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Review

Illuminate Resection Pathways with Fluorescence Guidance in Glioma Surgery: Case Reports and Systematic Review

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Abstract

Gliomas are the most common brain tumor in adults, with a poor prognosis despite intensive treatments. Complete surgical resection is difficult due to its infiltrative growth, but aggressive surgery improves outcomes. Fluorescence-guided surgery (FGS) is used to distinguish tumor tissue during surgery. 5-Aminolevulinic Acid (5-ALA) is a crucial fluorescent agent in FGS, transforming into a molecule that accumulates in tumor cells. We presented a 34-year-old female with a high-grade glioma in the left parietal lobe who underwent fluorescence-guided tumor resection using 5-ALA was reported. In addition, a review of the literature on fluorescence in glioma surgery, searching databases like PubMed and SCOPUS from 2021 to 2023, was performed. Fifteen papers were included in our review. This technique ensured gross-total tumor resection while preserving neurological function. FGS improves tumor identification, surgical outcomes, and survival.

Keywords

Glioma; fluorescence-guided surgery; 5-aminolevulinic acid; 5-ALA; gross-total resection

1. Introduction

Glioma is the most prevalent primary brain tumor in adults. High-grade gliomas have a dismal prognosis despite the current intensive treatment strategies [1, 2] and usually recur as they grow in an infiltrative manner that makes complete surgical resection difficult [3, 4]. Furthermore, adjuvant therapy, i.e., radiation therapy and chemotherapy, have limited effect. Gross-total tumor resection has been associated with a better prognosis for malignant gliomas [5-8]. In addition, senior and frail individuals are excluded from surgical consideration in some cancer centers [9]. To maximize the safe resection of tumors, fluorescence-guided surgery (FGS) has become a widely employed technique to identify the presence of tumor tissue intraoperatively [10-12]. FGS represents a pivotal turning point in the field of neurosurgery. The utility of fluorescent agents, particularly 5-aminolevulinic acid (5-ALA), has been established as a standard for enhancing the visual discrimination between tumors and healthy brain tissue during surgery [13, 14]. Fluorescein is another fluorophore that gained attention after introducing a dedicated filter for its visualization [14]. This fluorophore is, however, non-specific and can extravasate into the peritumoral edema [15].

5-ALA, which is most intensively studied in FGS for malignant brain tumors [14, 15], is one of the amino acids and a natural precursor in heme biosynthesis and, hence, is notably safe [16]. When 5-ALA is administered orally, it gets metabolized into the fluorescent molecule Protoporphyrin IX (PpIX) that accumulates specifically in tumor cells by various mechanisms, including a lack of enzymes that convert PpIX to heme and decreased activity of transporters [17-20]. In addition, 5-ALA is known to cross the blood-brain barrier (BBB) [21]. 5-ALA-induced fluorescence in brain tumors correlates with the malignancy of the tumor cells [22] and has >85% sensitivity and specificity [23]. Consequently, FGS with 5-ALA has been approved in many countries, enhancing the gross-total GBM tumor resection [24]. Studies have demonstrated that FGS can increase the extent of resection, an essential factor that improves survival and quality of life in glioma patients [14-16, 24, 25]. However,

the nuances of fluorescence application, interpretation, and potential complications remain areas of ongoing research and discussion.

In this article, we discuss a case of high-grade glioma where FGS was employed, highlighting its pivotal role in achieving gross-total safe resection. This case provides a practical, nuanced perspective on the theory and application of fluorescent agents. It offers insights into decision-making, potential challenges, and the overall impact on surgical outcomes. Complementing the case report, the article ventures into a comprehensive literature review, collating scientific research on fluorescence guidance in glioma surgery. This literature review will explore fluorescence-guided glioma surgery's advantages, limitations, and future. By offering a practical case study and synthesizing extensive research, this paper presents an encompassing perspective on fluorescence-guided glioma surgery, thereby advancing the understanding of this promising technique.

2. Case Report

2.1 Patient Presentation

A 34-year-old female presented to our neurosurgery department with a seven-month history of progressively worsening headaches. The patient described episodes of blurred vision and occasional "floating spots" in the visual field. The patient complained of intermittent numbness and tingling in the right side of the body. Her symptoms had gradually increased in severity, with a noticeable impact on her quality of life, compelling her to seek medical intervention. Written informed consent was obtained from the patient to publish this paper.

2.2 Medical History and Preliminary Evaluation

The patient's medical history was noncontributory, with no significant prior illnesses or familial history of malignancies. A comprehensive neurological examination was conducted. The patient exhibited right hemiparesis with a strength grade of 4/5. There was intermittent difficulty in speech, characterized by occasional word-finding difficulties. Cranial nerve examination was largely intact, except for a mild papilledema noted on fundoscopic examination. Sensory examination revealed decreased sensation to light touch and pinprick on the right side of the body. Deep tendon reflexes were brisk on the right side compared to the left. Coordination tests, including finger-to-nose and heel-to-shin, were standard. Gait assessment showed a mild dragging of the right foot.

2.3 Neuroimaging Findings

Magnetic Resonance Imaging (MRI) of the brain was performed, which revealed a large, non-homogenous mass in the left parietal lobe suggestive of high-grade glioma (Figure 1). The tumor was predominantly located in the postcentral gyrus, extending into the precentral gyrus, explaining the patient's clinical manifestation of motor and speech difficulties.

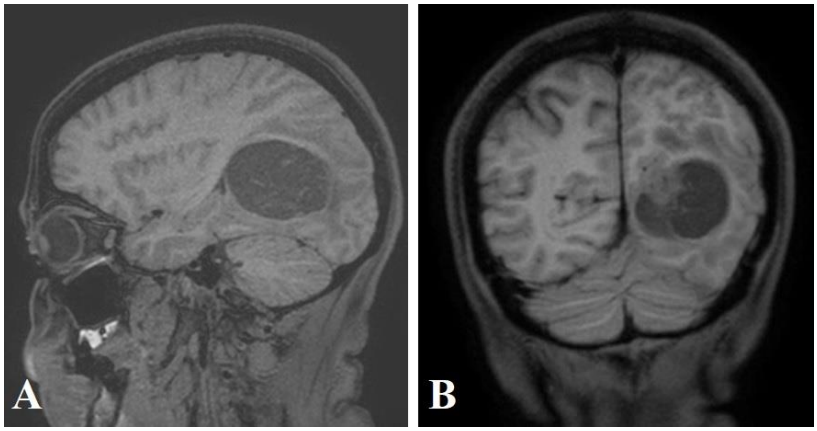

Figure 1 Sagittal (A) and coronal (B) T1-weighted MRI images show a hypointense area in the left parieto-occipital lobe that appears as a hypointense lesion compared to the surrounding normal brain tissue.

2.4 Surgical Planning and Intraoperative Findings

Given the diagnosis, the patient was scheduled for a fluorescence-guided tumor resection. After extensive discussion with the patient and family, informed consent for surgical intervention was obtained. Using the 5-ALA agent, a clear distinction between the tumor and healthy brain tissue was visualized, as the tumor tissue emitted a bright red/pink fluorescence under blue light excitation. During the surgery, the fluorescence-guided technique proved invaluable in delineating the tumor margins and guiding the extent of resection (Figure 2). Additionally, fluorescence imaging facilitated the identification of smaller tumor strands infiltrating the surrounding brain tissue, which would otherwise be challenging to depict. Despite the tumor's infiltration into eloquent brain areas, gross-total tumor resection was achieved, maintaining the patient's neurological function to the highest possible extent.

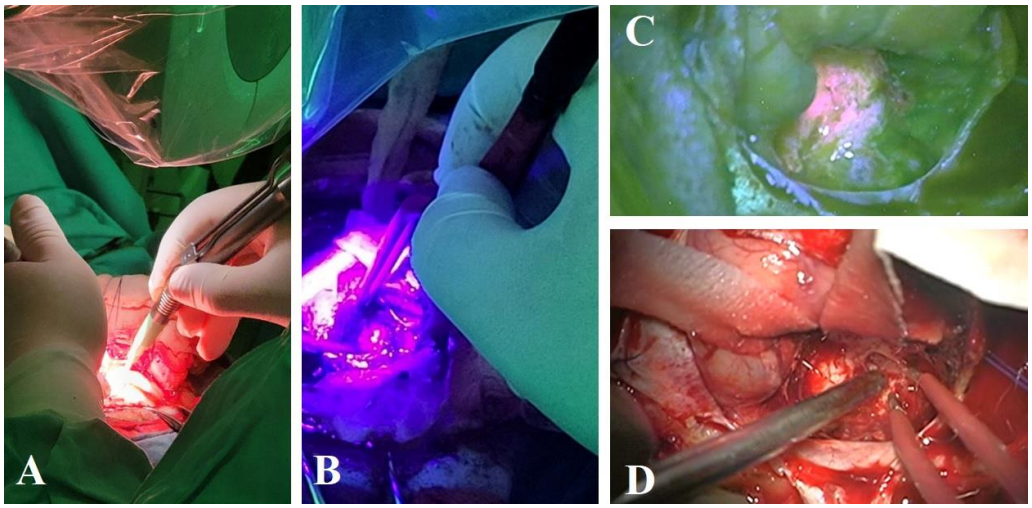

Figure 2 (A-B) showcases the striking purple fluorescence from 5-ALA. (C) Striking purple fluorescence from 5-ALA delineates the tumor boundaries against the pink hue of the surrounding healthy brain tissue, aiding in meticulous glioma resection. (D) It shows the brain tissue with a consistent color without 5-ALA, making it difficult to differentiate the glioma from the surrounding healthy tissue.

2.5 Histopathology and Postoperative Course

Postoperative CT scans show no sign of postoperative bleeding or other acute complications (Figure 3). Histopathological examination confirmed the clinical diagnosis of glioblastoma (WHO grade 4). She was subsequently enrolled in a comprehensive oncology program for further treatment, which included radiotherapy and chemotherapy. This case underscores the pivotal role of FGS in achieving maximal safe resection of gliomas and highlights the potential for improved outcomes when this innovative approach is adopted. In the following sections, we delve into an exhaustive review of the literature on this topic, aiming to validate further and understand the benefits and limitations of fluorescence in glioma surgery.

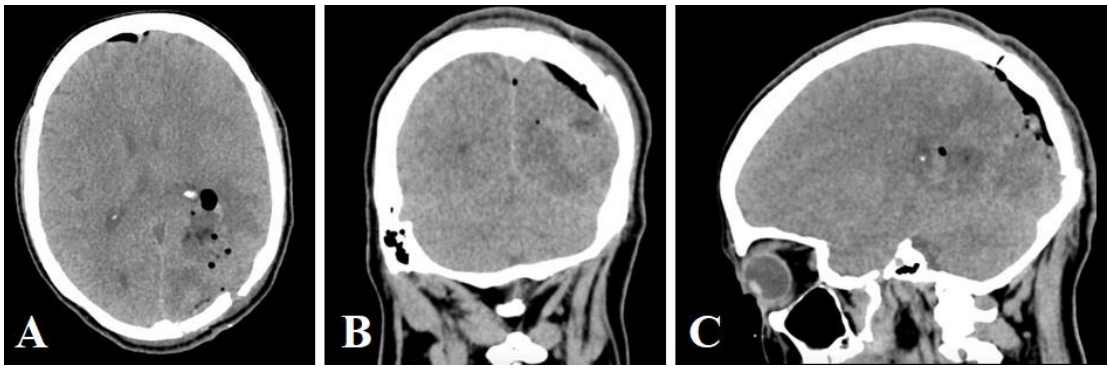

Figure 3 Postoperative axial (A), coronal (B), and sagittal (C) brain CT scan shows no sign of postoperative bleeding or any other acute complications.

3. Literature Review

3.1 Search Strategy

This literature review aimed to synthesize the current knowledge on fluorescence in glioma surgery. We comprehensively searched several databases, including PubMed and SCOPUS, from 2021 to November 2023. We used a combination of keywords and Medical Subject Heading (MeSH) terms related to 'glioma', 'fluorescence-guided surgery', '5-aminolevulinic acid (5-ALA)', 'extent of resection', 'survival', 'quality of life' and 'complications'. Our search strategy was tailored to each database to ensure the capture of all relevant studies.

3.2 Study Selection

The studies selected for review reported fluorescence-guidance use in glioma surgery, regardless of the tumor grade or the type of fluorescent agent used. We included prospective and retrospective studies, clinical trials, meta-analyses, and systematic reviews. We excluded studies not written in English, case reports, letters to the editor, and commentaries. The titles and abstracts of the identified articles were screened for relevance, after which the full text of potential articles was reviewed.

3.3 Data Extraction

Two independent reviewers (E.G. and R.N.) extracted data from the selected studies using a predefined template, whereas a third author (N.M.) solved any conflicts. Extracted data included author(s), year of publication, study design, sample size, type of fluorescent agent used, tumor grade, extent of resection, survival rates, quality of life measures, and complications.

3.4 Quality Assessment and Data Synthesis

The quality of the included studies was assessed using appropriate tools based on the study design. The Cochrane Risk of Bias Tool was used for randomized controlled trials, whereas the Newcastle-Ottawa Scale was utilized for observational studies. We used a narrative synthesis approach to analyze and present the findings due to the anticipated heterogeneity in the included studies. The results are organized by the Study, Year, Study Design, type of fluorescent agent, tumor grade, Sample Size, and Major Findings. This rigorous method ensured that our review was comprehensive, transparent, and reproducible, thereby accurately reflecting the current knowledge on FGS in gliomas.

3.5 Extent of Resection and Survival Benefits

869 previously published studies were screened, 382 duplicated studies were excluded, and 487 records screened were further evaluated. Fifteen papers [16, 20, 26-38] met the inclusion criteria and were included in our systematic review (Table 1). 3. All tumors reported are primary tumors. Our literature search concluded in November 2023. Several studies using 5-ALA have highlighted the increased extent of resection in high-grade [16, 28, 29, 32, 33, 36] and low-grade gliomas [27, 36]. Rynda et al. [29] demonstrated an increase in the median overall survival of 6.2 months in patients undergoing 5-ALA-guided resection, while Sun et al. [33] observed longer 6-month progression-free survival for patients undergoing 5-ALA resection. These findings demonstrate that maximizing resection, in this case with fluorescence-guided resection, translates into meaningful survival benefits.

Table 1 Study included in our systematic review.

Study, Year	Study Design	Sample Size	Type of Fluorescent Agent	Tumor Grade	Major Findings
Watts et al. [16], 2023	Prospective multicenter study	106	5-ALA	High-grade (3, 4)	5-ALA has clinical utility as an intraoperative surgical biomarker of high-grade gliomas
Noble et al. [26], 2023	Prospective study	12	Fluorescence lifetime imaging	High-grade (3, 4)	Film as an intraoperative tool for surgical guidance
Maeda et al. [27], 2023	No randomized controlled	14	5-ALA	High-grade (3, 4)	The resection helped determine the extent of the excision
Shimizu et al. [28], 2022	Randomized controlled Trial	32	5-ALA	High-grade (3, 4)	The most substantial fluorescence group exhibited the highest mean values of MET-PET uptake and Ki-67 index
Rynda et al. [29], 2022	Multicenter prospective randomized clinical trials	50	5-ALA	High-grade (3, 4)	Glioma resection showed an increased median overall survival of 6.2 months
Cao et al. [20], 2022	No randomized a controlled study was conducted	10	NIR-IIa/IIb imaging	High-grade (3, 4)	Multispectral images showed the arteries feeding the tumor
Shi et al. [30], 2022	Randomized control clinical trial	40	NIR-II FGS	High-grade (3, 4)	It has high sensitivity, and the resection rate improves without damaging neurological functions
Müther et al. [31], 2022	No randomized controlled	11	5-ALA	High-grade (3, 4)	Intraoperative fluorescence can serve as a prognostic marker
Zeppa et al. [32], 2022	Retrospective analysis	99	5-ALA	High-grade (4)	5-Ala and SF are equally helpful in achieving a total resection
Sun et al. [33], 2021	Randomized controlled trial	10	5-ALA	High-grade (3, 4)	Longer 6-month progression-free survival for patients undergoing 5-ALA resection

Chen et al. [34], 2021	Retrospective analysis	10	Claudin-5	High-grade (3, 4)	Claudin-5 may be related to the development of yellow fluorescence
Maragkos et al. [35], 2021	Randomized controlled trial	16	5-ALA	High-grade (3, 4)	5-ALA-guided resection of HGG can be safely performed more than 4 h after administration
Stummer et al. [36], 2021	Retrospective analysis	59	5-ALA	Low-grade (1, 2)	More extensive resection and there is strong evidence that complete resection of LGG is crucial to improve OS
Müther et al. [37], 2020	Prospective sampling study	198	5-ALA	High-grade (3, 4)	6 studies of patients treated with FGR using 5-ALA were included
Livermore et al. [38], 2020	Retrospective analysis	62	5-ALA	High-grade (2, 3)	The performance of Raman spectroscopy was significantly better than the predictive value of 5-ALA-induced fluorescence

3.6 Alternative Approaches and Novel Agents

While 5-ALA is the most commonly studied agent, research has also been conducted on Fluorescence lifetime imaging [16], NIR-II FGS [30], and Claudin-5 [34]. Livermore et al. [38] reported that Raman spectroscopy performed significantly better than 5-ALA-induced fluorescence. These findings highlight the potential for innovative approaches and novel agents to further optimize the utilization of fluorescence in glioma surgery. The study by Shi et al. [30] emphasized high sensitivity and improved resection rates without damaging neurological functions, highlighting the safety and efficiency of NIR-III FGS.

3.7 Prognostic Value and Timing

Studies such as those by Shimizu et al. [28] and Müther et al. [37] suggest that fluorescence could serve as a prognostic marker relating to MET- and 18F-FET-PET uptake and Ki-67 index or even as a broader prognostic indicator. Maragkos et al. [35] demonstrated flexibility in timing, showing that 5-ALA-guided resection can be safely performed more than 4 hours after administration. Zeppa et al. [32] noted that 5-ALA and SF were equally valuable in achieving total resection, which may offer surgeons more options in terms of fluorescent agents.

4. Discussion

The present article provides an in-depth examination of the use of FGS in treating glioma, accompanied by a real-world case highlighting its practical application. Through a comprehensive literature review, we have synthesized the current body of knowledge in this rapidly evolving field. As widely described, 5-ALA is a non-fluorescent prodrug, first absorbed by tumoral cells and then converted into a fluorescent protoporphyrin IX (PpIX). As a photosensitizer, PpIX is excited when placed under violet-blue light (370-440 nm) emitted by a specific filter added to the surgical microscope; tumor cells return red light in visible spectrum frequencies accordingly. To proceed with proper 5-ALA assessment, a second ultraviolet filter is added to the optical microscope lens [39]. Intraoperative visualization under a blue filter is generally dark, while a "lava red" appearance characterizes the tumor. Simultaneous visualization of fluorescence and anatomy is more accessible at the most superficial resection stages. In the deepest stages, where illumination is poor and the surgical cavity's edges further reduce illumination, anatomy is hardly distinguishable: vessels, brain parenchyma, nerves, and even dura can be transient [40, 41]. The increased extent of resection made possible by fluorescence-guided techniques, especially using 5-ALA, has been validated across multiple studies, reinforcing its critical role in maximizing tumor resection without compromising healthy brain tissue [42]. This translates into tangible survival and quality of life benefits, as seen in our patients and supported by the literature [16, 30, 32, 37, 43-45]. 5-ALA-guided resection can involve two phases continuously alternating during surgery: a blue filter should be used for identification since it has a low resolution. In contrast, white light should be used for proper resection. The microscope setting is paramount: under a blue filter, maximal resolution occurs when the focal distance is adequate (generally below 350 mm) and at lower magnification (below 4× or more), as higher zoom results in suboptimal light conditions. The continuous switching between blue and white light to visualize fluoresce and anatomy could be summed up as: "check under blue and resect under white." Such a paradigm is true, especially when approaching subarachnoid spaces

or the skull base, where the risk of damage to vascular or nervous structures is more relevant [46]. Nevertheless, resection under blue light can still be performed for most surgery, where these risks are negligible. Golub and colleagues [47] reported that intraoperative MRI and 5-ALA were superior to conventional navigation in achieving gross total resection in their meta-analysis, including 11 studies. In contrast, no significant difference in gross total resection was found between the two intraoperative MRI and 5-ALA [48, 49].

Second-generation devices, such as exoscopes and head-mounted displays for augmented reality, are improving 5-ALA-induced fluorescence visualization [50-52]. Fluorescence is captured under a blue filter, transferred via digital video chip technology, and processed and projected via an optimized data transfer link on high-resolution monitors [41]. While 5-ALA remains the gold standard, emerging research on alternative agents and approaches, such as Raman spectroscopy histology devices and near-infrared spectroscopy (NIR) imaging, opens exciting avenues for innovation. Although malignant glioma surgery guided by 5-ALA fluorescence entails a moderate increase in hospital costs compared to current surgical practice and can be considered a cost-effective innovation [53], these techniques' sensitivity and safety profiles are encouraging, but further research and clinical validation are needed to translate them into mainstream clinical practice [39].

4.1 Experience with FGS

In our case, a patient with a high-grade glioma in the left parietal lobe underwent FGS, where critical motor and speech functions are situated. Using 5-ALA facilitated the gross-total resection of the tumor with minimal compromise to the patient's neurological status. This approach substantially improved the patient's quality of life and long-term functional outcomes [34].

4.2 Strengths and Limitations

While the results are promising, several challenges and limitations must be acknowledged. Factors such as the type of glioma, its location, and the surgeon's experience with fluorescence-guided techniques may impact the outcomes. Furthermore, the availability of advanced fluorescence-guided technology in various healthcare settings might limit its widespread use. Moreover, this study covers a short period (2021 to 2023) and, therefore, cannot represent the entire literature on the topic. More randomized controlled trials and standardized protocols are needed to grasp this technique's potential and limitations fully [54]. Our patient outcome may resonate with other practitioners and researchers as an example of FGS's real-world applicability and effectiveness. Such experiences further the understanding of innovative surgical techniques, paving the way for enhanced patient care in neuro-oncology.

4.3 Future Directions

The future of fluorescence-guided glioma surgery seems bright, with ongoing research focusing on optimizing the visualization technique with new optimized filter systems being built, integrating hyper- and multispectral imaging, and exploring new fluorescent agents [55]. The evolving understanding of tumor biology may lead to the development of specific markers that could be targeted with fluorescence, further personalizing the surgical approach to individual patients.

5. Conclusions

This case highlights the transformative impact of FGS in neurosurgery. The success of the 34-year-old patient reinforces the benefits of FGS in treating gliomas. FGS offers precise tumor margin identification, improving surgical outcomes and patient survival rates. While FGS presents significant advancements, especially with emerging fluorescent agents and imaging techniques, challenges like study inconsistencies and small sample sizes persist. Standardized protocols and more extensive trials are needed. Combining FGS with other technologies and molecular profiling could lead to tailored surgical approaches, balancing precision with patient safety and long-term results.

Author Contributions

Conceptualization: M.D.J.E.R., J.L., E.S.M. and N.M.; methodology: M.D.J.E.R. and N.M.; formal analysis: N.K., S.K., K.I.Y. and N.M.; investigation: M.D.J.E.R., G.C., G.V.C. and N.M.; data curation: M.D.J.E.R., R.N., A.R.R. and N.M.; writing—original draft preparation: M.D.J.E.R. and N.M.; writing—review and editing: N.M.

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Competing Interests

The authors have declared that no competing interests exist.

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