

Comparison of fluorescein sodium, 5-ALA, and intraoperative MRI for resection of high-grade gliomas: A systematic review and network meta-analysis

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Highlights

- Fluorescein-sodium is comparable to 5-ALA and intraoperative MRI in terms of achieving gross-total resection of high-grade gliomas.
- The use of intraoperative Fluorescein Sodium (vs. control) was associated with improved OS, and comparable rates of PFS as 5-ALA.
- Fluorescein-sodium is an acceptable intraoperative agent that can be used effectively to guide surgical resection of high-grade gliomas.

Abstract

High grade gliomas (HGGs) are aggressive brain tumors associated with poor prognosis despite advances in surgical treatment and therapy. Navigated tumor resection has yielded improved outcomes for patients. We compare 5-ALA, fluorescein sodium (FS), and intraoperative MRI (IMRI) with no image guidance to determine the best intraoperative navigation method to maximize rates of gross total resection (GTR) and outcomes. A frequentist network meta-analysis was performed following standard PRISMA guidelines (PROSPERO registration CRD42021268659). Surface-under-the-cumulative ranking (SUCRA) analysis was executed to hierarchically rank modalities by the outcomes of interest. Heterogeneity was measured by the I² statistic. Publication bias was assessed by funnel plots and the use of Egger's test. Statistical significance was determined by p<0.05. Twenty-three studies were included for analysis with a total of 2,643 patients. Network meta-analysis comparing 5-ALA, IMRI, and FS was performed. The primary outcome assessed was the rate of GTR. Analysis revealed the superiority of all intraoperative navigation to control (no navigation). SUCRA analysis revealed the superiority of IMRI+5-ALA, IMRI alone, followed by FS, and 5-ALA. Overall survival (OS) and progression free survival (PFS) were also examined. FS (vs. control) was associated with improved OS, while IMRI was associated with improved PFS (vs. control, FS, and 5-ALA). Intraoperative navigation using IMRI, FS, and 5-ALA lead to greater rates of GTR in HGGs. FS and 5-ALA also yielded improvement in OS and PFS. Further studies are needed to evaluate differences in survival benefit, operative duration, and cost.

Keywords

5-Aminolevulinic acid; Fluorescein-sodium; Glioma; Gross total resection; Intraoperative MRI; Intraoperative navigation

< Previous article in this issueNext article in this issue >

Introduction

Gliomas are primary tumors of the central nervous system that arise from glial cells. Gliomas that have aggressive growth and invasion of brain tissue with signs of malignancy are classified as World Health Organization Grade 3 or 4, also known as high grade gliomas (HGGs) [1]. As of 2016, the WHO classification of HGGs relies on both histopathology and molecular analysis [2]. Significant molecular markers include O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, isocitrate dehydrogenase (IDH) mutation status, and 1p/19q codeletion status, which provide not only diagnostic but also prognostic information [2], [3]. Despite this new molecular classification, in general, HGGs are associated with poor prognosis, despite recent advances in surgical treatment and therapy. Currently, one of the most consistent prognostic metrics of intervention is the extent of tumor resection. Gross total resection (GTR) significantly improves survival compared to biopsy only, increasing median survival by four months [4]. Several modalities are under investigation in their ability to maximize tumor resection intraoperatively, including the use of intraoperative fluorescent agents, 5-aminolevulinic acid (5-ALA) or fluorescein sodium (FS), and the use of intraoperative MRI (IMRI).

5-ALA (Gliolan®) is presently the only intraoperative fluorescent agent approved by the U.S. Food and Drug Administration (FDA) for use in the resection of HGGs. 5-ALA is converted to protoporphyrin IX (PpIX), which selectively fluoresces HGG cells, as its metabolites are preferentially taken up by the malignant cell [5]. Using 5-ALA requires a surgical microscope connected to a xenon light source that can emit 370–440nm wavelength light to excite PpIX and the use of a filter to visualize the red tumor fluorescence with emission peaks at 635–704nm [6]. 5-ALA costs an average of \$1,124 per application, is orally ingested up to four hours prior to the surgery, and carries the risk of skin photosensitivity post-operatively [5]. A recent meta-analysis has shown that FS increases GTR rates in HGGs by 26.3% compared to control [9].

FS is another historically and frequently used intraoperative fluorescent agent that is FDA-approved for ophthalmologic procedures but is used off-label for resection of HGGs [10], [11]. FS is not selective for malignant cells but accumulates at disruptions of the blood brain barrier, such as at HGG tissue. Visualization typically requires a YELLOW 560nm surgical microscope filter, but at high doses of FS (20mg/kg), it can be visualized with the naked eye [5]. FS costs approximately \$30 per application and is administered intravenously at the onset of anesthesia. Unlike 5-ALA, FS does not increase the risk of skin photosensitivity post-operatively [5]. A recent meta-analysis has shown that FS increases GTR rates in HGGs by 29.5% when compared to white-light control groups [12].

IMRI-guided neurosurgery, first introduced in 1994, has been extensively studied [13]. Use of IMRI improves the extent of tumor resection and minimizes postoperative functional impairment compared to classic stereotactic navigation in patients with HGG [14]. However, IMRI-guided surgical resection is priced at \$13,447 additional to the cost of surgery, and requires hospitals to have MRI-compatible monitoring devices and anesthesia equipment, which increases the complexity and duration of the operation [14], [15]. While IMRI-based neuronavigation has proven to be effective at achieving GTR, the availability of the technology, cost to the patient, and impact on surgical scheduling must be considered.

Meta-analyses have shown superiority of 5-ALA independently, superiority of FS independently, and the benefit of 5-ALA compared to IMRI, but there is no analytical three-way comparison of these modalities [9], [12], [14]. In this meta-analysis, we sought to present a comparative analysis of IMRI, FS, and 5-ALA with respect to GTR rates and patient survival.

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Methods

The systematic review and meta-analysis were performed in accordance with PRISMA 2020 Guidelines [16]. The protocol for this systematic review was registered with PROSPERO prior to initiating the systematic review process (CRD42021268659). ...

Results

From a total of 509 articles found in our search, 23 articles with 2,643 patients were selected for inclusion into the NMA. Fig. 1 shows an evidence flow diagram adherent to PRISMA Guidelines. Studies consisted of cohort and RCTs and were of medium to high quality on the NOS. Table 1 demonstrates the definition of GTR, in addition to other features of the included studies. Because in-study and out-of-study heterogeneity for GTR, OS, and PFS was found to be statistically significant (p<0.001). ...

Discussion

Intraoperative guidance for the resection of HGGs has previously been shown to improve the degree of resection and patient outcomes [12], [14]. While the use of IMRI, FS, and 5-ALA has expanded, the modality of choice for intraoperative guidance continues to depend on surgeon preference, experience, as well as the cost and institutional availability of IMRI. A recent meta-analysis by Golub et al. compared the rates of GTR and patient outcomes in surgeries using 5-ALA versus IMRI [14]. While ...

Conclusion

Our NMA compared three methods used in the resection of HGGs, 5-ALA, FS, and IMRI, to conventional resections without intraoperative guidance. Our study found IMRI to be the most efficacious in achieving GTR, followed by FS, then 5-ALA. Though the difference in GTR rates between these three were not statistically significant, all three led to significantly increased GTR rates when compared to resections without intraoperative guidance. ...

Statements and declarations

Compliance with ethical standards

There are no conflicts of interest to disclose for any authors. This study is a meta-analysis, and is exempt from approval from the local institutional review board process. This study did not involve patient data, thus informed consent was not required. ...

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Author contributions

Authors AN, ES, AB, MN, SC, WH, PA contributed to conception and design. Material preparation, data collection and analysis were performed by authors AN, ES, AB, MN. The first draft of the manuscript was written by all authors. Critical revisions were provided by SC, DN, DK, PA, DN. All authors read and approved the final manuscript. ...

Data availability

No novel data set was generated during this manuscript. All data utilized for analysis were secondarily obtained from published sources, included in the manuscript (Table 1). For all additional reasonable analysis-related queries, the corresponding author can be contacted.

Ethics approval

Our study is a meta-analysis; thus no ethical approvals were required.

Consent to participate

This is not applicable, as our study is a meta-analysis.

Consent to publish

This is not applicable, as our study is a meta ...

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. ...

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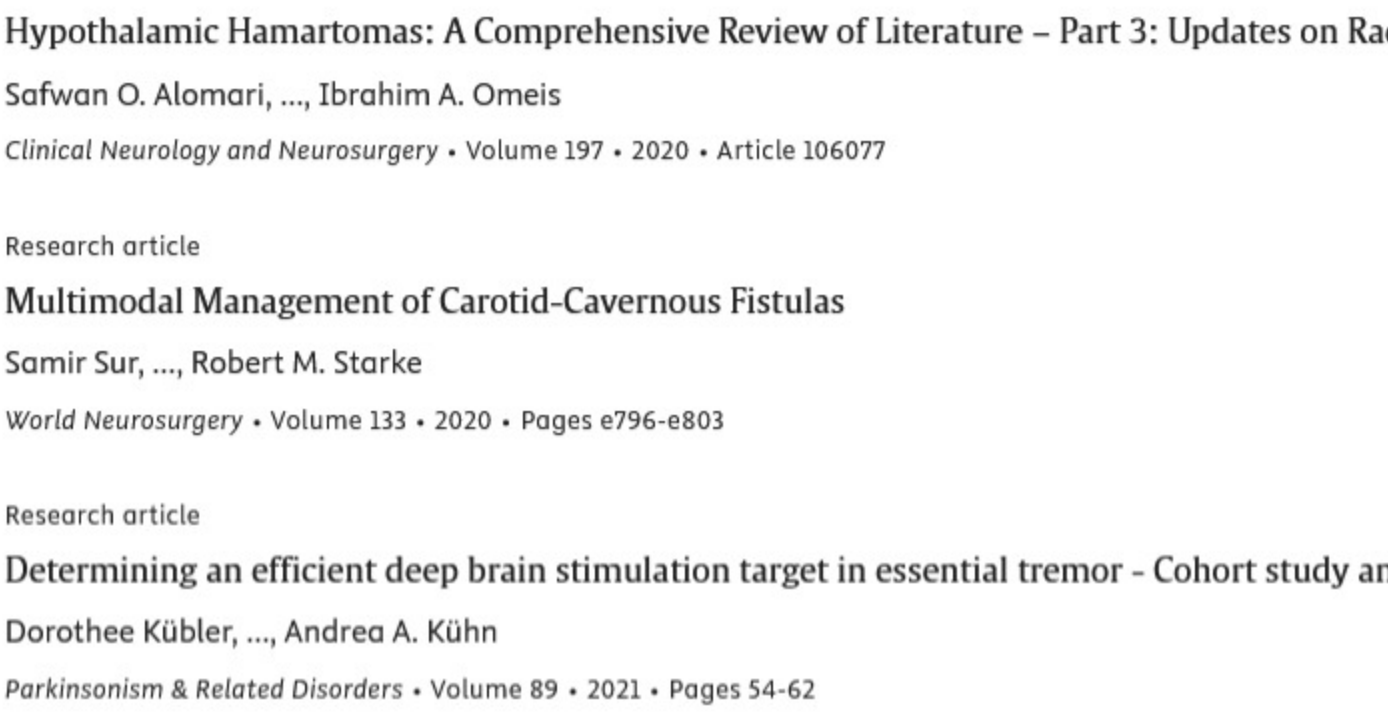
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...The same applies to various tumors of different etiologies that manifest in the human central nervous system by disturbing the intrinsic blood brain barrier (BBB) (Mazurek et al., 2020; Cavallo et al., 2018; Schebesch et al., 2016; Ahrens et al., 2022). Some authors have even concluded that the still off-label FL dye is non-inferior to the established and approved fluorescence marker 5-aminolevulinic acid (5-ALA) with regard to the extent of resection (EOR), progression-free survival (PFS), and overall survival (OS), although these conclusions are based on different levels of evidence (Zeppa et al., 2022; Naik et al., 2022). In a retrospective monocentric analysis, Hansen et al. found that patients with HGG had significantly increased PFS after FL-guided resection than after 5-ALA-guided resection (Hansen et al., 2019)...

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