Intraoperative 5-ALA Fluorescence-Guided Resection of High-Grade Glioma Leads to Greater Extent of Resection with Better Outcomes: A Systematic Review

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Abstract

Importance

High-grade gliomas (HGG) are the most aggressive and common malignant brain tumors in adults. They have a dismally fatal prognosis. Even if gross total resection of the enhancing tumor is achieved, inevitably, invading tumor cells that are indistinguishable to the un-aided eye are left behind, which eventually leads to tumor recurrence. 5-aminolevulinic acid (5-ALA) is an increasingly utilized intraoperative fluorescent imaging agent for patients with HGG. It enhances visualization of HGG tissue. Despite early promising randomized clinical trial data suggesting a survival benefit for 5-ALA-guided surgery, the growing body of literature must be analyzed to confirm efficacy on patient outcomes.

Objective

To perform a systematic review of the literature to evaluate whether there is a beneficial effect upon survival and extent of resection due to the utilization of 5-ALA in HGG surgery.

Evidence Review

Literature regarding 5-ALA usage in HGG surgery was reviewed according to the PRISMA guidelines. One database, PubMed, was searched for assorted combinations of the keywords “5-ALA,” “high-grade glioma,” “5-aminolevulinic acid,” and “resection” in July 2020 for case reports and retrospective, prospective, and randomized clinical trials assessing and analyzing 5-ALA intraoperative use in patients with HGG. Entailed studies on PubMed and SCOPUS were found for screening using a snowball search technique upon the initially searched PubMed papers. Systematic reviews and meta-analyses were excluded from our PRISMA table.

Findings

1,951 previously published studies were screened, 536 of which were further evaluated, and ultimately 45 were included in our systematic review. There were no date restrictions on the screened publications. Our literature search was finalized on July 16, 2020. We found an observed increase in the overall survival (OS) and progression-free survival (PFS) of the 5-ALA group compared to the white light group, as well as an observed increase in the OS and PFS of complete resections compared to incomplete resections. Of the studies that directly compared the use of 5-ALA to white light (13 of the total analyzed 45, or 28.9%), 5-ALA lead to a better PFS and OS in 88.4% and 67.5% of patients, respectively.

When the studies that reported postoperative neurologic outcomes of surgeries using 5-ALA vs. white light were analyzed, 42.2% of subjects demonstrated 5-ALA use was associated with less post-op neurological deficits, whereas 34.5% demonstrated no statistically significant difference between 5-ALA and without. 23.3% of studies showed that intraoperative 5-ALA guided surgeries lead to more post-op neurological deficits.

Conclusions and Relevance

Utilization of 5-ALA was found to be associated with a greater extent of resection in HGG surgeries, as well as longer OS and PFS. Postop neurologic deficit rates were mixed and inconclusive when comparing 5-ALA groups to white light groups. 5-ALA is a useful surgical adjunct for resection of HGG when patient safety is preserved.

Introduction

High grade gliomas (HGG) are tumors of the glial cells in the central nervous system. These gliomas are referred to as high grade because they are rapidly growing and categorized as WHO grade III or IV tumors. HGG are the most aggressive and common types of brain tumors in adults. They include gliosarcomas, anaplastic astrocytomas, oligoastrocytomas, diffuse brainstem gliomas/diffuse pontine gliomas, pleiomorphic xanthoastrocytomas, and glioblastoma multiforme (GBM). Despite surgical resection, radiation therapy, and chemotherapy, microscopic residual tumor is inevitable due to the highly invasive nature of HGG, which leads to tumor recurrence.

One emerging tool in the neurosurgical arsenal is using intraoperative 5-aminolevulinic acid (5-ALA) for fluorescence-guided surgery to maximize tumor resection and minimize residual tumor. In 2017, the U.S. Food and Drug Administration (FDA) approved 5-ALA for use as an intraoperative fluorescent imaging agent in patients with HGG [1]. 5-ALA enhances visualization of malignant brain tumor tissue to potentially result in a more complete resection of the tumor. Approximately a decade prior to its approval in the United States, it was first approved in Europe by the European Medicine's Agency (EMA) in 2007 [1]. The European approval followed Dr. Walter Stummer's 2006 randomized controlled multicenter phase III trial which substantiated that 5-ALA can lead to more complete HGG resection with better outcomes than white light visualization alone.[2] Stummer's work was a landmark paper describing a survival benefit from the use of 5-ALA. High-grade glioma patients fare better in terms of survival with gross-total resection.[3] The greater the extent of resection, the longer the overall survival of the patient [2]. Intraoperative 5-ALA can potentially help maximize tumor resection.

Currently, this solution is inadequately investigated, as it has been 14 years since Stummer's paper was written, and there has not been much generalized conclusion regarding the survival benefit from the use of 5-ALA in GBM resection. However, during the past 14 years, a copious amount of papers have been written about individual 5-ALA experiences. It is imperative to analyze these papers to see if they confirm the benefit observed in the Stummer 2006 study. Additionally, it appears that although 5-ALA is associated with a greater extent of resection, its use may be associated with a potential increase in post-op complication/neurological deficit. This postulation must be further explored as well.

Methods

Search Strategy

One database, PubMed, was searched in July 2020 for case reports, retrospective, prospective, and randomized clinical trials assessing and analyzing 5-ALA intraoperative use in patients with HGG. Entailed studies on PubMed and SCOPUS were found for screening using a snowball search technique upon the initially searched PubMed papers. Systematic reviews and meta-analyses were excluded from our PRISMA table. Assorted combinations of the keywords "5-ALA," "high-grade glioma," "5-aminolevulinic acid," and "resection" were used in the search. Our systematic review was reported in accordance to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[4] We performed searches in PubMed from inception to July 16, 2020. Case reports, retrospective, prospective, and randomized clinical trials evaluating the application, characteristics, and effects of 5-ALA use in HGG resection were included. There was no limit by year of publication. Editorials were excluded. The selection of sources was agreed upon by consensus. The first author, year, study design, country, number of participants, figures, content, diagnosis, pathology, prognosis, and timeline were all included data taken into consideration.

Study Selection

The included studies had to definitively use 5-ALA as an intraoperative imaging agent upon HGG neurosurgery. 1,951 full-text studies were assessed for eligibility and inclusion in this systematic review (Prisma Flowchart). 224 studies were initially excluded due to complete irrelevance and duplication. Upon screening the remaining 1,727 abstracts, a further 1,191 studies were excluded for substantial irrelevance. Of the 536 remaining full texts that were read, 491 were excluded for the following reasons: limited relevance, low-grade gliomas (WHO grade I and II), focus upon 5-ALA sensitivity, specificity, PPV, and NPV, and failure to include statistics/results regarding survival, extent of resection, and percent gross-total resection. Thus, 45 studies were included (Table 1).

Risk of Bias Assessment

Included research studies were assessed for risk of bias via the Cochrane risk of bias tool.[4] It appraises selection bias (allocation concealment and generation of random sequence), performance bias, detection bias, reporting bias, and attrition bias. Each author classified the risk of bias of each source as uncertain, low, or high. If a source received a high-risk rating in any type of bias, it was considered at high risk of overall bias.

Statistical Methods

Mean difference (MD) was used as the summary statistic for each outcome measure. Each outcome was presented as a forest plot; the weighted MD, the 95% Confidence Interval (CI) and the relative weightings were represented by the middle of the square, the horizontal line, and the relative size of the square respectively. In the present study, a random-effect model was tested to take into account the possible clinical diversity and methodological variation between studies. χ^2 tests were used to study heterogeneity between trials. I^2 statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance, with values greater than 50% considered as substantial heterogeneity.

I^2 can be calculated as: $I^2 = 100\% \times (Q - df)/Q$, with Q defined as Cochrane's heterogeneity statistics and df defined as degree of freedom. Publication bias was assessed through the generation of funnel plots for all outcomes and assessed for asymmetry. If there was substantial heterogeneity, the possible clinical and methodological reasons for this were explored qualitatively, and quantitatively, any outlying study was removed and effect on overall trend direction and significance was reassessed for any significant change. All P values were 2-sided. All statistical analysis was conducted with Review Manager Version 5.3.3 (Cochrane Collaboration, Software Update, Oxford, United Kingdom).

Results

Study Characteristics

The reviewed studies included 21 prospective, 20 retrospective, 3 randomized phase trials, and 1 parallel, randomized, balanced, group-sequential, two-armed, controlled multicenter phase III study. A total of 1,951 titles and abstracts were identified by the aforementioned search tactics, of which 45 met our inclusion criteria and were included in the qualitative synthesis. The total number of patients across all of the 45 included studies were at least 4,599 (Table 1). One study by Stepp et al. 2007[5] was carried out on patients at 18 clinics in Germany, however, the specific amount of patients was not specified in the text. The 45 studies all used 5-ALA to remove HGG tumors and often focused on 5-ALA vs. white light, 5-ALA only, and 5-ALA combined with technologies, such as intraoperative MRI (iMRI), contrast-enhanced ultrasound (CEUS), intraoperative ultrasound (ioUS), and intraoperative CT (i-CT).

Statistical Approach

Of the 45 analyzed studies, 13 of these studies (28.9%) compared HGG resection guided by 5-ALA vs. white light. These 13 studies totaled 2,060 patients. Of the 1,984 patients, a total of 1,525 patients were analyzed for progression-free survival (PFS), 1,616 analyzed for overall survival (OS), and 1,077 explored post-op neurological deficit. Regarding PFS, 5-ALA was better in 1,348 patients (88.4%) and there was no statistically significant difference shown between 5-ALA and lack of 5-ALA in 177 patients (11.6%). As for OS, 5-ALA was better in 1,090 (67.5%) and there was no statistically significant between 5-ALA and lack thereof in 526 (32.5%). Regarding post-op neurological deficits, 5-ALA was better that white light in 454 patients (42.2%), worse in 251 (23.3%), and showed no statistical difference between 5-ALA and white light in 372 patients (34.5%).

Findings

Fluorescence-guided resection (FGR) with 5-ALA for the removal of HGG tumors was associated with a higher extent of resection (EOR) [6],[7],[8] and a higher percentage of gross total resections (GTR) [6],[5],[2],[9] than white light. This corresponds to an ultimately longer PFS [10],[6],[7],[5],[2],[9] and OS [6],[11],[7],[8],[2],[9]. These findings coincide with the findings of Eljamel et al. and Eyüpoglu et al. that showed 5-ALA usage as compared to its absence correlates with a higher OS [12],[13]. Complete resection as opposed to incomplete resection correlates with a longer PFS [14],[15],[16] as well as OS [17],[14],[15],[16],[18],[19].

Panciani et al.'s study corroborates the conclusion that 5-ALA and neuronavigation leads to an increase in the obtained EOR than with conventional surgical strategy[20].

The rates of GTR when using FGR technique with 5-ALA greatly vary across studies. Multiple groups report rates of complete resection of 80% and greater when using 5-ALA [21], which can be considered a decent amount [22],[23],[24],[14],[25],[26],[27],[28]. Conversely, very low complete resection rates (< 50%) have been reported with the use of 5-ALA [29],[30]. Mediocre rates have also been reported, between 50–80% [31],[32],[33],[34],[35],[16],[36],[19],[37],[38]. These varying rates of resection and the cause of such disparity should be further inspected.

The combination of 5-ALA with different intraoperative technological modalities yielded mixed results. Barbagallo et al.[39] did not find a statistically significant difference between the PFS and OS of intraoperative 5-ALA usage only vs. 5-ALA + i-CT. A study by Coburger et al.[40] demonstrated that the combination of iMRI + 5-ALA versus iMRI without 5-ALA led to a greater amount of GTR and a greater OS. Similar studies by Eyüpoglu et al.[41] and Nickel et al.[42] both demonstrate that iMRI + 5-ALA led to a higher EOR as opposed to 5-ALA alone. Conversely, Tsugu et al.[43] concluded that 5-ALA alone resulted in a higher percentage of complete resection, but a lower EOR than iMRI + 5-ALA. Roder et al.[44] showed that surgery solely with iMRI led to a higher percentage of GTR, greater EOR, and a higher PFS than surgery solely with 5-ALA. Surgery guided by iMRI versus non-iMRI in a study by Schatlo et al.[45] indicated that iMRI usage led to a higher overall survival. Yamada et al.[46] reported an impressive amount of 95% complete resections executed by 5-ALA + iMRI. Additionally, Della Pepa et al.[47] studied the combined use of intraoperative 5-ALA + CEUS and found that the combination resulted in the highest EOR as compared with 5-ALA alone, CEUS alone, and conventional surgical technique. Neidert et al.[48] found that 5-ALA used in conjunction with ioUS resulted in a higher OS than 5-ALA alone.

Overall, there was an observed increase in the OS and PFS when comparing 5-ALA groups to white light groups as well as complete resection groups to incomplete resection groups. The most common post-operative neurological deficits were motor, language, and visual in nature. They consisted more specifically of aphasia, hemiparesis, and hemianopsia. Post-op seizures and hemorrhages were also observed. There was expected to be a substantially higher neurological complication rate of HGG resection using 5-ALA as compared to white light due to more aggressive surgical resection. Yet, the included studies were rather inconclusive and disparate regarding if 5-ALA lead to more complications. Across the studies that included complication rates, 5-ALA was better that white light in 454 patients (42.2%), worse in 251 (23.3%), and showed no statistical difference between 5-ALA and white light in 372 patients (34.5%). In multiple studies, there were surgeries that were halted, leaving behind residual 5-ALA-fluorescing tissue in order to avoid causing neurological deficit. For example, in the study by Chan et al., minimal residual 5-ALA fluorescence was left in three patients to avoid post-operative deficit [31]. Della Puppa et al. stopped surgery in 26% of cases to avoid neurological deficits [22]; Feigl et al. stopped 24% of surgeries, leaving residual 5-ALA fluorescence to avoid deficits [35]. Jacquesson et al. noted leaving 5-ALA fluorescence to avoid post-operative neurological deficits as well in 31.8% of their cases [16]. 0% of cases reported an allergy to 5-ALA reported. If a patient is known to have an allergy to 5-ALA or is an extremely atopic individual, proper prophylaxis is necessary to avoid allergenic complications. Or rather, as seen in studies such as Chan et al., 5-ALA was contraindicated in patients with an allergy to it [31]. Allergies to 5-ALA are rare, and anaphylaxis is incredibly rare. Supposedly, the first, and seemingly only, case of severe allergic reaction (anaphylaxis) to intravesical instillation of hexaminolevulinate hydrochloride in literature was reported by Colapaoli et al [49]. However, 5-ALA in this case was not used for HGG resection, but rather for fluorescence cystoscopy. Generally, neurosurgeons utilizing 5-ALA to guide HGG resections should be very conscientious of fluorescing functional, healthy tumor. It is important to note the need to respect the boundaries of the actual HGG tissue and proceed with proper caution.

Overall survival

The MD between the two approaches was compared in comparative cohort studies only. Pooling demonstrated that overall across seven studies, 5-ALA group had statistically significant longer OS than the WL by a MD of 3.4 months (95% CI, 0.81–5.97 months; I^2 = 81%, P-heterogeneity < 0.01) (Fig. 1). There was no obvious asymmetry concern on funnel plot generation (Fig. 2).

Discussion

Our analysis has demonstrated that 5-ALA is beneficial compared to white light alone. Additionally, our analysis has shown that gross total resection compared to incomplete resection correlates with a longer PFS and OS. These results are consistent with published findings in the literature showing that gross total, but not incomplete, resection of GBM prolongs survival in conjunction with radiochemotherapy[50]. Overall, there was an observed increase in the OS and PFS of the 5-ALA group compared to the white light group, as well as an observed increase in the OS and PFS of complete resection compared to incomplete resection. Of the studies that directly compared the use of 5-ALA to the lack thereof (13 of the total analyzed 45, or 28.9%), 5-ALA led to a better PFS and OS in 88.4% and 67.5% of patients, respectively (Table 2).

Table 2. (SUMMARY TABLES) PFS, OS, Neurological Deficit Benefit in Patients with 5-ALA vs. Control

Total # studies	% of the total 45 analyzed studies	Total patients
13	28.9	1984

PFS

Reference/Year	Number of HGG patients	PFS (months)	OS (months)	Post-op Neurological Deficit
Coburger et al., 2015	177 (33 in 5-ALA & iMRI, 144 in iMRI without 5-ALA)	No statistically significant difference	No statistically significant difference	No statistically significant difference
Della Pepa et al.,	230	5-ALA was better	5-ALA was better	Not specified
Diez Valle et al., 2014	251	5-ALA was better	Not specified	5-ALA was worse
Eljamel et al., 2008	27	Not specified	5-ALA was better	No statistically significant difference
Eyüpoglu et al., 2016	105	Not specified	5-ALA was better	5-ALA was better
Kim et al., 2014	80	5-ALA was better	5-ALA was better	Not specified
Ng et al., 2017	74	Not specified	5-ALA was better	Not specified
Picart et al., 2017	51	5-ALA was better	No statistically significant difference	No statistically significant difference
Roder et al., 2014	117	5-ALA was better	Not specified	No statistically significant difference
Slotty et al.,	253	Not specified	5-ALA was better	Not specified
Stepp et al., 2007	18 German clinic, unknown # exact patients	5-ALA was better	Not specified	Not specified
Stummer et al., 2006	270	5-ALA was better	5-ALA was better	Not specified
Stummer et al., 2011	349	5-ALA was better	No statistically significant difference	5-ALA was better

Category	# of patients	% of the total 45 analyzed studies
5-ALA was better	1348	88.4
No statistically significant difference	177	11.6
5-ALA was worse	0	0
Total	1525	100

OS

Category	# of patients	% of the total 45 analyzed studies
5-ALA was better	1090	67.5
No statistically significant difference	526	32.5
5-ALA was worse	0	0
Total	1616	100

Neurological Deficits

Category	# of patients	% of the total 45 analyzed studies
5-ALA was better	454	42.2
No statistically significant difference	372	34.5
5-ALA was worse	251	23.3
Total	1077	100

The results from analyzing the included literature support the utilization of intraoperative 5-ALA FGR in the removal of HGG tumor. 5-ALA use beneficially corresponds with a longer PFS and OS, which is what was found when pooling direct cohort studies only. This concept is consistent with the large body of literature demonstrating that increasing extent of resection correlates with longer overall survival[3, 51]. Illuminating cancerous tissue and its borders so that the surgeon can visualize what he/she must remove would sensibly lead to a more effective resection.

Combining intraoperative technological modalities with intraoperative 5-ALA utilization correlates with higher survival than does 5-ALA, iMRI, i-CT, ioUS, or CEUS each alone. This finding substantiates the need to further investigate the combination of fluorescent and technical modalities to potentially reach maximal survival rates and EOR. Such a combination may be the most optimized modality for HGG removal known to date.

There are some potential drawbacks to the use of intraoperative 5-ALA that should be considered. It appears that 5-ALA can help achieve a more complete resection, but with this comes a slight increase in post-op complication/neurological deficit. The reasoning behind this may be that the greater the amount resected, the higher the risk of excising healthy, functional tissue. There exists research positing that 5-ALA may enable extension of tumor resection beyond radiologically evident tumor. This extension may potentially put intact, functional adjacent tissue at risk of destruction. Therefore, 5-ALA may lead surgeons to resect too far beyond the HGG tumor's borders and damage healthy, eloquent brain matter. [52] This risk may explain the discrepancy in numbers of post-op neurological deficit reported. It is important to note that due to the increased vigilance and more conservative resection executed in these studies, we believe that the neurological complication rate due to the use of 5-ALA in HGG resection was far lower than it would have been if the neurosurgeons had not preventively acted with the responsible foresight with which they did. Multiple studies documented the halting of surgeries as to not aggressively resect tissue beyond the borders of the HGG.

The mixed findings regarding the effect of 5-ALA use on post-operative neurological deficit complicate interpretation of these studies. It is possible that differences in tumor location, surgeon skill, and patient medical comorbidities may confound neurologic deficit data. Thus, no clear conclusion regarding the risk of 5-ALA florescence guided surgery on neurologic deficit can be reached. We recommend that surgeons use vigilance when operating near eloquent brain areas, particularly when relying on 5-ALA fluorescence-guided surgery, to optimize patient safety. However, more data is needed to properly decipher whether or not 5-ALA-guided HGG resection causes a statistically significant increase in neurological deficits. The extent of deficit is partially reliant on the skill of surgeon and the eloquence of the areas in which the tumor sits. Neurological deficits when using 5-ALA can be minimized by using imaging techniques, such as intraoperative neurophysiological monitoring, ultrasound, MRI, and iCT.

Additionally, 5-ALA used intraoperatively has been rarely found to be below fluorescing threshold. 5-ALA succeeds in tissue uptake, but fails in properly and effectively fluorescing. This failure could inhibit the surgeon from seeing the borders of the tumor, eliminating the intended benefits of using intraoperative 5-ALA in the first place. Thus, intimate knowledge of neuroanatomy, and frequent anatomic re-orientation must be utilized in conjunction with 5-ALA, to avoid new neurologic deficits by injuring eloquent brain or white matter tracts.

Limitations

Limitations of our study exist. The included studies are associated with different sample sizes and methods of analyses. Due to the overall small sample sizes because of the novelty of 5-ALA intraoperative usage in HGG resection, especially in the United States, the ability to draw similarities between cases is somewhat limited. Additionally, the seemingly low risk of bias of the included studies compounds the risk of bias in our systematic review. Finally, the studies tend to be performed by high volume cranial surgeons at expert centers. Generalizability of these results to surgeons who perform few cranial surgeries each year must be exercised with caution.

Conclusion

Despite potential drawbacks, overall, utilization of 5-aminolevulinic acid (5-ALA) results in a more complete resection (higher EOR and complete resection rate) of HGG tissue. This capability ultimately leads to better outcomes and longer survival rates for patients who undergo 5-ALA FGR. An implication of this finding is that 5-ALA FGR may be a better alternative to conventional surgical resection of HGG. Combining 5-ALA with an additional technical modality, such as iMRI, i-CT, ioUS, or CEUS may be even more beneficial than 5-ALA alone. This possibility warrants further research.

The results regarding postoperative neurologic deficits of surgeries using 5-ALA compared to those using white light do not coincide enough with one another to arrive at a clear conclusion. The reasoning behind this may be that the greater the amount resected, the higher the risk of excising healthy, functional tissue. The extent of deficit appears to be partially reliant on the skill of surgeon and the eloquence of the areas in which the tumor sits. When using 5-ALA, neurological deficits can be minimized by using imaging techniques, such as intraoperative neurophysiological monitoring, ultrasound, MRI, and iCT.

Review of the literature illuminates potential avenues of use of 5-ALA FGR and combined modalities that most benefit patients with HGG. Further studies and more data on the subject should bring the most beneficial approach to light.

Abbreviations

HGG
high grade glioma; 5-ALA = δ-Aminolevulinic acid; OS = overall survival; PFS = progression-free survival; FDA = Food and Drug Administration; GBM = glioblastoma multiforme; EMA = European Medicine's Agency; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; WHO = World Health Organization; MD = mean difference; CI = confidence interval; iMRI = intraoperative magnetic resonance imaging; CEUS = contrast-enhanced ultrasound; ioUS = intraoperative ultrasound; iCT = intraoperative computed tomography scan; EOR = extent of resection; GTR = gross total resection

Declarations

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Ethics Approval: Ethics approval was not applicable for this study as only publicly accessible data was utilized.

Consent to Participate: Not applicable.

Abbreviations

HGG= high grade glioma; 5-ALA= δ-Aminolevulinic acid; OS= overall survival; PFS= progression-free survival; FDA= Food and Drug Administration; GBM= glioblastoma multiforme; EMA= European Medicine's Agency; PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses; WHO= World Health Organization; MD= mean difference; CI= confidence interval; iMRI= intraoperative magnetic resonance imaging; CEUS= contrast-enhanced ultrasound; ioUS= intraoperative ultrasound; iCT= intraoperative computed tomography scan; EOR= extent of resection; GTR= gross total resection

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Tables

Due to technical limitations, Table 1 is only available as a download in the Supplemental Files section.

Supplementary Files

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