Intraoperative MRI versus 5-ALA in high-grade glioma resection: a network meta-analysis

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OBJECTIVE High-grade gliomas (HGGs) continue to carry poor prognoses, and patient outcomes depend heavily on the extent of resection (EOR). The utility of conventional image-guided surgery is limited by intraoperative brain shift. More recent techniques to maximize EOR, including intraoperative imaging and the use of fluorescent dyes, combat these limitations. However, the relative efficacy of these two techniques has never been systematically compared. Thus, the authors performed an exhaustive systematic review in conjunction with quantitative network meta-analyses to evaluate the comparative effectiveness of 5-aminolevulinic acid (5-ALA) and intraoperative MRI (IMRI) in optimizing EOR in HGG. They secondarily analyzed associated progression-free and overall survival and performed subgroup analyses by level of evidence.

METHODS PubMed, Embase, Cochrane Central, and Web of Science were searched for studies evaluating conventional neuronavigation, IMRI, and 5-ALA in HGG resection. The primary study endpoint was the proportion of patients attaining gross-total resection (GTR), defined as 100% elimination of contrast-enhancing lesion on postoperative MRI. Secondary endpoints included overall and progression-free survival and subgroup analyses for level of evidence. Comparative efficacy analysis of IMRI and 5-ALA was performed using Bayesian network meta-analysis models.

RESULTS This analysis included 11 studies. In a classic meta-analysis, both IMRI (OR 4.99, 95% CI 2.65–9.39, $p < 0.001$) and 5-ALA (OR 2.866, 95% CI 2.127–3.863, $p < 0.001$) were superior to conventional navigation in achieving GTR. Bayesian network analysis was employed to indirectly compare IMRI to 5-ALA, and no significant difference in GTR was found between the two (OR 1.9 favoring IMRI, 95% CI 0.905–3.989, $p = 0.090$). A handful of studies additionally suggested that the use of either IMRI (2 and 4 studies, respectively) or 5-ALA (2 and 2 studies, respectively) improves progression-free and overall survival.

CONCLUSIONS IMRI and 5-ALA are individually superior to conventional neuronavigation for achieving GTR of HGG. Between IMRI and 5-ALA, neither method is clearly more effective. Future studies evaluating the comparative cost and surgical time associated with IMRI and 5-ALA will better inform any cost-benefit analysis.

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KEYWORDS intraoperative MRI; 5-aminolevulinic acid; glioma; glioblastoma; neuronavigation; oncology; surgical technique

GLIOMAS represent the largest group of primary central nervous system (CNS) tumors, making up nearly 80% of malignant CNS tumors.⁴¹ Despite decades of research, prognosis for high-grade glioma (HGG) remains poor.⁴ Extent of resection (EOR) is a key prognostic factor in glioma and has been positively asso-

ciated with overall survival, quality of life, delay in malignant transformation, seizure-free rate, and duration of functional independence.^{37,49,73} Preoperative surgical planning to maximize EOR with stereotactic image-guided neuronavigation has become nearly routine but is inherently limited by being based on preoperative imaging alone.

ABBREVIATIONS 5-ALA = 5-aminolevulinic acid; EOR = extent of resection; GTR = gross-total resection; HGG = high-grade glioma; IMRI = intraoperative MRI; LGG = low-grade glioma; QALY = quality-adjusted life year; RCT = randomized controlled trial; SDM = standard difference in means.

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Brain shift during surgery because of gravity, edema, fluid shifts, and other physiological changes associated with surgery makes preoperative image guidance unreliable as surgery progresses and limits the safe maximal resectability of invasive lesions.²³

Several innovations have recently emerged to compensate for the limitations of neuronavigation, such as fluorescent tumor markers.⁶¹ 5-aminolevulinic acid (5-ALA)—a naturally occurring heme precursor capable of producing fluorescent porphyrins in malignant tissue—is the most widely used marker and carries the highest level of evidence for expanding EOR and prolonging progression-free survival in glioma patients.^{60,61,75} Additionally, intraoperative imaging modalities such as intraoperative MRI (IMRI), introduced to neurosurgery in 1997, can update source images and spatial information for neuronavigation.⁶⁶ While IMRI is more effective than classic stereotactic navigation in improving EOR, it is expensive, prolongs operating time, and increases the complexity of the operating room.^{35,53}

While several studies have compared the use of either 5-ALA or IMRI with stereotactic navigation, quantitative comparison of 5-ALA with IMRI for maximizing EOR remains limited. But this question is important for several reasons. First, if one technology is superior, then the inferior technology may eventually fall out of favor. Second, if the two technologies are similarly efficacious, then institutions with limited resources may opt to invest in the less expensive technology. We performed an exhaustive systematic review in conjunction with quantitative network meta-analyses to evaluate the comparative effectiveness of 5-ALA and IMRI in optimizing EOR in HGG. We secondarily analyzed associated progression-free and overall survival and performed subgroup analyses by level of evidence.

Methods

Research Protocol and Search Question

Our review protocol was developed according to the PRISMA statement guidelines (see the PRISMA Checklist) and is registered with PROSPERO (registration no. CRD42018111524).³⁸ The search strategy was designed using a PICO (patient, intervention, comparator, outcome)–based research question: in adult patients with HGG, what is the comparative effectiveness of conventional stereotactic navigation, 5-ALA, and IMRI for achieving gross-total resection (GTR)?⁵⁰ Both observational and interventional studies were included, but given our intent to perform a quantitative meta-analysis, only those articles describing at least one comparator group were included.

Eligibility Criteria and Primary Outcome

Preliminary searches revealed a shortage of comparative prospective studies and randomized controlled trials (RCTs) on intraoperative navigational adjuncts. This is consistent with the findings of a recent systematic review on neuronavigation in glioma whose authors were unable to perform a comparative efficacy analysis because of limited data since an eligibility criterion limited studies to RCTs alone.³¹ For a more comprehensive analysis, we

included all types of peer-reviewed publications, with both observational and interventional studies meeting the eligibility criteria.

Studies eligible for inclusion met the following criteria: 1) observational or interventional peer-reviewed studies published in the English language between 1997 and 2019; 2) subjects were adults (age 16 or older) with HGG (WHO grades III–IV); 3) GTR of the lesion was intended for all subjects; 4) at least 2 neuronavigational adjuncts were used, including conventional stereotactic navigation, IMRI, or 5-ALA; and 5) the primary outcome of interest was reported, that is, the number or proportion of patients per neuronavigational adjunct who had attained GTR, which was defined as 100% resection of contrast-enhancing lesion on postoperative MRI. Relevant exclusion criteria were as follows: 1) case reports, case series, and review articles or other article types in which there was no comparator group; 2) the study included spinal or peripheral nerve lesions; 3) the study reported outcomes for additional tumor types (e.g., metastases, low-grade gliomas) that could not be separated from the HGG data; 4) surgery involved stereotactic radiosurgery or laser interstitial thermal therapy; and 5) neuronavigation involved virtual reality.

Search Strategy and Study Selection

PubMed, Embase, Cochrane Central, and Web of Science were searched for articles by systematically using a defined search strategy with a combination keyword and medical subject heading (MeSH)–based approach adapted for each database (see *Appendix*). The most recent search was performed on January 25, 2019. The reference lists of all publications were additionally reviewed.

A two-step review of all articles was performed. First, two reviewers independently screened all titles and abstracts for relevance. Second, two independent reviewers assessed the full text of screened articles for eligibility. An additional exclusion criterion for full-text assessment was overlapping data from the same cohort in different studies. All discrepancies were resolved by a third independent reviewer.

Data Collection and Quality Assessment

Data were independently extracted from the included articles by two reviewers (with disagreements resolved by discussion) and were stored in an electronic database. Data fields included study characteristics (authors, publication year, study design, period of study), neuronavigational intervention, sample size overall and by intervention, patient age, primary outcome as defined above, additional intraoperative navigational adjuncts used, and secondary outcomes including overall survival and progression-free survival.

Study quality and risk of bias were assessed independently for observational and interventional studies. Observational case-control and cohort studies, both retrospective and prospective, were assessed using a modified Newcastle-Ottawa Scale.⁶⁸ RCTs were assessed using the Cochrane Risk of Bias Tool.²⁸ Both assessments were performed by two reviewers, with discrepancies resolved by a third independent reviewer.

Statistical Analysis and Quantitative Data Synthesis

Neuronavigational interventions were compared using both classic random-effects meta-analysis and Bayesian network meta-analysis for the primary outcome. Analysis of secondary outcomes was limited to classic meta-analysis because of an insufficient number of studies. In both cases, the effect was expressed by an odds ratio and 95% confidence interval where a p value < 0.05 was considered statistically significant, and random-effects models were used throughout to account for interstudy heterogeneity.³ The network meta-analysis employed noninformative priors in the generalized linear model using a logit link and assuming a binomial distribution of patients with the outcome. Sensitivity analyses were conducted to ensure robustness by a) treating the study as a fixed effect and b) assuming different priors on the standard deviation of the random effect (study) in the random-effects model.¹⁶ Higgins I^2 tests were used to analyze study heterogeneity.²⁹ Publication bias was also graphically assessed using funnel plots.⁵⁹ Comprehensive Meta-Analysis (CMA) software version 3.0 (Biostat Inc.) was used for classic meta-analysis and assessment of publication bias. Bayesian network meta-analysis was performed using SAS 9.4 software (SAS Institute) and the Microsoft Excel-based tool NetMetaXL (Microsoft Corp.; using WinBUGS version 1.4.3, Medical Research Council Biostatistics Unit).⁵

Results

A total of 4721 articles were identified. After de-duplication and initial screening, 379 full-text studies were assessed for eligibility, resulting in 11 included studies (Fig. 1). Seven studies described the use of IMRI^{8,39,40,45,55,70,74} and 6 studies described the use of 5-ALA^{6,17,32,40,45,62} for HGG resection. General study characteristics, primary outcomes, and survival data for studies comparing IMRI to conventional navigation are listed in Table 1, and those for studies comparing 5-ALA to conventional navigation are listed in Table 2.

IMRI Versus Conventional Navigation

Of the 7 studies describing IMRI, 6 were observational and 1 was an RCT (Table 1). Overall, 236 cases using IMRI were compared to 233 cases using conventional navigation between 2004 and 2014. Rates of GTR with IMRI ranged from 31.4% to 100% of patients. Only 1 study evaluated low-field (< 1.5 T) IMRI.⁵⁵ The use of additional navigational adjuncts varied: diffusion tensor imaging (DTI) was used in 3 studies,^{8,70,74} neurophysiological monitoring was definitely used in 1 study⁴⁰ and may have been used in 2 additional studies,^{45,70} blood oxygen level-dependent functional MRI (BOLD fMRI) was used in 1 study,⁷⁴ and intraoperative ultrasound may have been used in 1 study.⁴⁵ Two studies did not comment on the use of additional navigational technologies.^{39,55}

All studies reported the number of patients in the IMRI and conventional navigation groups for whom GTR had been achieved. Moderate heterogeneity between trials was observed per the Higgins test ($I^2 = 28.18\%$), and given the differences inherent to institution and surgeon experience and across study types (retrospective vs prospective), ran-

FIG. 1. Flow diagram of search results and assessment of eligibility.

dom-effects models were used. In a classic meta-analysis, IMRI was superior to conventional stereotactic navigation for achieving GTR in adults with HGG (OR 4.99, 95% CI 2.65–9.39, $p < 0.001$; Fig. 2A). IMRI, as compared to conventional navigation, also prolonged both progression-free survival (standard difference in means [SDM] 0.656, 95% CI 0.330–0.983, $p < 0.001$; Fig. 2B) and overall survival (SDM 0.491, 95% CI 0.212–0.771, $p = 0.001$; Fig. 2C).

5-ALA Versus Conventional Navigation

Six studies described using 5-ALA for HGG resection; 5 were observational and the sixth was an RCT (Table 2). Overall, 487 cases using 5-ALA were compared to 495 cases using conventional stereotactic navigation between 1999 and 2016. Rates of GTR with 5-ALA ranged from 44.7% to 80%. Across studies, the administration of 5-ALA was consistent (20-mg/kg dose given 2–4 hours before surgery). Regarding additional neuronavigational adjuncts, 2 studies described the use of neurophysiological monitoring,^{32,40} 1 study may have used neurophysiological monitoring or intraoperative ultrasound,⁴⁵ and 3 studies were not specific about additional navigational tools.^{6,17,62}

In a classic meta-analysis, 5-ALA, as compared to conventional stereotactic navigation, significantly increased the likelihood of achieving GTR (OR 2.866, 95% CI 2.127–3.863, $p < 0.001$; Fig. 3A). Interstudy heterogeneity among the 5-ALA studies was limited according to the Higgins test ($I^2 = 12.56\%$). Two studies commented on survival outcomes, including the RCT: 5-ALA improved both progression-free survival (SDM 0.495, 95% CI 0.068–0.922, $p = 0.023$; Fig. 3B) and overall survival (SDM 0.245, 95% CI 0.010–0.480, $p = 0.041$; Fig. 3C).

TABLE 1. Study characteristics and outcomes: IMRI versus conventional navigation

Authors & Year	Study Period	Study Type	Age Range (yrs)	Mean FU (mos)	IMRI Type	IMRI No. (%)	Control No. (%)	Total No.		No. of Patients w/ GTR (%)		Median OS (mos)		Postop Deficits
								No.	No.	IMRI	Control	IMRI	Control	
Chen et al., 2017	07/2010–07/2014	Retrospective	23–72	27	High-field	51 (69.9)	22 (30.1)	73	16 (31.4)	1 (4.5)	28	18		Significantly reduced rate of overall neurological deficits immediately postop w/ IMRI; higher KPS at 3 mos w/ IMRI; lower rate (nonsignificant) of postop aphasia, seizure, hemiparesis, & sensory deficit w/ IMRI
Napolitano et al., 2014	03/2006–11/2011	Retrospective	19–82	NA	High-field	56 (59.6)	38 (40.4)	94	41 (73.2)	20 (52.6)	16.38	12.24		No difference in postop KPS
Nickel et al., 2018	02/2012–08/2013	Prospective cohort	NA (>18)	4	High-field	17 (21)	45 (55.5)	81*	16 (94.1)	33 (73.3)	NR	NR		Similar rates of postop aphasia & hemiparesis across IMRI, 5-ALA, & white light; significantly less postop hemianopia & fewer postop seizures (nonsignificant) w/ IMRI
Roder et al., 2014	06/2010–11/2012	Retrospective	18–84	6	High-field	27 (23)	43 (36.8)	117*	20 (74.1)	6 (14.0)	NR	NR		No difference in postop neurological deficits across all interventions
Senft et al., 2010	07/2004–12/2005	Retrospective	17–84	20.5	Low-field	10 (24.4)	31 (75.6)	41	10 (100)	19 (61.3)	22.03	16.98		NR
Wu et al., 2014	02/2012–08/2013	RCT	NA (>18)	11	High-field	22 (59.5)	15 (40.5)	37	20 (90.9)	11 (73.3)	NR	NR		Significantly reduced rate of aphasia in immediate postop period w/ IMRI; difference resolved at 6 mos
Zhang et al., 2015	02/2009–02/2012	Prospective cohort	16–77	6	High-field	53 (57.6)	39 (42.4)	92	40 (75.5)	19 (48.7)	19.6	13		NR

FU = follow-up; High-field = at least 1.5 T; KPS = Karnofsky Performance Status; Low-field = < 1.5 T; NA = not available; NR = not reported; OS = overall survival.

* Studies had multiple arms with numbers of cases that are spread across Tables 1 and 2, so the total number will be larger.

IMRI Versus 5-ALA: Network Meta-Analysis

Network meta-analysis methods were employed to compare GTR rates between IMRI and 5-ALA, using the assumption that the control group was conventional stereotactic navigation under white light. The results of the Markov chain Monte Carlo (MCMC) network meta-analysis are shown in Fig. 4A, and a network diagram illustrating the strength of the inferred comparisons is shown in Fig. 4B. Between IMRI and 5-ALA, neither intervention was found to be superior at facilitating GTR in HGG surgery (OR 1.9 favoring IMRI, 95% CI 0.905–3.989, $p = 0.090$), with a trend favoring IMRI. Sensitivity analysis comparing the outcomes of a fixed-effects model was also performed (Supplemental Fig. S1) and confirmed the effect in the same direction, but interstudy heterogeneity supports favoring the outcomes of the random-effects model.

Methodological Quality and Risk of Bias Assessments

The methodological quality of the included studies was assessed using the Cochrane Risk of Bias Tool for RCTs (Supplemental Table 1) and a modified Newcastle-Ottawa Scale for observational studies (Supplemental Table 2).^{28,68} Among the IMRI studies, the sole RCT, by Wu et al., reported only an interim analysis generating uncertainty in outcome and reporting, and surgeon blinding was not possible throughout the study.⁷⁰ Among the 6 observational studies on IMRI, 2 studies left selection of the exposed cohort up to surgeon discretion rather than based on IMRI availability,^{39,55} 2 studies either did not report selection of the nonexposed cohort or used historical controls,^{40,45} and 4 studies failed to achieve cohort comparability for lack of reporting outcomes by tumor location,^{39,40,45,55} yielding a mean Newcastle-Ottawa Scale score of 4.8/7. Among the 5-ALA studies, the RCT, by Stummer et al., had similar issues with surgeon blinding and used a per-protocol analysis since several patients were lost to follow-up or had technical issues with the 5-ALA—introducing attrition bias.⁶² Of the 5 observational studies, 4 were cohort studies and 1 was a case-control study; none of the cohort studies described an unbiased process for selection of the nonexposed cohort,^{17,32,40,45} and 2 did not report outcomes by tumor location,^{40,45} yielding a mean Newcastle-Ottawa Scale score of 4.5/7. In the case-control study, by Bruch et al., limited information on case representativeness, control selection, and nonresponse rate was available given the study's abstract format.⁶

Publication bias was also assessed using funnel plots of standard error by log odds ratio for the outcome of GTR rate for IMRI studies (Fig. 5A), 5-ALA studies (Fig. 5B), and the two in combination (Fig. 5C).⁵⁹ Among the IMRI studies, a lack of symmetry in the funnel plot and the presence of studies falling outside the 95% confidence interval was observed, while among the 5-ALA studies, plot symmetry indicated a lower risk of bias. Among all studies tested in the network meta-analysis, there was some asymmetry of the funnel plot (driven by the IMRI studies), but all studies fell within the confidence interval, suggesting an intermediate level of bias.

Lastly, the IMRI and 5-ALA studies were separately assessed in subgroup analyses by study type to determine

TABLE 2. Study characteristics and outcomes: 5-ALA versus conventional navigation

Authors & Year	Study Period	Study Type	Age Range (yrs)	Mean FU (mos)	No. of Patients w/ GTR (%)		Median OS (mos)		Postop Deficits
					5-ALA	Control	5-ALA	Control	
Bruch et al., 2011	NA	Retrospective	NA (>18)	NA	74 (50)	74 (50)	148	40 (54.1)	NR
Diez Valle et al., 2014	07/2011–01/2012	Retrospective	NA (>18)	6	131 (52.2)	120 (47.8)	251	88 (67.2)	NR
Kim et al., 2014	01/2009–05/2011	Retrospective	16–81	12	40 (50)	40 (50)	80	32 (80.0)	14
Nickel et al., 2018	06/2013–06/2016	Prospective cohort	NA (>18)	4	19 (23.5)	45 (55.5)	81*	14 (73.7)	NR
Roder et al., 2014	06/2010–11/2012	Retrospective	18–84	6	47 (40.2)	43 (36.8)	117*	21 (44.7)	NR
Stummer et al., 2011	11/1999–07/2004	RCT	23–73	35.4	176 (50.4)	173 (49.6)	349	112 (63.6)	13.7

Increased rate of aphasia & hemianopia in immediate postop period w/ 5-ALA; differences resolved w/ in a few mos

Significantly improved KPS at 3 mos w/ 5-ALA

Similar rates of postop aphasia & hemiparesis across IMRI, 5-ALA, & white light; less postop hemianopia w/ 5-ALA than w/ white light, but significantly higher rate of hemianopia compared to that w/ IMRI; slightly increased seizure rate (nonsignificant) w/ 5-ALA compared to that w/ white light

No difference in postop neurological deficits across all interventions

No statistically significant difference in postop & FU KPS btwn 5-ALA & white light; significantly reduced rate of intracranial hypertension w/ 5-ALA

FIG. 2. Forest plots depicting primary and secondary outcomes in a classic meta-analysis comparison of IMRI to conventional navigation (random-effects models). **A:** Odds ratio for achieving GTR. **B:** Standard difference (Std diff) in means for progression-free survival. **C:** Standard difference in means for overall survival.

the relative impact of retrospective versus prospective studies on observed outcomes. Among the IMRI studies, the prospective studies were sufficient to demonstrate an increased rate of GTR associated with IMRI (OR 3.549, 95% CI 1.680–7.501, $p = 0.001$), and retrospective studies contributed an artificially elevated outcome, with nearly four times greater odds of achieving GTR and a wide confidence interval, implying severe interstudy heterogeneity (OR 7.319, 95% CI 2.177–24.608, $p = 0.001$; Fig. 6A). Among the 5-ALA studies, the analysis of GTR in the prospective studies alone showed a nonsignificant relationship with increased GTR with 5-ALA (OR 2.019, 95% CI 0.758–5.377, $p = 0.160$; Fig. 6B). Retrospective studies only contributed a 1.5 times greater contribution to the odds ratio outcome (OR 3.079, 95% CI 2.159–4.391, $p < 0.001$), implying a lower contribution of bias from the retrospective literature among the 5-ALA studies versus the IMRI studies.

Discussion

In gliomas, EOR is a well-defined determinant of overall patient survival.⁴⁹ Since the late 1990s, both IMRI and 5-ALA have seen growing interest in the neurosurgical community for their potential to provide real-time feedback on tumor localization.^{13,23,36} Our meta-analysis confirms that both IMRI and 5-ALA individually improve the rate of GTR over conventional stereotactic navigation and, accordingly, prolong both progression-free and overall survival. Our network meta-analysis revealed that between IMRI and 5-ALA, neither intervention was clearly superior in attaining GTR, with a slight trend favoring IMRI. However, if carefully considering the potential risk of bias from the contribution of retrospective studies, as well as the increased interstudy heterogeneity among IMRI studies, it is likely that the effect size of IMRI is artificially elevated and that the two modalities are truly equally ef-

FIG. 3. Forest plots depicting primary and secondary outcomes in a classic meta-analysis comparison of 5-ALA to conventional navigation (random-effects models). **A:** Odds ratio for achieving GTR. **B:** Standard difference (Std diff) in means for progression-free survival. **C:** Standard difference in means for overall survival.

fective. It remains unclear whether these two techniques are complementary and if the use of both is additive. In our exhaustive literature search, we found only one article describing the combination of IMRI and 5-ALA that fit our inclusion criteria,⁴⁰ and including a “combination” arm into our network meta-analysis with data from this single study would introduce significant bias. All articles from our screening that describe the use of a combination of IMRI and 5-ALA for HGG resection (and reasons for exclusion) are reviewed in Table 3.^{10–12,20,21,24,26,40,44,51,67,71} While the outcomes of these studies were heterogeneous, some common themes emerged: 1) 5-ALA was more sensitive than IMRI for identifying tumor at the infiltrating edge, and 2) a high GTR rate and/or EOR were consistently achievable across series using the combination approach. These data and the potential for synergy between IMRI and 5-ALA have significant implications for patient care decisions, program development, and healthcare spending in neurosurgery.

The existing literature (and our study) clearly shows that IMRI increases the rate of GTR over conventional neuro-navigation.^{8,39,40,45,53,55,70,74} As with any technology, IMRI is imperfect and has several important limitations: IMRI is an “off-line” method that requires the surgeon to pause the procedure for image acquisition and often involves moving the patient to a separate room, adding surgical time and possibly increasing infection rates.^{2,21} Additionally, the cost of installing an IMRI suite can be prohibitive.² Image interpretation can be ambiguous as contrast can lead to false-positive interpretations, and blood and CSF artifact in the cavity can obfuscate images.^{27,33} In our review, the majority of IMRI studies used high-field (≥ 1.5 T) magnets, which provide enhanced image quality. However, multiple series have described the comparable efficacy of low- and high-field IMRI in detecting residual tumor tissue,^{54,56} especially when adjusting the gadolinium dose.³⁴ Low-field magnets may provide a more cost-effective option.²⁵

Likewise, 5-ALA (Gliolan) has become a popular in-

FIG. 4. A: Forest plot depicting Markov chain Monte Carlo Bayesian network analysis for direct comparison of IMRI and 5-ALA across all included studies using a random-effects model. Comparisons of 5-ALA and IMRI to conventional navigation are also shown. **B:** Comparison network indicating number of studies with direct comparison available.

traoperative imaging tool with widespread use in Europe and recent FDA approval in the US.⁵⁸ First described as an adjunct for HGG visualization by Stummer et al. in 1998, 5-ALA is a natural intermediate in the heme synthesis pathway that is converted intratumorally to fluorescent protoporphyrin IX (PpIX), which is visible intraoperatively under blue light (wavelength range 375–440 nm).⁶¹ The sensitivity and specificity of 5-ALA for HGG tissue have been as high as 95% and 100%, respectively.^{24,71} Several studies, ours included, have confirmed the utility of 5-ALA for increasing EOR over conventional stereotactic navigation.^{6,17,32,45,60,62} Moreover, oral 5-ALA has an excellent side effect profile; the most common side effect reported is hypotension, mostly seen in patients already on antihypertensives or in those with chronic hypotension.⁹ Additionally, despite a less than 1% reaction rate, patients are put on photosensitivity precautions, including complete skin and eye coverage, for up to 48 hours after ingestion of 5-ALA.⁶⁰ Transient increases in serum transaminases, as well as gastrointestinal complaints including nausea, vomiting, and diarrhea, have been reported after surgery with 5-ALA but are likely better explained by the effects of anesthetic agents (such as propofol and volatile gases).⁶⁴

Economic Impact

The cost of an IMRI unit is exorbitant, ranging between \$3 and \$7 million—not including the cost of remodeling the surgical suite, the IMRI-compatible instruments, and the extended surgical time.¹ All of the existing IMRI suites in the UK, and several in the US, were funded by large charitable donations.^{14,65} On the other hand, the fluorescence modules for surgical microscopes only cost between \$34,000 and \$51,000 in Europe.⁵⁷ 5-ALA itself also entails a relatively low additional cost of \$1100 per patient.⁵⁷ In an era of rising healthcare costs and value-based healthcare delivery, comparing the relative costs, benefits, and overall accessibility of IMRI and 5-ALA has become a critical responsibility of the neurosurgical and neuro-oncological community.

Economic outcomes in healthcare are measured in quality-adjusted life years (QALYs), and in HGG surgery, the threshold for cost-effectiveness is estimated at an addition-

al \$50,000 per QALY.¹⁸ Only 2 studies to date have reported the increase in cost per QALY associated with 5-ALA (around \$10,000 per QALY).^{19,57} One meta-analysis determined that 5-ALA costs about half of what IMRI does (\$16,218 vs \$32,954 per QALY).¹⁸ Another consideration is that IMRI increases surgical time given the increased complexity of the operative setup and the time required for patient transfer to the IMRI suite during surgery. Among our included studies, surgical time was either not reported or reported too heterogeneously for quantitative synthesis, but across the literature, IMRI was associated with an average increase of 33–60 minutes in surgical time.¹⁸ However, some of the cost of IMRI is likely ameliorated by its utility across multiple pathologies. IMRI has been shown in several series to improve the EOR of low-grade gliomas (LGGs) by using T2/FLAIR sequences.^{42,46} While useful for prognosticating LGG when there are pockets of fluorescence indicating malignant transformation,⁶⁹ 5-ALA is typically only visible intraoperatively in 15%–20% of LGGs.³⁰ IMRI is also highly beneficial for the resection of other contrast-enhancing tumors, particularly skull base lesions such as pituitary adenomas⁵² and meningiomas,⁷ as well as in other T2/FLAIR-hyperintense pathologies such as cortical dysplasia.⁴⁸ IMRI has also been shown to improve localization accuracy in stereotactic procedures such as deep brain stimulation¹⁵ and laser interstitial thermal therapy.⁴³ While further research is warranted to better determine cost-effectiveness (especially in the US), our data demonstrating equal clinical efficacy combined with previously reported economic outcomes favor 5-ALA over IMRI specifically for HGG resection in a crude cost-benefit analysis, with the caveat that IMRI currently has more applications in other pathologies.

The call for a better quality of evidence and for enhanced cost-benefit analysis of IMRI and 5-ALA has prompted a small number of clinical trials. The first head-to-head parallel assignment study evaluating IMRI versus 5-ALA-guided HGG resection is ongoing in Germany and will additionally assess outcomes based on molecular subgroups (NCT02379572). Another randomized study evaluating the added value of IMRI over 5-ALA alone is being planned in Germany as well (NCT01798771). Ad-

FIG. 5. Funnel plots of standard error versus log odds ratio for the primary outcome (GTR) for IMRI versus conventional navigation (classic meta-analysis, **A**), 5-ALA versus conventional navigation (classic meta-analysis, **B**), and IMRI and 5-ALA versus conventional navigation (network meta-analysis, **C**).

FIG. 6. Forest plots depicting the primary outcome, i.e., odds of GTR, by study type subgroup for IMRI versus conventional navigation (A) and 5-ALA versus conventional navigation (B; both comparisons are random-effects models).

ditionally, there are several ongoing studies evaluating an expanded role for 5-ALA in other pathologies such as LGG (NCT02473380, NCT01502280).

Study Limitations

Preliminary literature searches revealed that the most common definition of GTR in HGG was 100% resection of the contrast-enhancing lesion. At the expense of excluding a handful of articles with altered definitions (i.e., 95% or 98% resection of contrast-enhancing tumor), the primary endpoint of 100% resection was chosen to optimize data uniformity and study yield. We were additionally inclusive of studies using various additional navigational tools such as neuromonitoring or ultrasound given the current lack of evidence for any significant influence on GTR rates with these tools as compared to existing evidence and clinical interest related to IMRI and 5-ALA. Future studies on neuronavigational adjuncts and meta-analyses would benefit from outcome data based on a more standardized GTR definition.

It must be noted that using a primary endpoint based on postoperative MRI likely biases our data toward favoring IMRI over 5-ALA and thus may not be the ideal assessment of the tumor margin. Postmortem study of HGG specimens has demonstrated that resection of the contrast-enhancing lesion alone is insufficient—by a margin of at least 1 cm—to ensure removal of prognostically critical

infiltrating cells.⁷² Radiological studies comparing more highly sensitive and specific ¹⁸F-FET PET imaging to MRI have also corroborated the shortfalls of contrast MRI for visualization of the HGG margin.²² 5-ALA, on the other hand, may be a superior approximator of the true tumor margin based on both pathology and ¹⁸F-FET PET imaging.^{10,47} Therefore, we must view the trend favoring IMRI for GTR in our analysis more critically with the understanding of potential underlying bias stemming from the outcome measure of GTR on postoperative MRI.

Another limitation of this analysis was the need to include observational studies and the limited quality of evidence of the included RCTs given issues with blinding. We were also unable to quantitatively assess outcomes by tumor location (eloquent vs noneloquent). While several studies noted the distribution of eloquent and noneloquent tumors within study arms, none commented on differences in the achieved EOR within these subgroups (with the exception of 2 studies conducted entirely in eloquent tumors).^{8,74} Likewise, heterogeneity in reported neurological deficits did not permit meaningful quantitative synthesis. A descriptive synthesis of postoperative deficits was included in Tables 1 and 2; most studies did not find significant differences in postoperative deficits between interventions, and any differences found must be weighed against the confounding issue of unknown eloquence/localization of the lesion. The IMRI- and 5-ALA-specific

TABLE 3. Studies describing the use of a combination of IMRI and 5-ALA for HGG resection

Authors & Year	Reason for Exclusion From Meta-Analysis	Study Type	Study Arms	Outcomes Studied	Main Findings	Postop Deficits
Coburger et al., 2014	No comparator group (incompatible study design)	Prospective series	IMRI+5-ALA (n = 34)	Sensitivity & specificity of IMRI & 5-ALA for tumor margins	5-ALA has significantly higher sensitivity (0.85 vs 0.41, $p < 0.001$) & lower specificity (0.43 vs 0.70, $p < 0.001$) for tumor detection at margin	NR
Coburger et al., 2015	Does not report our primary outcome (GTR defined as >95% resection)	Retrospective cohort	IMRI (n = 33), IMRI+5-ALA (n = 33)	EOR, GTR, PFS, OS	Mean EOR significantly higher in IMRI+5-ALA group ($p < 0.004$); IMRI+5-ALA achieved significantly higher GTR rate (100%) than IMRI alone (82%; $p < 0.010$); median PFS & OS did not differ btwn study arms	Rate of complications did not differ btwn study arms
Coburger et al., 2017	No comparator group (incompatible study design)	Prospective series	IMRI+5-ALA (n = 33)	Sensitivity for tumor margin & molecular correlation at biopsy sites	Share of solid tumor highest in 5-ALA+ specimens (65%) vs specimens localized w/ IMRI (55%); sensitivity for invasive tumor higher in 5-ALA+ specimens (84%) vs specimens localized w/ IMRI (50%); 5-ALA positivity correlated w/ presence of necrosis, microproliferation, grading, & MGMT promoter methylation (IMRI did not)	NR
Eyüpoglu et al., 2012	No comparator group (incompatible study design)	Prospective series	IMRI+5-ALA (n = 37)	GTR	IMRI detected residual tumor after full resection of 5-ALA+ tissue in 38% of cases	NR
Eyüpoglu et al., 2016	Does not report our primary outcome	Prospective cohort	IMRI+5-ALA (n = 30), conventional nav (n = 75)	OS	IMRI+5-ALA arm demonstrated increased median OS (18.5 vs 14 mos)	No differences in postop KPS or other specific deficits (motor, visual, speech, cognitive, seizure)
Gessler et al., 2015	No comparator group (incompatible study design)	Prospective series	IMRI+5-ALA (n = 32)	GTR	9 patients (47.4%) showed discrepancies in identifying residual tumor btwn IMRI & 5-ALA; GTR achieved in 97% of patients	Overall complication rate of 9.4% (2 patients w/ hemiparesis, 1 w/ transient aphasia)
Hauser et al., 2016	No comparator group (incompatible study design)	Prospective series	IMRI+5-ALA (n = 12)	Sampling of tumor margins based on visualization w/ IMRI & 5-ALA	11 patients (92%) required additional resection based on IMRI after 5-ALA+ tissue fully resected; IMRI has limited accuracy in predicting tumor remnants (64.3% of biopsy samples at infiltration zone positive for tumor)	NR
Nickel et al., 2018	Meets inclusion criteria	Prospective cohort	IMRI (n = 17), 5-ALA (n = 19), IMRI+5-ALA (n = 20), conventional nav (n = 45)	GTR, health-related quality of life	GTR rate highest for IMRI+5-ALA arm (95%) compared to IMRI (94.1%), 5-ALA (73.7%), & conventional nav (73.3%); navigational modality did not predict estimates of health-related quality of life	Lowest rate of neurological deficits in combined IMRI+5-ALA arm ($p = 0.59$, nonsignificant)
Quick-Weller et al., 2016	No comparator group (incompatible study design)	Prospective series	IMRI+5-ALA (n = 7; in recurrent GBM alone)	OS	Median OS 27.8 mos for whole cohort, median survival since repeat surgery 7.6 mos; all patients attained GTR	1 patient w/ worsened hemianopia (expected based on localization of lesion), 1 patient developed postop status epilepticus
Schatlo et al., 2015	Does not report our primary outcome	Retrospective cohort	IMRI (n = 87), IMRI+5-ALA (n = 55), conventional nav (n = 58)	OS, PFS	In multivariate analysis considering KPS & EOR, IMRI had no effect on OS; 5-ALA improved rate of GTR but did not affect OS or PFS in multivariate analysis	NR

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TABLE 3. Studies describing the use of a combination of IMRI and 5-ALA for HGG resection

Authors & Year	Reason for Exclusion From Meta-Analysis	Study Type	Study Arms	Outcomes Studied	Main Findings	Postop Deficits
Tsugu et al., 2011	Does not report our primary outcome (GTR defined as >98% resection); includes other lesions	Retrospective cohort	5-ALA (n = 13), IMRI+5-ALA (n = 14), HGG only	EOR, GTR	EOR higher w/ IMRI+5-ALA (89.2%) vs 5-ALA alone (68.7%), including EOR for LGG; GTR rate 43% w/ 5-ALA alone & 47% w/ IMRI+5-ALA (including LGG)	No differences in postop deficits
Yamada et al., 2015	No comparator group (incompatible study design)	Prospective series	IMRI+5-ALA (n = 99)	Sampling of tumor margins & tumor bulk based on visualization w/ 5-ALA	Positive predictive values of 5-ALA for presence of tumor w/in & outside its boundaries on IMRI were 100% & 86%, respectively	Early postop complications noticed in 67% of patients, but after 3 mos, deficits remained in only 9% of patients

n = number of cases; nav = navigation; PFS = progression-free survival.

literature also spanned slightly different study periods (2004–2014 and 1999–2016, respectively), and both included studies that evaluated survival outcomes prior to the Stupp chemoradiation protocol published in 2005.⁶³ The variations in study period may also influence the use of additional navigational adjuncts (neurophysiological monitoring, DTI, ultrasound, etc.), with greater use of these tools in recent years. A sensitivity analysis removing studies that included surgeries performed prior to 2005^{55,62} was, nevertheless, found to be consistent with our original network meta-analysis findings for GTR (Supplemental Fig. S2). Lastly, only 2 of the 11 included studies gave GTR outcomes for both IMRI and 5-ALA, necessitating the use of Bayesian network meta-analysis methods to estimate their relative effectiveness. This analysis is inherently an indirect comparison and meant to be hypothesis generating; a randomized trial directly comparing the two methods is needed to definitively establish equipoise or the superiority of one method over the other.

Conclusions

IMRI and 5-ALA individually provide significant resection and survival benefit over conventional stereotactic navigation. When comparing IMRI and 5-ALA, neither intervention was found to be superior for achieving GTR. Additional literature review potentially supports a relatively greater benefit of 5-ALA in HGG surgery when considering histopathologically true tumor margins and cost burden; however, unlike 5-ALA, IMRI has demonstrated significant utility across multiple pathologies. While the limited availability of level I evidence and data heterogeneity limit the conclusiveness and generalizability of our analysis, it is clear that both adjuncts contribute meaningfully to HGG surgery, and attempts to incorporate at least one of these neuronavigational tools should be made across operating centers.

Importance of the Study

While HGG continues to have poor survival outcomes, surgical EOR has come to be known as a critical prognostic factor. Surgery using conventional stereotactic neuronavigation is limited by intraoperative brain shift and vague tumor margins. Intraoperative visualization adjuncts, such as IMRI and 5-ALA fluorescence, are becoming increasingly popular neuronavigational aids. While several prior studies have compared either IMRI or 5-ALA with stereotactic navigation, direct comparisons of surgical outcomes with IMRI versus 5-ALA remain limited. We performed an exhaustive systematic review and meta-analysis of the comparative effectiveness of IMRI and 5-ALA for achieving GTR in HGG surgery. We secondarily analyzed associated survival outcomes. Our findings indicate that between IMRI and 5-ALA, neither surgical adjunct is superior, but both are better than conventional image guidance alone. These results have significant implications for economically prudently incorporating these novel neuronavigational aids into routine neurosurgical care.

Appendix

Search strategy for PubMed (adapted for Embase, Cochrane

Central, Web of Science).

1. "magnetic resonance imaging, interventional"[MeSH]
2. "intraoperative MRI"[tw]
3. "intraoperative magnetic resonance imaging"[tw]
4. "intraoperative MR"[tw]
5. "IMRI"[tw]
6. 1 OR 2 OR 3 OR 4 OR 5
7. "5-ALA"[tw]
8. "aminolevulinic"[tw]
9. "5-aminolevulinic"[tw]
10. 7 OR 8 OR 9
11. "neuronavigation"[MeSH]
12. "neuronavigation"[tw]
13. "stereotactic"[tw]
14. "brain lab"[tw]
15. "brainlab"[tw]
16. "MRI guidance"[tw]
17. "MRI guided"[tw]
18. "magnetic resonance imaging guided"[tw]
19. "magnetic resonance imaging guidance"[tw]
20. "image guidance"[tw]
21. "image guided"[tw]
22. 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
- OR 20 OR 21
23. 6 OR 10 OR 22
24. "glioma"[MeSH]
25. "astrocytoma"[MeSH]
26. "oligodendroglioma"[MeSH]
27. "glioblastoma"[MeSH]
28. "glioma"[tw]
29. "astrocytoma"[tw]
30. "oligodendroglioma"[tw]
31. "glioblastoma"[tw]
32. "gbm"[tw]
33. "gliomas"[tw]
34. "astrocytomas"[tw]
35. "oligodendrogliomas"[tw]
36. "glioblastomas"[tw]
37. "gbms"[tw]
38. 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR
- 32 OR 33 OR 34 OR 35 OR 36 OR 37
39. 23 AND 38
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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this study.

Author Contributions

Conception and design: Golub, Nicholson, Schwartz. Acquisition of data: Golub, Hyde, Dogra. Analysis and interpretation of data: Golub, Nicholson, Kirkwood, Loftus, Schwartz. Drafting the article: Golub, Hyde, Dogra, Gohel. Critically revising the article: Golub, Hyde, Dogra, Nicholson, Kirkwood, Schwartz. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Golub. Statistical analysis: Golub, Kirkwood, Loftus. Administrative/technical/material support: Nicholson, Schwartz. Study supervision: Nicholson, Schwartz.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplemental Figures and Tables. <https://thejns.org/doi/suppl/10.3171/2019.12.JNS191203>.

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