetheless, these assertions need systematic validation through controlled studies. This likely reflects selection bias, where challenging cases in eloquent areas are treated preferentially with awake techniques. These arguments are supported by studies where "awake surgery is indicated when the patient is able to perform some language tasks in a preoperative language function test" and also that "patients with no paralysis or mild paralysis who are able to perform social activities" are considered eligible for awake surgery, thereby creating systematic differences between treatment groups, which confound outcome comparisons. This can also be done for anesthetic management, we have long used a traditional opioid approach despite recent and accumulating evidence replication success with other strategies.[9] In recent years, researchers have started to define clearer criteria for choosing candidates for awake procedures. Weller *et al*.[28] developed a practical grading approach that links factors such as younger age, higher language eloquence, and specific patterns of aphasia with the likelihood of tolerating awake surgery. Their findings suggest that using measurable preoperative variables can make the selection process more consistent and reduce the influence of surgeon preference.[22]

However, the assumptions of superiority lack the degree of comparative evidence. It is stated, "practice among the community is premised on theoretical advantages rather than comparative effectiveness data," with awake surgery being broadly referred to as the "gold standard" for localizing brain function and a safe and effective means of achieving a high rate of resection of lesions located in and around the eloquent cortex with a low degree of postoperative neurological deficit. This view is supported by Cheon *et al*., who reaffirmed that awake surgery remains the gold standard for intraoperative mapping of language areas because it allows direct cortical stimulation and functional verification during resection, while also noting that patient- or tumor-related factors can limit its feasibility.[4]

Broader context of evidence scarcity in neuro-oncology

This lack of evidence reaches beyond surgical approaches to treatment decisions throughout the care of gliomas. A recent Cochrane network meta-analysis showed that there were not enough data to perform analyses for treatment recommendations for second or later recurrence treatments. This illustrates how widespread the issue of evidence scarcity is for contemporary neuro-oncology practice.[24]

Even authoritative clinical practice guidelines point to these limitations of the evidence, as exemplified by the recent Congress of Neurological Surgeons systematic review for management of diffuse low-grade glioma, which provided mostly Level III recommendations with low evidence quality, emphasizing that the field relies on expert consensus more frequently than comparative data. The European Association of Neuro-Oncology has similarly highlighted that many of its recommendations stem from consensus among multidisciplinary experts rather than randomized data, reflecting both the rarity of controlled trials and the rapid evolution of glioma classification.[18] In parallel, the 2024 CNS guideline update underscored this same evidence gap through its predominance of Level III recommendations, illustrating the ongoing dependence of surgical decision-making on collective expert judgment rather than high-tier comparative studies.[19]

This scarcity of evidence is evident in specific areas of practice of AC in general, with more extensive literature reviews revealing significant gaps in our understanding of functional mapping techniques, and in particular for the right hemisphere gliomas, which have only recently gained more inkling into cognition function as standards to express and understand evidence has yet to be articulated and validated.[16,17] Recent work by Tomaselli *et al*. highlighted the emerging cognitive relevance of the right,[26] non-dominant hemisphere, showing that awake surgery can help preserve visuospatial, executive, and social cognitive functions, though standardized intraoperative testing protocols are still lacking.

Such evidence limitations highlight practical issues for clinical uptake, as obstruction to developing AC programs is exacerbated in resource constrained settings when we cannot apply evidence at all and again face identified barriers of infrastructure, workforce, and specialization to a multidisciplinary team.

Ethical and cognitive challenges in surgical research

The absence of a clear evidence base may be attributed to the ethical concerns associated with randomization in surgical trials, as clinical equipoise, in a proper context, requires bona fide uncertainty among medical professionals with regard to the comparative benefit of different interventions. Neurosurgeons make decisions which are further complicated, given the obstinacy of cognitive biases, including confirmation bias, where surgeons tend to seek advice from surgeons who will likely agree with their proposed management plan. They cite literature that supports their impression and dismiss literature that does not support their treatment plan.[5]

Rethinking survival outcomes and molecular determinants

Now, this casts doubt on the assumption that preservation of function equates with a better chance of survival. The lack of survival advantage after multiplate adjustment indicates that much more so than previously thought, survival outcomes may be dictated by molecular and biological factors, as evidenced by findings that "IDH status (HR for IDH-mutant status, 0.26; 95% confidence interval [CI], 0.17–0.41; $P < 0.001$)" and "MGMT status (HR for unmethylated status, 1.55; 95% CI, 1.14–2.10; $P = 0.005$)" were significantly associated with overall survival; the relationship between resection volume and survival may be more complex.[23] Large meta-analyses have shown that "patients with newly diagnosed GBM undergoing GTR were 61% more likely to survive 1 year (Relative risk [RR], 0.62; 95% CI, 0.56–0.69; $P < 0.001$)" and "19% more likely to survive 2 years (RR, 0.84; 95% CI, 0.79–0.89; $P < 0.001$)" than those with subtotal resection, while recent evidence raises the possibility that "supramarginal resection," which encompasses tumor beyond the boundaries of enhancement, might confer a survival advantage through the maximal resection of CE tumor followed by additional removal of non-CE tumor.[8,20]

Recent meta-analyses have strengthened the evidence supporting awake surgical techniques in eloquent gliomas. Honeyman *et al.* systematically compared glioblastoma resections performed under awake versus GA and observed that awake procedures achieved a greater extent of resection and a lower incidence of postoperative neurological deficits, with a modest but significant survival advantage.[10] Similarly, Gerritsen *et al.* demonstrated that the use of intraoperative stimulation mapping during high-grade glioma surgery was associated with higher rates of gross total resection, longer median survival, and fewer postoperative complications.[9] Collectively, these findings highlight that function-guided awake approaches can enhance both oncological and neurological outcomes in patients with eloquent high-grade gliomas.[14]

Resource allocation and healthcare barriers

Healthcare resource allocation becomes critical when evidence shows that infrastructure and personnel limitations represent major barriers to implementing AC in resource-constrained settings, where studies have identified challenges including inadequate facilities, insufficient trained staff, extended waiting periods, and suboptimal training quality as key obstacles to neurosurgical care delivery.[11,12] Evidence from high-resource centers suggests that structured programs can offset such barriers. Awake craniotomy program implementation reported that implementing a standardized multidisciplinary AC protocol reduced hospital stay, ICU use, and costs without compromising outcomes, emphasizing the value of organized team-based approaches in improving efficiency and care delivery.[1]

Study limitations

Major methodological limitations included the small number of direct comparative studies, only 2 out of 6, which limited the direct comparison of both the groups. Furthermore, small cohorts (e.g., Pesce *et al.*,[22] 15 patients), and predominantly retrospective, non-randomized designs that increase selection bias. Similar concerns have been observed in neurocognitive glioma research, where nearly half of pretreatment studies-based patient inclusion on tumor location, leading to heterogeneous data.[1] The scarcity of randomized evidence in glioma management further underscores this issue. Additional weaknesses included inconsistent outcome definitions, short follow-up durations, and attrition rates exceeding 20%.[25,31] Due to high heterogeneity and limited direct comparisons, no meta-analysis could be conducted, constraining the strength of comparative conclusions between awake and GA approaches.

Clinical implications and future directions

Future research should focus on large-scale randomized trials with well-matched patient cohorts, standardized outcome measures, and health economic evaluations. Integration of molecular profiling and computational tools, including AI-guided predictive models, may enhance surgical decision-making and patient selection. Long-term evaluation of functional outcomes and quality of life, alongside evidence-based criteria for awake versus GA approaches, will be critical to optimize neurological and oncological outcomes.

CONCLUSION

The finding of this systematic review shows that evidence in favor of AC as opposed to GA for glioma resection is actually more subtle than mostly assumed. Awake techniques certainly have clear advantages in real-time functional assessment of eloquent tumors, but outcomes are not systematically superior and tend to be more expensive. The choice of surgical method should be individualized based on parameters ranging from the tumor's location and patient factors to its molecular characteristics and institutional expertise, rather than on the presumption of one technique's supremacy over the other. Future directions should, therefore, be to develop evidence-based selection criteria for patients and standardized outcome assessments to enhance the surgical decision-making process being navigated in such a complex clinical scenario.

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