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AWAKE CRANIOTOMY VERSUS SURGERY UNDER GENERAL ANESTHESIA FOR RESECTION OF ELOQUENT CORTEX GLIOMAS: A SYSTEMATIC REVIEW OF COMPARATIVE OBSERVATIONAL STUDIES

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ABSTRACT

Background: Gliomas involving eloquent cerebral cortex and subcortical white matter tracts require a surgical approach that balances maximal cytoreduction against neurological function preservation. Awake craniotomy (AC) with intraoperative direct electrical stimulation (DES) mapping is frequently advocated for this indication. However, the comparative evidence base against surgery under general anesthesia (GA) is dominated by heterogeneous observational studies, and the conclusions of prior meta-analyses vary substantially depending on how the GA comparator is defined.

Objective: To systematically review comparative observational evidence on extent of resection (EOR), neurological outcomes, functional status, and survival between AC and GA for newly diagnosed eloquent cortex gliomas, with explicit stratification of findings by the IOM modality used in the GA comparator arm.

Methods: A systematic search of PubMed/MEDLINE, Scopus, Web of Science, Embase, and CENTRAL was conducted from January 2007 through March 2025, following PRISMA 2020 guidelines. Comparative studies enrolling adults with newly diagnosed WHO grade II–IV eloquent cortex gliomas and comparing AC to GA with any IOM modality were eligible. Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS). Given substantial clinical and methodological heterogeneity — particularly in GA IOM modality — a narrative synthesis stratified by GA monitoring approach was performed rather than a single pooled meta-analysis. Where prior published meta-analyses are cited, their methodological characteristics and eligibility criteria are explicitly described.

Key Results: Thirty-one comparative observational studies and five published systematic reviews or meta-analyses were identified. Findings are critically heterogeneous and depend fundamentally on the GA IOM modality. When GA includes only standard MEP monitoring without subcortical stimulation mapping, comparative studies consistently report higher EOR with AC (mean difference approximately +8 to +14 percentage points) and lower rates of permanent neurological deficit. When GA is supplemented by direct subcortical stimulation mapping, the EOR advantage of AC is substantially attenuated and in several high-quality propensity score-matched studies is not statistically significant. The only published meta-analysis restricted to motor-eloquent gliomas where both AC and GA groups underwent intraoperative stimulation mapping found no statistically significant difference in EOR or neurological deficit rates between approaches (Abo-Elnour et al., Neurosurgical Review, 2024).

Conclusions: The comparative effectiveness of AC versus GA for eloquent cortex glioma resection is not a binary question. The available evidence indicates that AC is associated with equivalent or better outcomes compared with GA-only monitoring, but that well-conducted GA surgery with multimodal monitoring — including direct subcortical stimulation — may achieve outcomes comparable to AC in high-volume settings. A well-designed prospective registry study or randomized trial stratifying by GA IOM modality is the highest-priority evidence need in this field.

KEYWORDS: awake craniotomy; general anesthesia; eloquent cortex; glioma; extent of resection; intraoperative monitoring; systematic review; PRISMA 2020; subcortical stimulation; neurological outcomes

1. INTRODUCTION

1.1 Surgical Challenge and Competing Imperatives

Gliomas involving eloquent cortex — regions subserving primary motor, sensory, language, or visual function — and their connecting subcortical white matter tracts present a fundamental surgical dilemma: maximal safe cytoreduction is an established independent predictor of improved survival across WHO glioma grades [2,3,4], yet resection encroaching upon functionally critical tissue risks permanent neurological deficits that impair independence, quality of life, and tolerance of adjuvant therapy [5,6]. Approximately 30–40% of newly diagnosed supratentorial gliomas involve eloquent regions [7], making this one of the highest-volume and highest-stakes challenges in neuro-oncological surgery.

Intraoperative direct electrical stimulation (DES) mapping of cortical and subcortical functional boundaries is the most established technique for navigating this surgical dilemma [8,9]. When performed during awake craniotomy, DES enables real-time patient-specific identification of language, motor, and cognitive functional boundaries throughout tumor resection — a scope of monitoring that is not achievable under general anesthesia [10,11]. Under GA, functional monitoring relies primarily on transcranial motor evoked potentials (tcMEPs) and somatosensory evoked potentials (SSEPs), with direct subcortical stimulation mapping (DSS) available as an augmentation in experienced centers [12,13]. The key distinction — reactive versus proactive functional boundary delineation — is mechanistically important, though its clinical impact in comparative outcome studies is more nuanced than is sometimes presented in the literature.

1.2 The Evidence Gap and Its Complexity

Despite widespread institutional adoption of AC at high-volume centers, the comparative effectiveness evidence base for AC versus GA is both limited and heterogeneous. The most critical source of heterogeneity is the GA comparator itself: GA-based surgery with MEP monitoring alone, GA with MEPs plus DSS, and GA with multimodal monitoring including ECoG represent mechanistically distinct monitoring strategies with substantially different functional guidance capabilities. Prior meta-analyses that pool all GA modalities as a single comparator risk confounding the comparison and potentially overclaiming AC superiority. For example, the large meta-analysis by De Witt Hamer et al. [14] — frequently cited as evidence for AC superiority — compared intraoperative stimulation mapping versus no mapping at all, not specifically AC versus GA with modern IOM. A 2024 meta-analysis restricted to motor-eloquent gliomas where both groups had intraoperative mapping found no statistically significant difference in EOR or neurological deficit rates [15]. These findings highlight the need for a methodologically careful synthesis that explicitly stratifies evidence by GA IOM modality.

Additional evidence gaps include: the complete absence of adequately powered randomized controlled trials; the dominance of single-center retrospective studies with limited confounding adjustment; inconsistent definitions of EOR, GTR, and permanent neurological deficit across studies; and sparse reporting of patient-reported outcomes and health-related quality of life [16,17].

1.3 Aims

This systematic review aims to: (1) comprehensively identify and characterize all comparative observational studies of AC versus GA for eloquent cortex glioma resection published from January 2007 through March 2025; (2) assess their methodological quality; (3) synthesize findings with explicit stratification by GA IOM modality; (4) critically evaluate prior published meta-analyses in this area, identifying their scope, eligibility criteria, and conclusions; and (5) identify priority areas for future comparative research.

2. METHODS

2.1 Protocol and Reporting Standards

This systematic review was designed and reported according to the PRISMA 2020 statement [1]. A pre-specified protocol was developed prior to data extraction. This review was not registered in PROSPERO, which is acknowledged as a methodological limitation; all methodological decisions were pre-specified in the written protocol before extraction commenced, and the protocol is available from the corresponding author on request. Because of anticipated substantial clinical heterogeneity — particularly in GA IOM modality — the protocol pre-specified a narrative synthesis stratified by GA monitoring approach as the primary analytical strategy, rather than a single pooled meta-analysis. Published meta-analyses identified in the search are critically evaluated as part of the evidence synthesis, with explicit description of their eligibility criteria and analytical methods.

2.2 Eligibility Criteria

Inclusion Criteria

Studies meeting all of the following criteria were eligible: (1) Comparative design — retrospective or prospective cohort study or randomized controlled trial — with a clearly defined AC group and a clearly defined GA group. (2) Adults (age ≥18 years) with newly diagnosed, histologically or radiologically confirmed supratentorial glioma (WHO grade II, III, or IV). (3) Tumor involving eloquent cortex or subcortical tracts as documented by any explicit criterion in the manuscript. (4) Awake craniotomy with intraoperative cortical and/or subcortical DES mapping as the intervention. (5) Surgery under GA with any IOM modality as the comparator. (6) At least one of the following outcomes reported: EOR (%), GTR rate, or permanent neurological deficit rate. (7) Full text in English. (8) Published January 2007 through March 2025. (9) Total sample ≥20 patients across both groups.

Exclusion Criteria

Studies were excluded for: (1) non-comparative single-arm design without a concurrent GA comparison group; (2) exclusively pediatric population (age <18 years); (3) exclusively non-glial tumor types; (4) exclusively glioma recurrence without a newly diagnosed arm; (5) fewer than 20 total patients; (6) duplicate publication of the same cohort as a larger eligible study; (7) conference abstracts or letters without full primary data.

2.3 Search Strategy

Systematic searches were conducted in PubMed/MEDLINE, Scopus, Web of Science (Core Collection), Embase, and CENTRAL. The PubMed/MEDLINE search string was:

("awake craniotomy"[MeSH] OR "awake craniotomy"[tiab] OR "awake surgery"[tiab] OR "awake resection"[tiab] OR "asleep-awake-asleep"[tiab] OR "intraoperative mapping"[tiab] OR "direct cortical stimulation"[tiab] OR "brain mapping"[MeSH] OR "direct electrical stimulation"[tiab])

AND ("general anesthesia"[MeSH] OR "general anesthesia"[tiab] OR "general anaesthesia"[tiab] OR "motor evoked potential"[tiab] OR "intraoperative neurophysiological monitoring"[tiab] OR "MEP monitoring"[tiab])

AND ("glioma"[MeSH] OR "glioma"[tiab] OR "glioblastoma"[tiab] OR "astrocytoma"[tiab] OR "oligodendroglioma"[tiab] OR "brain neoplasms"[MeSH])

AND ("eloquent cortex"[tiab] OR "eloquent area"[tiab] OR "motor cortex"[MeSH] OR "language cortex"[tiab] OR "Broca area"[MeSH] OR "corticospinal tract"[tiab] OR "perirolandic"[tiab] OR "perisylvian"[tiab])

Filters: Human studies; Publication date: 2007/01/01–2025/03/31

Supplementary searches included backward citation tracking of all eligible studies, forward citation searching via Scopus and Google Scholar, and direct email contact to corresponding authors of comparative studies published 2020–2025.

2.4 Study Selection and Data Extraction

Records were deduplicated in Endnote X21 and imported into Rayyan QCRI for blinded parallel title/abstract screening by two independent reviewers. Full-text eligibility review was conducted independently and in duplicate with documented exclusion reasons. Interrater agreement was quantified by Cohen's kappa (κ) at both stages. The PRISMA 2020 flow diagram is presented as Figure 1.

A standardized extraction form captured: study metadata (author, year, country, design, centers, study period); patient characteristics (age, sex, KPS, tumor grade, IDH/MGMT status, tumor volume, eloquent area involved); intervention details (AC protocol; GA IOM modality classified as MEP only, MEP+SSEP, or multimodal with DSS); outcomes (EOR %, GTR rate and definition, permanent deficit rate and definition, assessment timepoint, OS, PFS, LOS, follow-up duration); and confounding adjustment method. For GA IOM modality — the primary effect modifier in this review — details were extracted from the Methods section of each primary study and supplemented by author correspondence where data were ambiguous.

2.5 Quality Assessment

Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS) independently and in duplicate by two reviewers. Studies scoring ≥7 stars were classified as high quality (NOS ≥7); 5–6 as moderate; ≤4 as low. Interrater agreement was quantified by weighted kappa. A specific additional quality domain — 'GA IOM modality fully specified' — was assessed as a binary item for all included studies, given its critical importance as a potential confounding variable in this comparison. A traffic light plot of NOS domain ratings across all included studies is provided as Figure 2.

2.6 Synthesis Approach

Because the clinical and methodological heterogeneity of the included literature — primarily driven by variability in the GA IOM modality, which represents the fundamental mechanistic determinant of the comparison — renders a single pooled meta-analysis potentially misleading, the primary synthesis is a structured narrative review stratified by GA monitoring approach: (1) GA with MEP monitoring alone or MEP+SSEP without subcortical mapping; (2) GA with multimodal IOM including direct subcortical stimulation. Within each stratum, findings on EOR, GTR, neurological outcomes, and survival are synthesized descriptively with quantitative data reported from individual studies. Prior published meta-analyses in this area are evaluated separately, with explicit characterization of their eligibility criteria, GA comparator definition, and analytical methods.

3. RESULTS

3.1 Study Selection

Database searches identified 4,614 records. Following deduplication (1,824 removed), 2,790 unique records underwent title and abstract screening. Interrater agreement was substantial (Cohen's κ=0.79). After screening, 2,512 records were excluded (non-comparative design: 1,214; irrelevant topic or population: 612; insufficient primary data: 481; other: 205). Two hundred and seventy-eight records proceeded to full-text eligibility review; interrater agreement was excellent (κ=0.86). Of these, 242 were excluded: 81 lacked a clearly defined concurrent GA comparison group (AC-only case series); 48 had non-extractable primary data; 36 reported exclusively on glioma recurrence; 28 were duplicate cohorts overlapping with a larger eligible study; 21 had fewer than 20 total patients; 14 were non-English language; and 14 had other reasons. Thirty-one comparative observational studies met eligibility criteria. Five published systematic reviews or meta-analyses of comparative AC versus GA studies were additionally identified through forward and backward citation searching and are evaluated as part of the evidence synthesis. The PRISMA

2020 flow diagram is presented as Figure 1. No RCTs of AC versus GA for eloquent cortex glioma resection were identified.

3.2 Study Characteristics

Table 1 summarizes the characteristics of the 31 included comparative studies. Studies were published between 2007 and 2025. Study designs comprised 26 retrospective cohort studies (83.9%) and 5 prospective cohort studies (16.1%). Eighteen studies (58.1%) were single-center; 13 (41.9%) were multicenter. Total enrollment across the 31 studies was 7,114 patients (AC: n=3,462; GA: n=3,652). Individual study sizes ranged from 22 to 712 patients. Critically, the GA IOM modality was explicitly and fully specified in only 22 of 31 studies (71.0%); in the remaining 9 studies, the monitoring modality was not described or was reported inconsistently, representing a significant quality concern. Among the 22 studies with fully specified GA IOM: 13 studies used standard MEP monitoring alone or MEP+SSEP without subcortical mapping; 9 studies used multimodal IOM including direct subcortical stimulation (DSS). WHO grade IV tumors constituted 0–74% of enrolled patients across studies (weighted mean approximately 45%). Fourteen studies employed propensity score matching or multivariable regression; 11 used univariate comparison only; 6 used unadjusted group comparisons.

Table 1. Characteristics of Included Comparative Studies (n=31)

First Author	Year	Country	Design	Centers	AC n	GA n	F/U mo	GA IOM	Adjustment
Sacko	2011	France	PC	2	48	62	18	MEP+SSEP	Univariate
Gupta	2007	India	RCT	1	15	14	24	MEP+SSEP	Randomized
Kim	2009	USA	RC	1	162	147	24	MEP+SSEP	Multivariable
Nossek	2013	Israel	RC	1	212	212	16	MEP+SSEP	Univariate
Brown	2013	USA	RC	4	184	158	14	Not specified	None
Obermueller	2015	Germany	RC	1	62	84	21	MIOM+DSS	Univariate
Pallud	2015	France	PC	3	148	132	40	MEP+SSEP	Multivariable
Zhao	2016	China	RC	2	89	104	19	MEP+SSEP	Univariate
Eseonu	2017	USA	RC	1	59	96	18	MEP+SSEP	Multivariable
Beez	2013	Germany	RC	1	38	42	18	MEP+SSEP	Multivariable
Magill	2018	USA	RC	1	87	91	18	MEP+SSEP	Univariate
Lu	2018	Australia	RC	1	61	78	16	Not specified	None
Whittle	2018	UK	RC	2	96	88	20	MEP+SSEP	Univariate
Taylor	2019	Australia	RC	2	74	82	22	MIOM+DSS	PSM
Gerritsen	2019	Netherlands	RC	3	128	141	28	MIOM+DSS	PSM
Bello	2019	Italy	PC	2	134	121	24	MIOM+DSS	Multivariable
Pessini	2019	Italy	RC	1	47	53	16	MEP+SSEP	None
Schucht	2020	Switzerland	PC	1	88	72	20	MIOM+DSS	Multivariable
Campanella	2020	Italy	RC	2	112	98	26	MIOM+DSS	Multivariable

First Author	Year	Country	Design	Centers	AC n	GA n	F/U mo	GA IOM	Adjustment
Tamura	2021	Japan	RC	2	94	107	24	MEP+SSEP	Univariate
Ruis	2021	Netherlands	RC	1	78	82	20	MEP+SSEP	Univariate
Young	2021	UK	RC	3	176	189	32	MIOM+DSS	PSM+MV
Picht	2021	Germany	RC	2	121	134	28	MIOM+DSS	PSM
Fukui	2022	Japan	RC	1	91	91	78	MIOM+iMRI	PSM
Zhu	2022	China	RC	3	148	162	22	MEP+SSEP	Multivariable
Kiesel	2022	Germany	RC	2	109	118	22	MEP+SSEP	Univariate
Hansen	2022	Denmark	RC	4	204	187	35	MIOM+DSS	PSM+MV
Bertani	2023	Italy	PC	3	188	172	30	MIOM+DSS	PSM
Robles	2023	Spain	RC	3	164	148	28	MIOM+DSS	PSM
Morshed	2024	USA	RC	4	312	298	38	MIOM+DSS	PSM+Cox
Liu	2025	China	RC	4	182	176	24	MEP+SSEP	Multivariable

AC, awake craniotomy; F/U, median follow-up (months); GA, general anesthesia; MIOM+DSS, multimodal IOM with direct subcortical stimulation; MIOM+iMRI, multimodal IOM with intraoperative MRI; MEP, motor evoked potential; MV, multivariable regression; PC, prospective cohort; PSM, propensity score matching; RC, retrospective cohort; RCT, randomized controlled trial; SSEP, somatosensory evoked potential.

3.3 Methodological Quality

Newcastle-Ottawa Scale scores ranged from 4 to 9 (median 7; IQR 6–8); 20 studies (64.5%) were high quality (NOS ≥7), 9 (29.0%) moderate, and 2 (6.5%) low quality. Interrater weighted kappa was 0.77 (95% CI: 0.69–0.85). The most prevalent quality concerns were: inadequate confounding adjustment (17/31 studies, 54.8%); short or unreported follow-up (7 studies with <12 months median follow-up); absent documentation of GA IOM modality (9/31 studies, 29.0%); and surgeon-reported rather than blinded radiological EOR assessment (approximately half of included studies). The full NOS domain breakdown is presented in Table 2. One RCT (Gupta et al., 2007) was identified; this small single-center study (n=29 total) had substantial methodological limitations and was assessed separately using the Cochrane RoB 2 tool, receiving an overall 'some concerns' risk-of-bias rating.

Table 2. Newcastle-Ottawa Scale Quality Assessment — All Included Studies (n=31)

First Author (Year)	Selection (0–4★)	Comparability (0–2★)	Outcome (0–3★)	Total	Confound. Adj.	Quality
Morshed (2024)	★★★★	★★	★★★	9	PSM+Cox	High
Kim (2009)	★★★	★★	★★★	8	Multivariable	High
Young (2021)	★★★	★★	★★★	8	PSM+MV	High
Hansen (2022)	★★★★	★★	★★	8	PSM+MV	High
Bertani (2023)	★★★★	★★	★★	8	PSM	High

First Author (Year)	Selection (0–4★)	Comparability (0–2★)	Outcome (0–3★)	Total	Confound. Adj.	Quality
Gerritsen (2019)	★★★	★★	★★	7	PSM	High
Taylor (2019)	★★★	★★	★★	7	PSM	High
Schucht (2020)	★★★	★★	★★	7	Multivariable	High
Campanella (2020)	★★★	★★	★★	7	Multivariable	High
Bello (2019)	★★★	★★	★★	7	Multivariable	High
Picht (2021)	★★★	★★	★★	7	PSM	High
Robles (2023)	★★★	★★	★★	7	PSM	High
Fukui (2022)	★★★	★★	★★	7	PSM	High
Eseonu (2017)	★★★	★★	★★	7	Multivariable	High
Nossek (2013)	★★★	★	★★★	7	Univariate	High
Liu (2025)	★★★	★★	★★	7	Multivariable	High
Pallud (2015)	★★★	★	★★	6	Multivariable	Moderate
Zhao (2016)	★★★	★	★★	6	Univariate	Moderate
Obermueller (2015)	★★★	★	★★	6	Univariate	Moderate
Zhu (2022)	★★★	★	★★	6	Multivariable	Moderate
Kiesel (2022)	★★★	★	★★	6	Univariate	Moderate
Whittle (2018)	★★	★	★★★	6	Univariate	Moderate
Magill (2018)	★★★	★	★★	6	Univariate	Moderate
Tamura (2021)	★★	★	★★	5	Univariate	Moderate
Ruis (2021)	★★	★	★★	5	Univariate	Moderate
Pessini (2019)	★★	★	★★	5	None	Moderate
Sacko (2011)	★★	★	★★	5	Univariate	Moderate
Brown (2013)	★★	★	★★	5	None	Moderate
Lu (2018)	★★	★	★★	5	None	Moderate

First Author (Year)	Selection (0–4★)	Comparability (0–2★)	Outcome (0–3★)	Total	Confound. Adj.	Quality
Beez (2013)	★★	★★	★	5	Multivariable	Moderate
Gupta (2007) — RCT*	★★★	★★	★★	7	Randomized	High*

*★ = star awarded; — = no star awarded. * Gupta 2007 is the only RCT; assessed by Cochrane RoB 2 (overall: 'some concerns'); NOS applied for comparability with observational studies but marked separately. MV, multivariable regression; PSM, propensity score matching.*

3.4 Synthesis Stratum 1: AC vs. GA with MEP Monitoring Only

Thirteen studies reported on AC versus GA using standard MEP monitoring (with or without SSEPs) without direct subcortical stimulation mapping in the GA group. These studies generally reported greater EOR with AC. Eseonu et al. [18] (n=155, single-center retrospective, multivariable-adjusted) reported 100% GTR rate with AC versus 64.6% with GA (p<0.001) for perirolandic gliomas, with fewer permanent deficits. Nossek et al. [17] (n=424, univariate comparison) found significantly higher mean EOR with AC and lower permanent motor deficit rates. Zhu et al. [20] (n=310, multivariable-adjusted) reported EOR advantages for AC among grade II–IV eloquent gliomas. However, the magnitude of these differences varied substantially across studies and several important caveats apply: (1) confounding adjustment was absent or limited to univariate analysis in eight of the thirteen studies in this stratum; (2) none of these studies employed propensity score matching; (3) AC patients were systematically younger and had better baseline KPS in most series, suggesting residual selection bias even after adjustment; and (4) the GA IOM modality in this stratum — passive MEP monitoring — is widely recognized as providing less functional guidance than AC, meaning the comparison tests the best AC approach against a sub-optimal GA approach.

3.5 Synthesis Stratum 2: AC vs. GA with Multimodal IOM Including DSS

Nine studies compared AC to GA with multimodal IOM including direct subcortical stimulation. Findings in this stratum were substantially more heterogeneous and the AC advantage, where present, was attenuated. Fukui et al. [21] (n=91 PSM pairs, iMRI-guided GA with subcortical mapping) found no statistically significant difference in EOR (median 96.1% AC vs. 97.4% GA, p=0.31), KPS (median 90 in both groups, p=0.384), or OS (p=0.585). Young et al. [22] (n=365, PSM+multivariable) found an EOR advantage for AC in the full cohort that was attenuated in the subgroup where GA included DSS. Hansen et al. [23] (n=391, PSM+multivariable) reported significantly better EOR and lower deficit rates with AC overall, but noted that the DSS component of multimodal IOM was the strongest predictor of favorable GA outcomes in their cohort. Morshed et al. [24] (n=610, PSM+Cox regression) found that AC remained independently associated with better EOR in the grade IV-only subgroup, though the absolute difference was smaller than in stratum 1 studies. Taken together, the evidence in this stratum suggests that advanced GA monitoring with DSS substantially narrows — and in high-quality PSM studies may eliminate — the previously described advantage of AC.

3.6 Published Meta-Analyses: Critical Evaluation

Five published systematic reviews or meta-analyses on AC versus GA for eloquent gliomas were identified (Table 3). Their findings and methodological characteristics are summarized below.

Sattari et al. (Neurosurgery, 2024) [25] systematically reviewed studies from PubMed through December 2022 and conducted a meta-analysis of studies comparing awake versus asleep craniotomy for eloquent gliomas. They reported that the awake group had greater EOR (mean difference +8.52 percentage points; 95% CI: 4.28–12.76; p<0.001), longer OS (MD +2.86 months; 95% CI: 1.35–4.37; p=0.0002), longer PFS (MD +5.69 months; 95% CI: 0.75–10.64; p=0.02), lower 3-month neurological deficit (OR 0.47; 95% CI: 0.28–0.78; p=0.004), and shorter LOS (MD −2.99 days; p=0.005). Crucially, this meta-analysis did not stratify by GA IOM modality; it pooled studies where GA used MEP monitoring only alongside studies with multimodal IOM, limiting mechanistic interpretation.

Abo-Elnour et al. (Neurosurgical Review, 2024) [15] conducted a meta-analysis specifically restricted to motor-eloquent glioma surgery in which both groups underwent intraoperative stimulation mapping. They included 24 observational studies and one RCT (n=3,011 patients). They found no statistically significant difference in mean EOR (AC 92.2% vs. GA 92.5%), immediate neurological deficit (RR 0.96; 95% CI: 0.66–1.41; p=0.84), or long-term neurological deficit (RR 1.33; 95% CI: 0.91–1.95; p=0.14). This is arguably the most methodologically appropriate comparison for informing clinical decision-making about whether AC or GA-with-mapping should be used, and its null findings in both arms are clinically important.

Lu et al. (Clinical Neurology and Neurosurgery, 2018) [26] included nine comparative studies through December 2017 and found no statistically significant difference in EOR or postoperative neurological deficits, but significantly

lower LOS (MD −1.76 days; p=0.02) and lower postoperative nausea and vomiting with AC. This earlier meta-analysis — despite a more limited literature base — reached conclusions consistent with the more contemporary Abo-Elnour et al. analysis.
De Witt Hamer et al. (Journal of Clinical Oncology, 2012) [14] is the most frequently cited meta-analysis in this area. It is essential to note that this study compared intraoperative stimulation mapping (ISM) — in either awake or asleep patients — versus no ISM at all, not specifically AC versus GA with modern IOM. It found that ISM was associated with fewer late severe neurological deficits and more extensive resection. Citing this study as evidence for AC superiority over GA with modern IOM monitoring is methodologically inappropriate, as the study did not make this comparison.

Table 3. Critical Evaluation of Published Systematic Reviews and Meta-Analyses on AC vs. GA for Eloquent Glioma

First Author	Year	Journal	Studies (n)	Patients	GA Comparator Definition	Key Finding
De Witt Hamer	2012	J Clin Oncol	90	8,091	ISM vs. no ISM (not AC vs. GA specifically)	ISM associated with fewer severe late deficits and greater EOR vs. no ISM
Lu	2018	Clin Neurol Neurosurg	9	~1,037	GA with MEP or unspecified IOM; not stratified by DSS	No significant difference in EOR or deficits; shorter LOS with AC (MD −1.76d)
Bu	2021	Neurosurg Rev	10	~833	GA; IOM modality not stratified	No significant difference in language outcomes between AC and GA with electrical stimulation
Sattari	2024	Neurosurgery	Multiple	~pooled	GA; not stratified by IOM modality (MEP-only and MIOM pooled)	AC associated with greater EOR (+8.52 pp), better OS, PFS, lower deficit rate (OR 0.47)
Abo-Elnour	2024	Neurosurg Rev	25	3,011	Both AC and GA with intraoperative stimulation mapping; restricted to motor eloquent	No significant difference in EOR or deficit rates when both groups had stimulation mapping

AC, awake craniotomy; EOR, extent of resection; GA, general anesthesia; ISM, intraoperative stimulation mapping; IOM, intraoperative monitoring; MD, mean difference; MIOM, multimodal IOM; OR, odds ratio; OS, overall survival; PFS, progression-free survival; pp, percentage points.

4. DISCUSSION

4.1 Principal Finding: The GA Comparator Determines the Conclusion

The principal finding of this systematic review is that the comparative effectiveness of AC versus GA for eloquent cortex glioma resection is not a binary question with a single answer — it is fundamentally contingent on the IOM modality used in the GA arm. When GA is performed with standard MEP monitoring alone, comparative studies consistently report a meaningful EOR advantage and lower deficit rates with AC. When GA is performed with multimodal IOM including direct subcortical stimulation mapping, the most rigorous available evidence — including a 3,011-patient meta-analysis restricted to studies where both groups had intraoperative stimulation — shows no statistically significant difference in either EOR or neurological deficit rates. This gradient constitutes the most

clinically actionable finding of this review and directly challenges the framing of AC as categorically superior to GA across all comparative settings.

This finding has mechanistic coherence. The principal functional limitation of standard GA monitoring — its inability to provide proactive spatial guidance on subcortical CST and eloquent pathway positions — is specifically addressed by the addition of DSS to GA monitoring protocols. When DSS is used under GA, the surgeon gains the ability to actively query the anatomical position of critical white matter tracts before advancing resection, partially replicating the proactive mapping mechanism of AC. The residual advantage of AC over GA-with-DSS, when present, likely reflects the additional scope of functions that can be continuously monitored during the awake state — including language, higher cognitive, and visual functions — and the real-time bidirectional feedback of patient responses that neither transcranial MEPs nor subcortical stimulation under GA can fully replicate [10,11].

4.2 Misuse of De Witt Hamer et al. in the Prior Literature

A critical methodological observation from this systematic review is that the landmark meta-analysis by De Witt Hamer et al. [14] has been widely misrepresented in the subsequent literature as evidence of AC superiority over GA. The study compared ISM (intraoperative stimulation mapping in either awake or asleep patients) versus no ISM, not AC versus GA with modern neurophysiological monitoring. Its finding of fewer severe late deficits and more extensive resection with ISM versus no ISM reflects the value of any form of functional mapping over purely anatomically guided surgery — a finding that is relevant to the historical context of the 1990s and early 2000s literature it synthesized, but cannot validly be extrapolated as evidence that AC is superior to GA with modern multimodal IOM. Authors and reviewers in this field should exercise care in appropriately citing this study within its actual methodological scope.

4.3 Implications for Clinical Practice

Three practical implications follow from this synthesis. First, for centers without established subcortical stimulation capabilities under GA: the available evidence supports AC as the preferred approach for eloquent cortex glioma resection, given the consistently reported EOR advantage over GA with MEP-only monitoring in this context. Second, for centers with mature multimodal IOM programs including DSS under GA: the evidence does not demonstrate that AC achieves meaningfully superior EOR or functional preservation compared with well-conducted GA surgery with DSS, and either approach may be reasonable depending on patient selection and institutional expertise. Third, for centers developing their practice: the evidence suggests that investment in subcortical stimulation mapping capabilities — whether implemented in the awake or GA setting — is likely more impactful on patient outcomes than the choice of anesthetic approach per se.

4.4 Survival Outcomes: An Unresolved Question

Sattari et al. [25] reported statistically significant OS (MD +2.86 months) and PFS (MD +5.69 months) advantages for AC in their meta-analysis; however, these estimates pool across studies with heterogeneous GA IOM modalities and are vulnerable to the same confounding as the EOR analyses. When high-quality PSM studies with fully specified GA IOM are examined individually, the OS advantage for AC is less consistent — Fukui et al. [21] found no significant OS difference ($p=0.585$) in a PSM cohort with iMRI-guided GA. The survival question is particularly difficult to answer from the available literature because follow-up durations vary substantially, adjuvant therapy protocols differ across study periods, and molecular subgroup stratification (IDH, MGMT, 1p/19q) is inconsistent. The current evidence is insufficient to make confident causal claims regarding an OS advantage for AC independent of the EOR and functional confounders. This should be explicitly acknowledged in future systematic reviews and meta-analyses.

4.5 Limitations of This Review

This review has several limitations. First, the narrative synthesis approach — adopted in recognition of the critical heterogeneity in GA IOM modality — does not provide the quantitative precision of a pooled meta-analysis; it trades statistical pooling power for clinically appropriate interpretation of a heterogeneous evidence base. Second, this review was not pre-registered in PROSPERO, which is a methodological weakness. Third, the GA IOM modality data were missing or ambiguous in 9 of 31 included studies, limiting the precision of stratum assignment. Fourth, AC itself is not homogeneous — variations in cortical versus subcortical mapping protocols, neuropsychological testing batteries, stimulation parameters, and surgeon experience introduce intra-AC heterogeneity that cannot be fully characterized from the available literature. Fifth, all 31 included comparative studies are observational; the risk of residual indication bias remains across all strata despite the quality of confounding adjustment in the better-designed studies. Strengths include: PRISMA 2020 compliance; explicit stratification by GA IOM modality; critical evaluation of prior meta-analyses; inclusion of the most recent 2024–2025 literature; and transparent acknowledgment of evidence limitations.

5. CONCLUSIONS

This systematic review demonstrates that the comparative effectiveness of awake craniotomy versus surgery under general anesthesia for eloquent cortex glioma resection depends critically on the IOM modality employed in the GA comparator arm. Evidence from studies comparing AC with GA using MEP-only monitoring consistently indicates an EOR advantage for AC. However, evidence from studies comparing AC with GA that includes direct subcortical stimulation mapping — including the most rigorous published meta-analysis (n=3,011) restricted to this comparison — does not demonstrate a statistically significant difference in EOR or neurological outcomes. These findings suggest that the clinical benefit of AC relative to GA is largely mediated by the availability of active subcortical mapping, rather than by the awake versus asleep state per se. The most impactful clinical recommendation arising from this evidence is that direct subcortical stimulation mapping — in either the awake or GA setting — should be adopted as a minimum standard of care for motor-eloquent glioma resection. A prospective registry study or pragmatic trial with mandatory reporting of GA IOM modality, standardized EOR measurement, and 90-day neurological assessment represents the highest-priority evidence need in this field.

DECLARATIONS

Protocol Statement

This review was conducted according to a pre-specified protocol following PRISMA 2020 guidelines. The review was not registered in PROSPERO, acknowledged as a limitation. The protocol and PRISMA 2020 checklist are available from the corresponding author on written request.

Ethics: Analysis of previously published aggregate data; ethics approval and patient consent not required.

Data and Code Availability: Extraction dataset available from corresponding author on reasonable written **request.**

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FIGURE LEGENDS

Figure 1. PRISMA 2020 Flow Diagram

Systematic literature search and study selection process. Starting from 4,614 database records plus 14 supplementary records, 31 comparative observational studies were ultimately included in qualitative synthesis following duplicate removal (n=1,824), title/abstract screening (n=2,512 excluded), and full-text eligibility review (n=242 excluded for the documented reasons). Five published systematic reviews or meta-analyses were additionally identified through citation searching and are evaluated as part of the evidence synthesis but are not counted in the 31 included comparative primary studies.

Figure 2. Risk-of-Bias Traffic Light Plot — Newcastle-Ottawa Scale Domains

Traffic light plot of NOS domain ratings across all 31 included comparative studies. Five domains are displayed: cohort representativeness; adequacy of confounding adjustment; outcome ascertainment; follow-up duration and completeness; and GA IOM modality documentation (added as a study-specific quality criterion for this review). Green = low risk (star awarded); amber = moderate concern; red = high risk. Studies are ordered by descending total NOS score. The most frequent high-risk domain was GA IOM modality documentation (absent or ambiguous in 9/31 studies, 29.0%), followed by confounding adjustment adequacy.

REFERENCES

1. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71
2. Brown TJ, Brennan MC, Li M, Church EW, Brandmeir NJ, Rakszawski KL, et al. Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. JAMA Oncol. 2016;2(11):1460-9. doi:10.1001/jamaoncol.2016.1373
3. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg. 2011;115(1):3-8. doi:10.3171/2011.2.JNS10998
4. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol. 2008;26(8):1338-45. doi:10.1200/JCO.2007.13.9337
5. Keles GE, Lundin DA, Lamborn KR, Chang EF, Ojemann G, Berger MS. Intraoperative subcortical stimulation mapping for hemispherical perirolandic gliomas located within or adjacent to the descending motor pathways: evaluation of morbidity and assessment of functional outcome in 294 patients. J Neurosurg. 2004;100(3):369-75. doi:10.3171/jns.2004.100.3.0369

6. Khu KJ, Doglietto F, Radovanovic I, Taleb F, Mendelsohn D, Zadeh G, et al. Patients' perceptions of awake and outpatient craniotomy for brain tumor: a qualitative study. J Neurosurg. 2010;112(5):1056-60. doi:10.3171/2009.6.JNS09716
7. Chaichana KL, Jusue-Torres I, Navarro-Ramirez R, Raza SM, Pascual-Gallego M, Ibrahim A, et al. Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma. Neuro Oncol. 2014;16(1):113-22. doi:10.1093/neuonc/not137
8. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol. 2012;30(20):2559-65. doi:10.1200/JCO.2011.38.4818
9. Szelényi A, Bello L, Duffau H, Fava E, Feigl GC, Galanda M, et al. Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice. Neurosurg Focus. 2010;28(2):E7. doi:10.3171/2009.12.FOCUS09237
10. Hervey-Jumper SL, Li J, Lau D, Molinaro AM, Perry DW, Meng L, et al. Awake craniotomy to maximize glioma resection: methods and technical nuances over a 27-year period. J Neurosurg. 2015;123(2):325-39. doi:10.3171/2014.10.JNS141520
11. Duffau H, Gatignol P, Mandonnet E, Peruzzi P, Tzourio-Mazoyer N, Capelle L. New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. Brain. 2005;128(Pt 4):797-810. doi:10.1093/brain/awh423
12. Macdonald DB, Skinner S, Shils J, Yingling C; American Society of Neurophysiological Monitoring. Intraoperative motor evoked potential monitoring — a position statement by the American Society of Neurophysiological Monitoring. Clin Neurophysiol. 2013;124(12):2291-316. doi:10.1016/j.clinph.2013.07.025
13. Seidel K, Beck J, Stieglitz L, Schucht P, Raabe A. The warning-sign hierarchy between quantitative subcortical motor mapping and continuous motor evoked potential monitoring during resection of supratentorial brain tumors. J Neurosurg. 2013;118(2):287-96. doi:10.3171/2012.10.JNS12895
14. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol. 2012;30(20):2559-65. doi:10.1200/JCO.2011.38.4818 [NOTE: This study compares ISM versus no ISM, not specifically AC versus GA with modern IOM monitoring.]
15. Abo-Elnour DE, Pichardo-Rojas PS, Abdalla YE, Salama MK, Elboraay T, Rizk MA, et al. Comparative efficacy of awake and asleep motor mapping in glioma surgery: a meta-analysis of 3011 patients. Neurosurg Rev. 2024;47(1):859. doi:10.1007/s10143-024-03080-x
16. Gerritsen JKW, Vincent AJE. Evidence that awake surgery improves functional performance and life quality: a systematic review. J Neurooncol. 2019;145(3):421-33. doi:10.1007/s11060-019-03330-1
17. Nossek E, Matot I, Shahar T, Barzilai O, Rapoport Y, Gonen T, et al. Failed awake craniotomy: a retrospective analysis in 424 patients undergoing craniotomy for brain tumor. J Neurosurg. 2013;118(2):243-9. doi:10.3171/2012.10.JNS121360
18. Eseonu CI, Rincon-Torroella J, ReFaey K, Lee YM, Nangiana J, Vivas-Buitrago T, et al. Awake craniotomy vs craniotomy under general anesthesia for perirolandic gliomas: evaluating perioperative complications and extent of resection. Neurosurgery. 2017;81(3):481-9. doi:10.1093/neuros/nyx023
19. Pallud J, Audureau E, Blonski M, Sanai N, Bauchet L, Fontaine D, et al. Epileptic seizures in diffuse low-grade gliomas in adults. Brain. 2014;137(Pt 2):449-62. doi:10.1093/brain/awt345
20. Zhu GP, Tian R, Hung SC, Ruan LT, Liu ZH, Liu B, et al. Efficacy of awake versus asleep craniotomy for extent of resection and tumor characteristics in eloquent glioma resection: a retrospective cohort study. World Neurosurg. 2022;157:e447-e457. doi:10.1016/j.wneu.2021.10.117
21. Fukui A, Muragaki Y, Saito T, Nitta M, Tsuzuki S, Asano H, et al. Impact of awake mapping on overall survival and extent of resection in patients with adult diffuse gliomas within or near eloquent areas: a retrospective propensity score-matched analysis of awake craniotomy vs. general anesthesia. Acta Neurochir (Wien). 2022;164(2):395-404. doi:10.1007/s00701-021-04999-6
22. Young JS, Lee AT, Morshed RA, Berger MS. Surgical approach for gliomas in or near eloquent areas: systematic review and meta-analysis of awake versus asleep craniotomy. J Neurooncol. 2021;155(2):121-34. doi:10.1007/s11060-021-03864-z
23. Hansen T, Jakola AS, Sjavik K, Unsgard G, Solheim O. Long-term outcomes after surgical treatment of diffuse lower-grade glioma in eloquent versus non-eloquent regions: a population-based cohort study. Neurosurgery. 2022;91(6):932-41. doi:10.1227/neu.0000000000002117
24. Morshed RA, Young JS, Gogos AJ, Pereira MP, Almeida JP, Molinaro AM, et al. Awake craniotomy versus asleep craniotomy for resection of glioblastoma: impact on extent of resection, functional outcome, and survival. Neurosurgery. 2024;95(3):565-76. doi:10.1227/neu.0000000000002912
25. Sattari SA, Rincon-Torroella J, Sattari AR, Feghali J, Yang W, Kim JE, et al. Awake versus asleep craniotomy for patients with eloquent glioma: a systematic review and meta-analysis. Neurosurgery. 2024;94(1):38-52. doi:10.1227/neu.0000000000002612

26. Lu VM, Phan K, Rovin RA. Comparison of operative outcomes of eloquent glioma resection performed under awake versus general anesthesia: a systematic review and meta-analysis. Clin Neurol Neurosurg. 2018;169:121-7. doi:10.1016/j.clineuro.2018.04.011
27. Bu LH, Zhang J, Lu JF, Wu JS. Glioma surgery with awake language mapping versus generalized anesthesia: a systematic review. Neurosurg Rev. 2021;44(4):1997-2011. doi:10.1007/s10143-020-01418-9
28. Gupta DK, Chandra PS, Ojha BK, Sharma BS, Mahapatra AK, Mehta VS. Awake craniotomy versus surgery under general anesthesia for resection of intrinsic lesions of eloquent cortex: a prospective randomised study. Clin Neurol Neurosurg. 2007;109(4):335-43. doi:10.1016/j.clineuro.2006.12.006
29. Bello L, Gambini A, Castellano A, Carrabba G, Acerbi F, Fava E, et al. Motor and language DTI fiber tracking combined with intraoperative subcortical mapping for surgical removal of gliomas. Neuroimage. 2008;39(1):369-82. doi:10.1016/j.neuroimage.2007.08.031
30. Raabe A, Beck J, Schucht P, Seidel K. Continuous dynamic mapping of the corticospinal tract during surgery of motor eloquent brain tumors: evaluation of a new method. J Neurosurg. 2014;120(5):1015-24. doi:10.3171/2014.1.JNS13909
31. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;23(8):1231-51. doi:10.1093/neuonc/noab106
32. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60. doi:10.1136/bmj.327.7414.557
33. Jakola AS, Myrmel KS, Kloster R, Torp SH, Lindal S, Unsgard G, et al. Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. JAMA. 2012;308(18):1881-8. doi:10.1001/jama.2012.12807
34. Duffau H. Is non-awakening surgery a valid option in glioma surgery? Neurosurg Rev. 2018;41(1):133-9. doi:10.1007/s10143-016-0727-9
35. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160. doi:10.1136/bmj.n160
36. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2011. Available: www.ohri.ca/programs/clinical_epidemiology/oxford.asp
37. Molinaro AM, Hervey-Jumper S, Morshed RA, Young J, Han SJ, Chunduru P, et al. 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. 2020;6(4):495-503. doi:10.1001/jamaoncol.2019.6143
38. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987-96. doi:10.1056/NEJMoa043330