

5-Aminolevulinic Acid-Guided Glioma Resection During Awake Craniotomy: Systematic Review of Functional Safety and Oncologic Benefit

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Systematic Review

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Abstract

Introduction:

Maximal safe resection remains the cornerstone of glioma surgery, particularly in eloquent regions where oncologic gain must be balanced against functional preservation. While 5-aminolevulinic acid (5-ALA) fluorescence-guided surgery improves extent of resection in high-grade gliomas under general anesthesia, its role during awake craniotomy (AC) remains underdeveloped. We aimed to evaluate the oncologic and functional outcomes of 5-ALA-guided tumor resection during AC.

Methods

PubMed, Scopus, and Web of Science were searched from inception to February 2026 for studies reporting original data on AC using 5-ALA following PRISMA guidelines. Study quality was assessed using Joanna Briggs Institute tools.

Results

Across 10 studies comprising 108 patients, fluorescence positivity was 76.5% in high-grade gliomas and 17.5% in low-grade gliomas. Gross-total resection was achieved in 57.4% overall, reaching 66.7% in the largest cohort. Transient aphasia occurred in 25.9% of patients, while permanent aphasia and persistent hemiparesis were observed in 8.3% and 14.8%, respectively. In multiple studies, resection was intentionally halted despite persistent fluorescence when functional mapping identified an eloquent cortex, underscoring that mapping remained the decisive determinant of surgical boundaries. No study reported conversion to general anesthesia.

Conclusions

5-ALA-guided resection during AC appears feasible, functionally safe, and clinically useful, particularly for high-grade gliomas in eloquent regions. Across the available literature, 5-ALA consistently enhances intraoperative tumor visualization, supports identification of residual fluorescent disease, and integrates well with cortical and subcortical mapping without clear evidence of increased permanent neurological morbidity. Although functional mapping remains the decisive determinant of the final resection boundary, the available evidence supports 5-ALA as a valuable complementary adjunct in onco-functional glioma surgery. Prospective multicenter studies with standardized volumetric and survival endpoints are now needed to refine patient selection and quantify its added benefit.

Introduction

Maximal safe resection of the tumor tissue remains the cornerstone of glioma surgery. The extent of resection (EOR) correlates strongly with both progression-free and overall survival in low- and high-grade gliomas [1–5]. Achieving gross-total resection (GTR) near eloquent cortical or subcortical areas remains challenging, as aggressive removal risks permanent neurological deficit [6–10]. Awake craniotomy (AC) with direct cortical and subcortical mapping enables maximal tumor removal while preserving motor, language, and cognitive networks [11–15].

Parallel advances in fluorescence-guided surgery using 5-aminolevulinic acid (5-ALA) have improved intraoperative tumor visualization and EOR under general anesthesia [16–18]. Following oral administration, 5-ALA is metabolized to protoporphyrin IX, emitting red-pink fluorescence under blue light and delineating malignant tissue [19–22]. Randomized trials have shown that 5-ALA improves complete resection rates and progression-free survival in glioblastoma, making it a routine adjunct in high-grade glioma management [23, 24]. Figure 1 demonstrates application of 5-ALA in resection of a right frontal Glioblastoma in a 64-year-old female by one of the authors. Under the standard white-light microscope, the distinction between tumor and surrounding brain tissue is limited, however, tumor is highlighted by pink fluorescence under the Blue-light in the same surgical cavity, facilitating maximum resection of neoplastic tissue.

Awake mapping and 5-ALA fluorescence offer distinct but highly complementary intraoperative information. Whereas direct electrical stimulation defines the functional limits of safe resection, 5-ALA enhances visualization of metabolically active tumor tissue and may improve identification of residual disease, particularly in high-grade gliomas [25, 26]. Although fluorescence cannot substitute for mapping in eloquent cortex and may be less sensitive in lower-grade gliomas, its integration into awake surgery offers an appealing onco-functional strategy in which tumor visualization and functional preservation are pursued simultaneously. Conversely, non-fluorescent infiltrative tumor may extend beyond visible margins, particularly in lower-grade gliomas, limiting the reliability of fluorescence as a sole guide [27].

The literature examining 5-ALA specifically within the context of AC, however, remains limited, consisting predominantly of small retrospective series and case reports. Data regarding fluorescence behavior during cortical versus subcortical phases, concordance with histopathology in eloquent regions, and the influence of 5-ALA on surgical stopping points during awake procedures are sparse.

Other adjuncts, including intraoperative MRI, may further refine resection, but 5-ALA remains attractive because it is of lower cost and more readily available, immediately actionable at the operative field, can guide selective continuation of resection in non-eloquent fluorescent regions, and may increase surgeon confidence at the tumor-brain interface [28–32]. Accordingly, the key question is not whether mapping or fluorescence should take priority - mapping clearly must - but how much additional practical and oncologic value fluorescence provides when used alongside awake functional monitoring [33–35].

Despite growing use of 5-ALA in functional neuro-oncology, no prior systematic review has specifically evaluated its integration within awake mapping paradigms. This systematic review synthesizes available evidence on the combined use of 5-ALA and awake functional mapping in glioma surgery, focusing on fluorescence behavior, oncologic and functional outcomes, and intraoperative decision-making.

Methods

Data Source and Search Strategy

We conducted this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [36] to identify published literature on AC in patients using 5-ALA. PubMed, Scopus, and Web of Science databases were searched from inception to February 21st, 2026, for relevant articles. The following Boolean terms were used for the search: (“awake craniotomy” OR “awake brain surgery” OR “awake neurosurgery” OR “awake brain mapping” OR “awake tumor resection” OR “craniotomy while awake”). Given the rarity of 5-ALA usage in AC, a deliberately broad search strategy was used. Full Boolean strings are provided in **Supplementary Table 1**.

Inclusion and Exclusion Criteria

Eligible studies met these criteria: (1) original human data; (2) English language; (3) AC performed with 5-ALA administration; (4) sufficient intraoperative and postoperative detail for data extraction. Studies were excluded if they included only general anesthesia cases, combined multiple fluorescence agents, or lacked extractable clinical information. No preregistered protocol was created because limited and heterogeneous data precluded a predefined quantitative synthesis.

Article selection process

Initial screening of titles and abstracts was independently performed by two reviewers (M.M. and M.S.M.). Potentially eligible articles underwent full-text review for final inclusion. Discrepancies were resolved by consensus. Reference lists of all included studies were additionally screened to identify relevant articles not captured by the database search.

Data Extraction and Synthesis

Two reviewers (M.M. and M.S.M.) independently extracted study and patient-level variables, including demographics, tumor features, operative technique, fluorescence findings, and outcomes. The methodological quality of included case reports was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports [Munn et al., 2020]. Disagreements were resolved by consensus.

Results

Study selection

A total of 14,908 records were identified. After deduplication and screening, ten studies comprising 108 patients were included (Fig. 2). Publication years ranged from 2015 to 2025 and originated mainly from Europe and North America.

Study Characteristics

A total of ten studies with 108 patients undergoing 5-ALA-guided AC were included [37–46]. Six studies were single-patient case reports, one was a retrospective case series (n = 19), one was a prospective observational cohort (n = 40), and one was a retrospective comparative cohort (n = 42). Larger cohort studies accounted for 101 of 108 patients (93.5%), whereas case reports contributed 7.4%. Recurrent tumors were reported in 16 of 108 patients (14.8%), most frequently in the retrospective case series and comparative cohort (Table 1).

Table 1
A Summary of Study Characteristics

Study	Title	Country	Study design	Sample size	Study period	Inclusion/exclusion criteria
Corns et al., 2015 [37]	5-aminolevulinic acid guidance during awake craniotomy to maximise extent of safe resection of glioblastoma multiforme	United Kingdom	Single case report	1 patient	Initial surgery July 2012; recurrence 16 months later	Recurrent left frontal GBM encroaching on Broca's area; candidate for awake craniotomy and 5-ALA
Skjøth-Rasmussen et al., 2017 [38]	Awake craniotomy with 5-ALA in high grade gliomas gives simultaneous guidance of tumor and functional border	Denmark	Retrospective case series	19 patients	Not reported	Suspected HGG undergoing combined 5-ALA-assisted surgery and awake mapping craniotomy
Brosnan et al., 2022 [39]	Anesthetic Selection for an Awake Craniotomy for a Glioma with Wernicke's Aphasia	United States	Single case report	1 patient	2022	High-grade glioma near Wernicke's area undergoing SAS awake craniotomy with 5-ALA
Drosos et al., 2022 [40]	Awake brain surgery for autistic patients: Is it possible?	United Kingdom	Single case report	1 patient	2022	To present a case of a patient with autistic spectrum disorder that was successfully operated for a brain tumor through awake craniotomy.
Goryaynov et al., 2022 [41]	5-ALA-guided tumor resection during awake speech mapping in gliomas located in eloquent speech areas	Russia	Prospective single-centre observational study	40 patients	2008–2020	Patients age over 18 years old, and diagnosis of left frontal or temporal glioma requiring awake surgery with intraoperative detection of the eloquent speech cortical areas and tracts, including superior longitudinal fasciculus, arcuate fasciculus, or frontal aslant tract
Haider et al., 2022 [42]	Clinically useful tumor fluorescence greater than 24 hours after 5-aminolevulinic acid administration	United States	Single case report	1 patient	Not specified	Newly diagnosed dominant hemisphere high-grade glioma planned for AC with 5-ALA
Price et al., 2023 [43]	Awake resection of recurrent astroblastoma with intraoperative 5-ALA-induced fluorescence: illustrative case	United States	Single case report	1 patient	Recurrence 21 years after initial diagnosis; index surgery age 32	Recurrent astroblastoma in dominant hemisphere undergoing AC with 5-ALA

Study	Title	Country	Study design	Sample size	Study period	Inclusion/exclusion criteria
Matei et al., 2024 [44]	Awake surgery during 5-ALA high grade glioma fluorescence guided resection	Romania	Single case report	1 patient	Surgery performed May 2023	Frontal high-grade glioma requiring AC with 5-ALA
Moldabekov et al., 2024 [45]	Awake magic: glioblastoma resection under 5-aminolevulinic acid guidance during awake craniotomy. A case report with video demonstration	Kazakhstan	Single case report	1 patient	Surgery performed June 2022	Contrast-enhancing left frontotemporal glioma involving Broca's area requiring awake mapping + 5-ALA
Tagle-Vega et al., 2025 [46]	Integration of 5-ALA fluorescence and intraoperative MRI in awake craniotomy for glioma resection	Brazil	Retrospective single-centre cohort study	42 patients	2016–2022	To analyse the integration of 5-ALA fluorescence-guided surgery and iMRI during AC for glioma resection at a single center in Brazil

AC, awake craniotomy; ALA, aminolevulinic acid; GBM, glioblastoma multiforme; HGG, high-grade glioma; iMRI, intraoperative magnetic resonance imaging; SAS, asleep-awake-asleep

Quality Assessment of Included Studies

Quality assessment using the Joanna Briggs Institute (JBI) critical appraisal tools [47] demonstrated overall variable methodological rigor across the included studies (Table 2). Collectively, the body of evidence consists predominantly of observational data with inherent susceptibility to selection bias and confounding. No randomized or prospective controlled studies were included in our review. Therefore, the overall strength of evidence supporting 5-ALA-guided AC in eloquent glioma surgery should be interpreted as moderate in reporting quality but limited by study design.

Table 2
Joanna Briggs Institute (JBI) Critical Appraisal Summary of Included Studies with Overall Risk-of-Bias Classification.

Study	Yes	No	Unclear	Quality Score (%)	Overall Risk of Bias
Corns et al., 2015 (Case Report) [37]	7	0	1	87.5%	Low
Skjott-Rasmussen et al., 2017 (Case Series – Abstract) [38]	2	0	8	20.0%	High
Brosnan et al., 2022 (Case Report) [39]	7	0	1	87.5%	Low
Drosos et al., 2022 (Case Report) [40]	8	0	0	100.0%	Low
Goryaynov et al., 2022 (Cohort Study) [41]	6	1	4	54.5%	Moderate
Haider et al., 2022 (Case Report) [42]	7	0	1	87.5%	Low
Price et al., 2023 (Case Report) [43]	8	0	0	100.0%	Low
Matei et al., 2024 (Case Report) [44]	4	0	4	50.0%	Moderate
Moldabekov et al., 2024 (Case Report) [45]	7	0	1	87.5%	Low
Tagle-Vega et al., 2025 (Cohort Study) [46]	7	1	3	63.6%	Moderate

Case reports were assessed using the 8-item JBI Case Report Checklist; the case series was assessed using the 10-item JBI Case Series Checklist; cohort studies were assessed using the 11-item JBI Cohort Checklist. Quality Score (%) represents the proportion of criteria rated 'Yes' relative to total checklist items. Overall Risk of Bias classification: Low (> = 80%), Moderate (50–79%), High (< 50%).

Patient Demographics and Baseline Characteristics

Across the 108 patients, age ranged from 32 to 73 years, with median or mean ages in cohort studies between 42 and 54 years. 62 patients were male (57.4%) and 46 were female (42.6%). Preoperative Karnofsky Performance Status (KPS) was reported in 49 patients, with a median of 90 and a minimum reported value of 70. Preoperative neurological deficits were common: aphasia in 21 patients (19.4%), seizures in 31 (28.7%), motor deficits in 37 (34.3%), and cognitive impairment in 10 (9.3%). Dominant hemisphere tumors accounted for approximately three-quarters of reported cases. Special populations included one patient with autism spectrum disorder (0.9%), one elderly patient aged > = 70 years (0.9%), and multiple reoperations in 13 patients (12.0%). (Table 3).

Table 3
Patient Demographics and Baseline Characteristics

Study	Age (mean, range)	Sex	Handedness	Preoperative Karnofsky Performance Status (KPS)	Preoperative neurological deficits: Language, Motor, Cognitive / neuropsychological	Special populations (e.g., ASD, elderly, epilepsy history, comorbidities)
Corns et al., 2015 [37]	32 years	Female: 1 (100%); Male: 0 (0%)	Right-handed: 1 (100%)	Not reported	Subtle word-finding difficulties: 1 (100%)	Recurrent GBM; prior Stupp-protocol chemoradiotherapy: 1 (100%)
Skjøth-Rasmussen et al., 2017 [38]	Median 54 years (range 35–70)	Female: 9 (47.4%); Male: 10 (52.6%)	Not reported	Not reported	Not reported	Reoperations: 9/19 (47.4%) had ≥2nd surgery (5 second surgery [26.3%]; 4 third or more [21.1%])
Brosnan et al., 2022 [39]	73 years	Female: 1 (100%)	Left language dominance on fMRI	Not reported	Profound naming and word-finding difficulty (Wernicke's aphasia); Short-term memory loss: 1 (100%)	Elderly (≥ 70): 1 (100%); Comorbidities: diabetes, hypertension, anxiety, Hashimoto's thyroiditis, osteoarthritis, lumbar spinal stenosis
Drosos et al., 2022 [40]	42 years	Male: 1 (100%);	Right-handed: 1 (100%)	Not reported	Mild speech hesitation, seizures	Autism spectrum disorder diagnosed in childhood; learning difficulties; Anxiety features; Dependent on primary caregiver
Goryaynov et al., 2022 [41]	Not reported	Not reported	Assessed via Annett questionnaire (numbers not reported)	Not reported	Variable, including aphasia	Not reported
Haider et al., 2022 [42]	66 years	Male: 1 (100%)	Right-handed: 1 (100%)	Not reported	Mild cognitive difficulty, dysphasia, gait difficulty, subtle neglect, acalculia, extinction to double simultaneous stimuli	Dominant hemisphere tumor
Price et al., 2023 [43]	32 years	Female: 1 (100%)	Right-handed: 1 (100%)	Not reported	Generalized tonic-clonic seizure, language and motor deficit: None reported preoperatively	Bipolar disorder; intractable migraines, Multiple prior resections (3 prior surgeries); prior radiation therapy
Matei et al., 2024 [44]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Moldabekov et al., 2024 [45]	55 years	Female: 1 (100%)	Right-handed: 1 (100%)	70	Disorientation (space/time); reduced executive function; central right facial paresis (HB grade 3); right tongue deviation; mild-moderate dynamic aphasia	Dominant hemisphere GBM

Study	Age (mean, range)	Sex	Handedness	Preoperative Karnofsky Performance Status (KPS)	Preoperative neurological deficits: Language, Motor, Cognitive / neuropsychological	Special populations (e.g., ASD, elderly, epilepsy history, comorbidities)
Tagle-Vega et al., 2025 [46]	42–50 years	Male: 30 (71.4%); Female: 12 (28.6%)	Not reported	Median 90	Aphasia, seizures, motor deficits	Not reported

ASD, autism spectrum disorder; GBM, glioblastoma multiforme; HB, House-Brackmann

Tumor Characteristics

High-grade gliomas predominated, with 68 of 108 tumors (63.0%) classified as WHO Grade IV, 19 (17.6%) as Grade III, and 21 (19.4%) as Grade II. IDH status was variably reported but most Grade IV tumors were IDH-wildtype. Eloquent region involvement was documented in 93 patients (86.1%), most commonly affecting frontal, temporal, insular, and perisylvian regions. Contrast enhancement was present in all Grade IV tumors and in the majority of Grade III tumors. (Table 4).

Table 4
An Overview of Tumor Characteristics

Study	Tumour type	WHO grade (II–IV)	Molecular markers	Tumour location	Contrast-enhancing vs non-enhancing	Tumour volume
Corns et al., 2015 [37]	GBM (recurrent)	Grade IV	Not reported	Left frontal lobe encroaching on Broca's area	T1 contrast-enhancing lesion present	Not reported
Skjøth-Rasmussen et al., 2017 [38]	Suspected high-grade glioma (19, 100%)	Not reported	Not reported	Close relationship with eloquent structures (100%)	Not reported	Not reported
Brosnan et al., 2022 [39]	Glioma (histology confirmed GBM)	Grade IV	Not reported	Left temporal lobe, adjacent to Wernicke's area and arcuate fasciculus	Heterogeneously enhancing 4 cm mass	4 cm mass with vasogenic edema and 3–4 mm midline shift
Drosos et al., 2022 [40]	Diffuse astrocytoma	Grade: III	IDH mutant	Left superior frontal gyrus (mid-posterior), involving SMA, extension to cingulate gyrus	Non-contrast enhancing tumor	26.8 cm ³
Goryaynov et al., 2022 [41]	Diffuse gliomas	Grades: II (n = 10, 36%), III (n = 6, 21%), IV (n = 12, 43%)	Not reported	Left frontal or temporal, eloquent speech areas (Broca, Wernicke, AF, SLF, FAT)	Mixed (HGG mostly enhancing)	Not reported
Haider et al., 2022 [42]	Diffuse Astrocytoma	Grade III	IDH wild-type	Left supramarginal gyrus (dominant parietal lobe)	Partially cystic contrast-enhancing mass	Not reported
Price et al., 2023 [43]	Astroblastoma	Astroblastoma, MN1-altered	In-frame MN1::BEND2 fusion	Left parietal region (anterior inferior aspect of prior resection cavity)	Strongly enhancing lesion	3.8 × 2.9 × 3.0 cm
Matei et al., 2024 [44]	High-grade glioma	Not reported	Not reported	Frontal lobe (language area)	Not reported	Not reported
Moldabekov et al., 2024 [45]	Glioblastoma	Grade IV	IDH wild-type	Left frontotemporal region involving Broca's area	Enhancing lesion	Not reported
Tagle-Vega et al., 2025 [46]	LGG 40–47%, HGG 53–59%	Grades: II (n = 18, 42.9%), III (n = 6, 14.3%), IV (n = 18, 42.9%)	Not reported	Majority in eloquent areas (67–85%)	Not reported	Not reported

AF, Arcuate fasciculus; FAT, Frontal aslant tract; HGG, High-grade glioma; IDH, isocitrate dehydrogenase; IV, intravenous; LGG, Low-grade glioma; SLF, Superior longitudinal fasciculus; SMA, supplementary motor area

Awake Craniotomy Protocols

The asleep-awake-asleep technique was used in 100 of 108 cases (92.6%), while fully awake protocols were used in 8 patients (7.4%). Direct cortical stimulation was used in all cases (100%). Positive cortical or subcortical mapping responses were

observed in approximately half of patients in larger cohorts. Intraoperative seizures occurred in 4 patients (3.7%), and one patient (0.9%) developed a postoperative hematoma requiring reoperation. No study reported conversion to general anesthesia (Table 5).

Table 5
Awake Craniotomy Protocols

Study	Awake craniotomy technique	Anesthetic agents	Patient positioning and fixation	Mapping	Intraoperative testing	Intraoperative complications
Corns et al., 2015 [37]	Asleep-awake technique: initial GA for craniotomy and partial debulking, then awake for mapping and resection	General anesthesia (agents not specified); dexamethasone preoperatively	Not reported	Cortical speech mapping	Expressive speech monitored by speech and language therapist	None
Skjøth-Rasmussen et al., 2017 [38]	Not reported	Not reported	Not reported	Awake functional mapping (100%)	Not reported	Not reported
Brosnan et al., 2022 [39]	Asleep-awake-asleep	Propofol infusion (100–150 mcg/kg/min), Remifentanyl (0.02–0.03 mcg/kg/min), Dexmedetomidine (0.2 mcg/kg/hr), Propofol boluses	Not reported	Awake cortical speech mapping	Continuous object naming, speech arrest testing, conversation	Fatigue and intermittent somnolence during awake phase; no neurological deterioration
Drosos et al., 2022 [40]	Awake throughout	Dexmedetomidine	Supine, head rotated 30° right, horseshoe headrest (no pin fixation)	Motor and language	Motor tasks, 9-peg test, speech (counting, free speech, Stroop), multitasking	Single focal seizure (controlled with cold saline); Fully cooperative throughout (100%)
Goryaynov et al., 2022 [41]	Asleep-awake-asleep	Not reported	Not reported	Bipolar cortical stimulation; monopolar subcortical stimulation	Continuous neuropsychological speech assessment	None
Haider et al., 2022 [42]	Not reported	Not reported	Not reported	Cortical mapping; subcortical motor-evoked potentials; phase reversal	Not reported	Preoperative fever (surgery delayed); no intraoperative complications
Price et al., 2023 [43]	Not reported	Not reported	Not reported	Direct cortical stimulation for speech mapping	Not reported	Not reported
Matei et al., 2024 [44]	Asleep-awake-asleep	Not reported	Not reported	Direct cortical stimulation (Penfield bipolar technique)	Boston Naming Test; calculation tasks; structured language tasks	Not reported

Study	Awake craniotomy technique	Anesthetic agents	Patient positioning and fixation	Mapping	Intraoperative testing	Intraoperative complications
Moldabekov et al., 2024 [45]	Asleep-awake-asleep	Dexmedetomidine (200 mg total reported); fentanyl 0.2 mg	Not reported	Not reported	Broca area language mapping; motor tasks (right hand/leg movement)	Not reported
Tagle-Vega et al., 2025 [46]	Asleep-awake-asleep	Not reported	Not reported	Direct cortical stimulation in 100%	Language, motor, cognition	Not reported

5-ALA Fluorescence Characteristics

Standard 5-ALA dosing (20 mg/kg administered 2–3 hours preoperatively) was used in the majority of cases. Overall fluorescence positivity was observed in 55 of 108 patients (50.9%). Among high-grade gliomas, fluorescence was present in 52 of 68 tumors (76.5%), whereas only 7 of 40 low-grade gliomas (17.5%) demonstrated visible fluorescence. Bright fluorescence was almost exclusively observed in Grade IV tumors. Fluorescence–histology concordance was consistently reported where evaluated. In several cases, persistent fluorescence in eloquent regions was overruled by functional mapping to preserve language or motor function (Table 6).

Table 6
5-ALA Specific Variables

Study	Dose and timing of 5-ALA administration	Fluorescence detection method	Presence and rate of fluorescence	Fluorescence–histology concordance	Use of 5-ALA in: Cortical phase Subcortical phase Only non-eloquent regions	Reported limitations of 5-ALA
Corns et al., 2015 [37]	1.5 g orally (single dose), 6 hours prior to induction of GA	Intense fluorescence in tumour core with subtle pink fluorescence at tumour margins	Present: 1 (100%), Intense fluorescence core + subtle pink border zone	Fluorescing tumour was remote from speech cortex; resection guided by awake mapping at eloquent boundary	Yes (cortical); Yes (non-cortical, guided extended resection)	Not reported
Skjøth-Rasmussen et al., 2017 [38]	Not reported	Not reported	Not reported	Not reported	Yes (cortical); subcortical implied but not specified	Not reported
Brosnan et al., 2022 [39]	5-ALA use: Administered preoperatively (Gliolan)	Fluorescence-guided resection used in conjunction with stereotactic navigation	Used to guide deeper tumor resection	Not reported	cortical yes; subcortical yes- allowed continued resection when mapping limited by fatigue	Not reported
Drosos et al., 2022 [40]	Not reported	Blue light visualization intraoperatively	Used to identify residual tumor in non-eloquent cavity regions	Not reported	Used as adjunct for non-eloquent residual tumour	Not reported
Goryaynov et al., 2022 [41]	Dose: 20 mg/kg orally, 2 h pre-op	Zeiss BLUE400	Fluorescence present (14, 50%), Bright fluorescence (10, 36%)- all Grade IV, Weak fluorescence (4, 14%), No fluorescence (14, 50%)	Not reported	Fluorescence used to guide biopsy and resection	Not reported
Haider et al., 2022 [42]	20 mg/kg orally, given 5:50 AM; surgery performed ~ 32–36 hours later	Blue-light microscopy	Yes, clinically useful fluorescence present at 32–36 hours	All fluorescent specimens positive for tumor	Yes (cortical and subcortical)	Prolonged interval beyond recommended 2–4 h window; concern regarding photobleaching and metabolic clearance
Price et al., 2023 [43]	Not reported	Blue-light fluorescence during surgery	Yes (heterogeneous fluorescence)	Fluorescent tumor confirmed histologically	Yes (cortical), implied (subcortical)	Not reported

GA: general anaesthesia; GBM: glioblastoma multiforme

Study	Dose and timing of 5-ALA administration	Fluorescence detection method	Presence and rate of fluorescence	Fluorescence–histology concordance	Use of 5-ALA in: Cortical phase Subcortical phase Only non-eloquent regions	Reported limitations of 5-ALA
Matei et al., 2024 [44]	Not reported	Blue-light fluorescence during surgery	Yes	Not reported	Yes (cortical and subcortical)	Requirement for low-light conditions due to photosensitization risk
Moldabekov et al., 2024 [45]	Not reported	BLUE400 fluorescence microscopy	Yes (intense residual fluorescence in Broca region)	Fluorescent areas confirmed GBM	Yes (cortical and subcortical)	Conflict between fluorescence persistence and functional preservation
Tagle-Vega et al., 2025 [46]	20 mg/kg, 3 h pre-op	Not reported	Not reported	Not reported	Fluorescence strongly associated with high-grade tumours ($p < 0.001$)	Not reported

GA: general anaesthesia; GBM: glioblastoma multiforme

Extent of Resection and Adjuncts

GTR was achieved in 62 of 108 patients (57.4%). Subtotal resection exceeding 90% was reported in 24 patients (22.2%), while biopsy or partial resection was performed in 6 patients (5.6%). Extent of resection was not specified in 16 cases (14.8%). In the largest comparative cohort, GTR was achieved in 66.7% of patients. Achieving a 5-ALA–free cavity was significantly associated with GTR. Adjuncts frequently used alongside 5-ALA included neuronavigation, diffusion tractography, and intraoperative MRI (16.0% of patients). In eloquent regions, functional mapping frequently determined the stop point even when residual fluorescence was visible (Table 7).

Table 7
Adjuncts and Extent of Resection

Study	Adjuncts Used Alongside 5-ALA	Extent of resection	Method of assessment	Residual tumour location	Whether 5-ALA directly influenced stopping points
Corns et al., 2015 [37]	Functional MRI (preoperative); Awake cortical mapping; Carmustine (BCNU) wafers placed intraoperatively	GTR of all T1-contrast-enhancing tumour	Postoperative contrast-enhanced MRI	Partial residual T2/FLAIR signal left intentionally	Yes- resection included intense and subtle fluorescence but preserved normal brain tissue
Skjøth-Rasmussen et al., 2017 [38]	Not reported	Complete or near-complete resection (10/19, 52.6%); > 90% tumor volume resection (12/19, 63.2%); First-time GBM subgroup GTR (6/9; 66.7%)	Postoperative MRI with volumetric measurement	Not reported	Implied yes (tumor + functional border guidance)
Brosnan et al., 2022 [39]	Neuronavigation; Bispectral index (BIS) monitoring; Functional MRI (preoperative)	~ 95% tumour resection	Surgeon estimate (postoperative imaging implied but not quantified)	Deep borders (not fully detailed)	Yes- allowed continued resection when patient became fatigued
Drosos et al., 2022 [40]	Intraoperative ultrasound (iUS); Frameless stereotactic navigation; IOM; ECoG	Resection: 81%	Postoperative MRI volumetric measurement (26.8 cm ³ → 5.2 cm ³)	Posterolateral margin near corticospinal tract. Residual left due to functional boundaries	Yes- used to resect enhancing tumor in non-eloquent regions
Goryaynov et al., 2022 [41]	Neuronavigation; Tractography; Neurophysiological monitoring	GTR* (12, 43%), Subtotal (3, 11%), Partial (3, 11%)	MRI available within 48h (18, 64%)	Residual fluorescence often intentionally left due to positive speech mapping	Yes- resection deliberately stopped in presence of fluorescence when speech disturbance occurred (60% of fluorescent cases).
Haider et al., 2022 [42]	Awake cortical mapping; subcortical MEPs; intraoperative MRI	GTR of contrast-enhancing tumor	Postoperative MRI (POD2)	Non-enhancing T2 hyperintensity at superior margin	Yes- fluorescence used to guide resection despite delayed surgery
Price et al., 2023 [43]	Awake speech mapping	GTR	Postoperative MRI (3 months confirmed GTR)	None on follow-up MRI	Yes- used to confirm complete resection (no residual fluorescence)
Matei et al., 2024 [44]	DTI tractography; neuronavigation; intraoperative neurophysiological monitoring	GTR	Not reported	Not reported	Yes- used alongside mapping to achieve GTR
Moldabekov et al., 2024 [45]	Awake language mapping; neuronavigation; DTI tractography	GTR of enhancing tumor (immediate postoperative imaging)	Postoperative MRI + CT	Slight residual tissue at 3-month MRI, stable	Yes- resection halted despite fluorescence when speech arrest occurred

Study	Adjuncts Used Alongside 5-ALA	Extent of resection	Method of assessment	Residual tumour location	Whether 5-ALA directly influenced stopping points
Tagle-Vega et al., 2025 [46]	Neuronavigation; Direct cortical stimulation; Intraoperative MRI (selected cases)	GTR: 66.7% in both groups	GTR is defined as residual tumor ≤ 0.175 cm ³ , however it is not cleared whether it is based on enhancing T1 or T2 FLAIR sequences	Not reported	5-ALA-free cavity strongly associated with GTR

DTI, Diffuse Tensor Imaging; ECoG, Electrocorticography; GTR, gross-total resection; IOM, intraoperative monitoring; MEP, Motor-evoked potentials

* In this study the extend of resection is defined based on comparing pre and postoperative T1 contrast enhancement for glioblastomas or T2 FLAIR data for non-contrast enhancing gliomas.

Functional Outcomes and Survival

Transient postoperative aphasia occurred in 28 of 108 patients (25.9%), while permanent aphasia was reported in 9 patients (8.3%). Persistent hemiparesis occurred in 16 patients (14.8%). In contrast, none of the single-patient case reports described permanent neurological deficits. Postoperative median KPS, where reported, remained 90, with improvement documented in approximately one-fifth of reported cases. Follow-up duration ranged from 3 to 15 months. Recurrence was reported in 14 of 22 patients (63.6%) in studies providing follow-up data. Across studies, authors consistently concluded that 5-ALA enhanced tumor visualization, but functional mapping remained the decisive determinant of resection boundaries in eloquent cortex (Table 8).

Table 8
Postoperative Functional Outcomes and Follow-up Across Included Studies

Study	Functional outcome	Follow-up	Authors' conclusion
Corns et al., 2015 [37]	No new or worsened speech deficit; Transient pseudomeningocele requiring lumbar drainage	Immediate postoperative period	Combined use of AC and 5-ALA enables maximal safe resection in eloquent GBM without neurological deficit
Skjøth-Rasmussen et al., 2017 [38]	No exacerbation of neurological condition	Not reported	Combined 5-ALA and awake mapping allows satisfactory tumor removal despite proximity to eloquent structures, maintaining onco-functional balance
Brosnan et al., 2022 [39]	Repetition and naming intact; mild residual word-finding difficulty	Immediate postoperative course described	Careful anesthetic titration enables successful awake mapping even in patients with significant preoperative aphasia; minimum effective sedation recommended
Drosos et al., 2022 [40]	No new postoperative deficits	Early postoperative and during chemoradiotherapy	AC with 5-ALA is feasible in carefully selected ASD patients. ASD is not an absolute contraindication to awake craniotomy; with meticulous preparation, safe resection is feasible
Goryaynov et al., 2022 [41]	Transient aphasia (14, 50%), Permanent aphasia (4, 14%), Hematoma requiring reoperation (1, 3%).	None reported	5-ALA and awake speech mapping are complementary; allow maximal safe resection while preserving eloquent speech networks; fluorescence useful in HGG and prognostically informative in LGG
Haider et al., 2022 [42]	No new focal deficits	Immediate postoperative period	Clinically useful fluorescence may persist > 24 hours after single 5-ALA dose; strict adherence to 2–4 h window may not be necessary
Price et al., 2023 [43]	Returned to neurological baseline	3 months (MRI confirmed GTR)	5-ALA can assist in achieving GTR in astroblastoma; fluorescence may be strong despite rarity; maximizing resection critical for survival
Matei et al., 2024 [44]	Language preserved	Not reported	Combining AC with 5-ALA fluorescence is safe and enables gross total resection while preserving language function
Moldabekov et al., 2024 [45]	Speech and calculations improved, no permanent deficits	Not reported	5-ALA combined with AC maximizes safe GTR while preserving executive and motor function; multidisciplinary approach is essential
Tagle-Vega et al., 2025 [46]	Persistent aphasia: 18–20%; Persistent hemiparesis: 20–40%	Not reported	Neurological sequelae significantly associated with eloquent location. 5-ALA improves intraoperative tumour delineation; iMRI provides complementary benefit but functional mapping remains decisive

AC: awake craniotomy; ALA: aminolevulinic acid; ASD, autism spectrum disorder; GBM, glioblastoma multiforme; GTR, gross total resection; HGG, high-grade glioma; LGG, low-grade glioma; MRI, magnetic resonance imaging.

Discussion

This systematic review synthesizes the currently available evidence on utility of 5-ALA-guided resection during awake craniotomy for gliomas in eloquent regions. Across 10 studies comprising 108 patients, the combined use of fluorescence guidance and functional mapping appears not only feasible and functionally safe, but also clinically useful in supporting maximal safe resection. Gross-total resection was achieved in 57.4% overall and in 66.7% of patients in the largest cohort, while permanent morbidity remained within the expected range for eloquent glioma surgery. Although the evidence base remains largely

observational, the consistency of the reported intraoperative utility of 5-ALA across case reports, case series, and cohort data supports its role as a valuable adjunct - particularly in high-grade tumors where fluorescence positivity is much more frequent.

Oncologic Impact of 5-ALA in the Awake Setting

The oncologic benefit of 5-ALA in glioma surgery has been well established in the general anesthesia setting [48–53]. The landmark randomized controlled trial by Stummer et al. [54] demonstrated improved rates of complete resection of contrast-enhancing tumor and progression-free survival in glioblastoma when 5-ALA was used. Subsequent meta-analyses have confirmed its high sensitivity for high-grade glioma (HGG), particularly WHO Grade IV tumors [24].

Our findings extend the established oncologic utility of 5-ALA into the awake setting. Fluorescence positivity was observed in 76.3% of high-grade gliomas, closely mirroring the wider fluorescence-guided surgery literature and supporting the reliability of 5-ALA even when surgery is performed under awake conditions. Bright fluorescence was seen predominantly in Grade IV tumors, reinforcing the biological link between protoporphyrin IX accumulation and aggressive tumor metabolism. In the studies reporting tissue correlation, fluorescence-histology concordance was high, indicating that 5-ALA remains a dependable intraoperative marker of tumor tissue even when the surgeon must work within functionally constrained margins [42, 43, 45].

Although fluorescence was less frequent in low-grade gliomas (17.1%), this does not diminish the overall value of 5-ALA in awake glioma surgery; rather, it helps define where its utility is greatest. The present evidence most strongly supports use in high-grade and contrast-enhancing lesions, where fluorescence can meaningfully improve detection of residual tumor and assist resection strategy. In lower-grade lesions, its role is more selective and adjunctive.

Functional Boundaries Versus Fluorescent Boundaries

One of the most important messages from this review is not that fluorescence and mapping are in conflict, but that they answer different intraoperative questions. Awake mapping defines what must be preserved; 5-ALA highlights where biologically active tumor remains. When the two boundaries diverge, the surgeon gains richer decision-making information rather than a contradiction. In several studies, resection was appropriately halted despite persistent fluorescence when stimulation identified essential language or motor pathways [41, 46]. This should not be interpreted as a limitation of 5-ALA, but rather as evidence that fluorescence can successfully reveal residual tumor even when that tissue cannot be safely removed.

This distinction is biologically and surgically meaningful [55–57]. Fluorescence reflects altered tumor metabolism, whereas awake mapping identifies indispensable cortico-subcortical networks [58]. Because infiltrative gliomas may extend into or alongside eloquent pathways without immediately abolishing function, discordance between fluorescent and functional borders is expected rather than problematic [59, 60]. In practice, this makes 5-ALA a particularly valuable complement to awake surgery: it enhances tumor conspicuity, facilitates targeted biopsy and selective resection in non-eloquent fluorescent regions, and helps the surgeon recognize when residual disease persists at a functionally protected margin [25, 61–63]. The largest comparative study [46] supports this interpretation, showing that a "5-ALA-free" cavity was associated with gross-total resection while mapping remained the decisive safeguard of function.

Extent of Resection and Comparison to Awake Literature

The pooled GTR rate of 57.4% overall, and 66.7% in the largest cohort, compares favorably with published awake-surgery series in eloquent gliomas [8, 14, 15]. Importantly, these resection rates were achieved in anatomically and functionally challenging tumors while maintaining permanent neurological morbidity within accepted expectations for eloquent glioma surgery. This pattern supports the practical value of 5-ALA in helping surgeons pursue maximal safe resection under awake conditions.

The benefit of 5-ALA in this setting should not be judged solely by whether pooled GTR percentages dramatically exceed historical awake-series benchmarks [8, 14, 15]. In eloquent tumors, the final stopping point is intentionally governed by functional mapping, so the full theoretical cytoreductive advantage of fluorescence may be constrained by design [14, 15, 41, 46]. Even so, 5-ALA appears to provide meaningful operative benefit by improving visualization at the tumor-brain interface, increasing confidence in resection of non-eloquent fluorescent tissue, helping identify residual tumor that may otherwise be overlooked under white light, and offering an immediate metabolic correlate to the surgeon's anatomical and electrophysiological findings

[16, 17, 41, 42, 46]. In essence 5-ALA empowers the surgeon to make an informed choice on safety of resection within constraints of eloquence.

This interpretation is supported by studies in the present review in which residual fluorescent foci were specifically identified and resected, as well as by the association between a "5-ALA-free" cavity and gross-total resection in the largest cohort [39–41, 46]. Viewed in this way, fluorescence does not need to override mapping to be valuable; rather, it strengthens the surgeon's ability to maximize resection up to the functional limit [41, 46]. Taken together, the current evidence supports the selective use of 5-ALA particularly in high-grade, contrast-enhancing, or otherwise complex eloquent gliomas, where the added visual information is most likely to influence operative decision-making [16, 17, 41, 42, 46].

Notably, no study reported conversion to general anesthesia. Although publication bias cannot be excluded, the available data suggest that incorporation of fluorescence guidance does not materially disrupt the workflow of awake surgery when used in experienced hands.

The transient aphasia rate of 25.5% is consistent with the established awake-craniotomy literature [64–66], where temporary postoperative language worsening is relatively common and often improves over time. More importantly, the available studies do not indicate that 5-ALA increases permanent neurological morbidity. This is reassuring, because it suggests that the oncologic advantages of fluorescence can be pursued without an obvious functional penalty, provided that cortical and subcortical mapping remain the operative safeguard. This interpretation is also concordant with broader glioma literature suggesting that 5-ALA-guided resection may improve extent of resection while maintaining acceptable neurological outcomes [16, 17].

Timing and Technical Considerations

Most studies used the conventional 20 mg/kg dosing regimen administered 2–3 hours preoperatively, indicating that standard 5-ALA workflows are readily transferable to awake craniotomy. Although study done by Stummer et al. [67] showed that the peak fluorescence happens 6 hours after administration of 5-ALA, Haider et al. [42] reported clinically useful fluorescence 32–36 hours after administration, suggesting that, in selected circumstances, the fluorescence window may be more forgiving than traditionally assumed. Although this observation remains preliminary, it highlights the practical robustness of the technique.

Awake fluorescence-guided surgery does introduce specific technical considerations, including low-light conditions during patient interaction and the need to coordinate blue-light visualization with real-time language or motor testing [41–45]. Nevertheless, the available reports show that these challenges are manageable, and no study described abandonment of fluorescence because of patient intolerance. Taken together, this supports the view that 5-ALA can be integrated into awake workflows without major practical compromise [41–46].

Integration With Intraoperative MRI and Adjuncts

In the only comparative study, adding intraoperative MRI to 5-ALA did not significantly change GTR rates, with both groups achieving 66.7% gross-total resection. Rather than diminishing the value of fluorescence, this finding suggests that 5-ALA alone already provides meaningful operative guidance in many awake glioma cases. At the same time, fluorescence and iMRI appear to provide different but potentially synergistic information: fluorescence reflects metabolically active tissue at the operative surface, whereas iMRI identifies structural residual disease that may not be visibly fluorescent. Multimodal integration may therefore be best viewed as an escalation of guidance for selected complex tumors rather than a replacement for 5-ALA.

Future Directions

Future research should now move beyond feasibility and focus on defining where 5-ALA adds the greatest value within awake glioma surgery. Prospective multicenter studies using standardized volumetric extent-of-resection metrics, survival outcomes, and structured neurocognitive follow-up would help quantify the magnitude of benefit and refine patient selection. Comparative cohort designs evaluating awake mapping alone versus mapping combined with 5-ALA would be especially valuable, not because the utility of fluorescence is in doubt, but because its contribution should now be measured more precisely across tumor grades, locations, and operative strategies. Standardization of fluorescence grading, incorporation of quantitative spectroscopy, and integration of molecular profiling may further strengthen the precision of fluorescence-guided onco-functional surgery.

Technological convergence offers a transformative opportunity for the field. Augmented reality (AR) platforms capable of overlaying fluorescence maps, tractography, and real-time functional mapping data directly into the operative field could reduce cognitive load and improve spatial precision when oncologic and functional boundaries diverge [68–70]. Virtual reality (VR)–based preoperative simulation may further enhance surgical planning in complex eloquent tumors, allowing rehearsal of anticipated fluorescence–function conflicts [68, 69]. Coupled with artificial intelligence–driven predictive modeling of safe resection margins, these innovations have the potential to create an integrated, data-driven operative ecosystem in which tumor visualization and network preservation are dynamically balanced [70–74]. Prospective evaluation of these technologies will determine whether digital augmentation can meaningfully improve both oncologic and functional outcomes in precision neuro-oncology.

Limitations

Several limitations must be acknowledged. First, the overall evidence base is predominantly composed of case reports and retrospective observational studies. Seven of ten included studies were single-patient reports, inherently subject to selection and publication bias. Positive or technically successful cases are more likely to be published, potentially overestimating safety and oncologic efficacy. Second, there was substantial heterogeneity in study design, reporting standards, tumor grade distribution, adjunct usage, and outcome definitions. Extent of resection was not uniformly assessed using volumetric analysis, and long-term survival data were limited. More specifically, different paradigms have been used to estimate extent of resection based on T1 enhancing regions vs T2 FLAIR hyperintensities which makes pooling the extent of resection data less accurate. Further studies with precise uniform definition of extent of resection is required to evaluate the role of 5-ALA in increasing the extent of resection. Third, follow-up duration was inconsistently reported. Only a subset of patients had documented medium-term imaging or survival outcomes. Therefore, pooled recurrence and survival estimates should not be interpreted as representative incidence rates. Fourth, the timing between administration of 5-ALA and tumor resection is not reported in some of the studies or it is reported beyond the time interval of fluorescence peak which can affect the efficacy of 5-ALA in showing tumor cells [67]. Fifth, no randomized controlled trials or prospective comparative studies were identified. Consequently, the precise magnitude of the added benefit conferred by 5-ALA within the awake setting, beyond what is achieved with mapping alone, cannot yet be quantified with high certainty. Finally, fluorescence detection thresholds and intraoperative interpretation were not standardized across studies. Variability in microscope technology, surgeon experience, and subjective interpretation may influence reported fluorescence rates.

Conclusion

5-ALA-guided resection during awake craniotomy is a feasible, safe, and clinically valuable adjunct for glioma surgery in eloquent regions. The available evidence supports its ability to enhance intraoperative tumor visualization, assist identification of residual disease, and facilitate maximal safe resection without clear evidence of increased permanent neurological morbidity. Functional mapping remains the decisive determinant of the final resection boundary, but this does not diminish the contribution of fluorescence; rather, the two modalities appear complementary and together support an onco-functional surgical strategy. Prospective, standardized, multicenter studies are warranted to quantify the magnitude of benefit, optimize patient selection, and clarify long-term oncologic impact.

Declarations

Consent for publication:

Not applicable.

Human Ethics and Consent to Participate declarations:

Not applicable.

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All data analyzed in this systematic review were obtained from published studies and are presented within the article and supplementary materials.

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M.M. conceptualized the study. M.M. and M.S.M. performed screening and data extraction. M.M. wrote the main manuscript text. M.M., M.S.M., J.S. and K.A. reviewed and edited the manuscript. M.M., M.S.M. and J.S. prepared the tables and visualizations. K.A. supervised the study. All authors read and approved the final manuscript.

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Figures

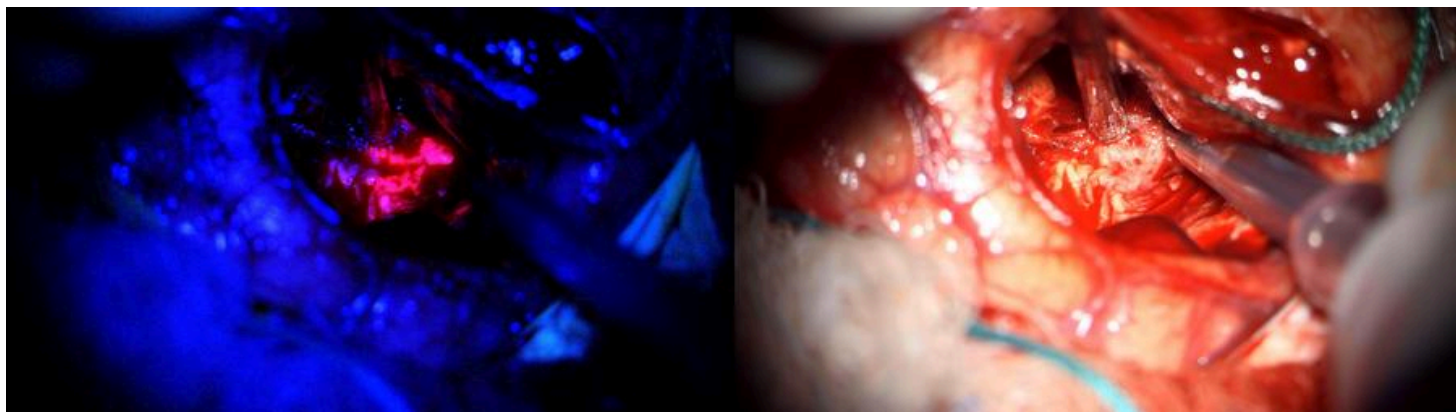


Figure 1

Intraoperative images during resection of a left frontal Glioblastoma in a 64-year old female using 5-ALA by one of the authors. Right: White-light view of surgical cavity demonstrating limited distinction between tumor and surrounding healthy brain tissues. Left: Demonstration of the same view under Blue-light fluorescence with highlighted residual tumor by bright pink color. ALA, aminolevulinic acid.

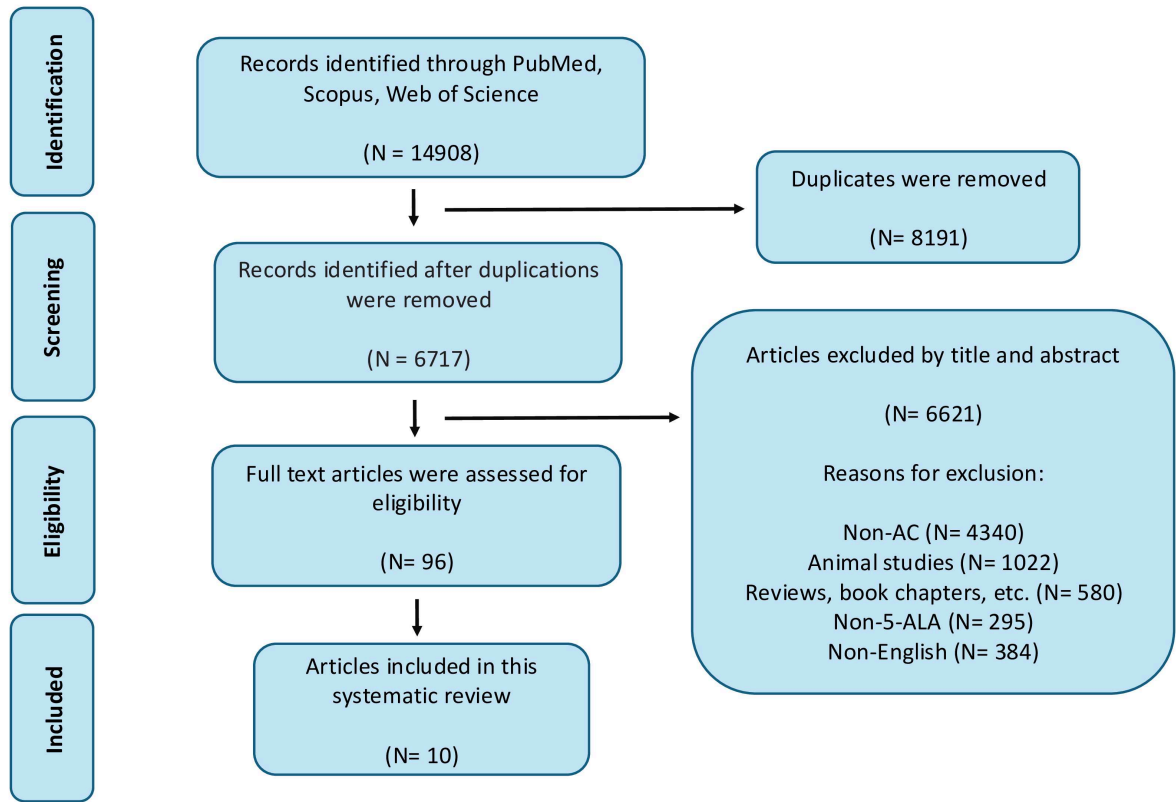


Figure 2

A flowchart of the current study demonstrating identification, screening, eligibility, and inclusion process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). AC, awake craniotomy. ALA, aminolevulinic acid.

Supplementary Files

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- [SupplementaryTable1.docx](#)