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THE USE OF 5-ALA IN GLIOMA SURGERY: MECHANISM OF ACTION, CLINICAL BENEFITS, AND TECHNICAL LIMITATIONS: A NARRATIVE REVIEW

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ABSTRACT

Aims: Glioblastoma is the most aggressive primary brain tumor, characterized by rapid proliferation and diffuse infiltration into surrounding brain tissue. Maximal safe resection is a critical prognostic factor, yet complete tumor removal remains difficult. This review aims to synthesize current data on the application of 5-aminolevulinic acid (5-ALA) in glioma surgery, with particular emphasis on its mechanism of action, clinical utility, limitations, and integration with other intraoperative imaging techniques.

Methods: A narrative review was conducted using the PubMed and Google Scholar databases. The search included combinations of keywords such as *"5-ALA," "5-aminolevulinic acid," "glioblastoma," "high-grade glioma,"* and *"neurosurgery."* Peer-reviewed English-language articles were selected to examine the clinical and technical aspects of 5-ALA-guided fluorescence imaging in glioma resection. No time restriction or formal inclusion criteria were applied.

Results: 5-ALA induces selective fluorescence in malignant glioma tissue, enabling improved intraoperative visualization and facilitating gross total resection. Studies have demonstrated enhanced surgical outcomes, including prolonged progression-free and overall survival in patients undergoing 5-ALA-guided resection. However, limitations include reduced sensitivity in low-grade gliomas, the risk of false-positive or false-negative signals, and dependency on specialized equipment and optical conditions. Adjunctive use with intraoperative MRI and sodium fluorescein has shown preliminary benefits. Off-label applications in non-glioma tumors are under investigation.

Conclusions: 5-ALA represents a clinically validated tool for improving tumor delineation and surgical precision in high-grade glioma surgery. Despite certain limitations, especially in low-fluorescence tumors and deep-seated lesions, future research into combined imaging strategies, enhanced metabolic targeting,

and photodynamic applications may broaden its clinical utility.

Keywords: 5-aminolevulinic acid (5-ALA), glioblastoma, fluorescence-guided surgery, neuronavigation, high-grade glioma

LIST OF ABBREVIATIONS:

- 5-ALA - 5-aminolevulinic acid
- FDA - Food and Drug Administration
- HGG - high-grade gliomas
- iMRI- intraoperative magnetic resonance imaging
- LGG - low-grade gliomas
- MGMT – O6-methylguanine-DNA methyltransferase
- PpIX - protoporphyrin IX
- SF - sodium fluorescein

INTRODUCTION

Gliomas account for 30% of primary brain tumors and 80% of all malignant brain tumors [1]. The World Health Organization (WHO) classifies gliomas into four grades based on malignancy, which helps guide the selection of an appropriate therapeutic approach. Glioblastoma is classified as grade IV (G4) [2]. It is the most common and most aggressive primary brain tumor in adults [3]. Histopathological features indicating its malignancy include necrosis and endothelial proliferation. Treating patients remains a significant challenge due to the tumor's infiltrative nature, rapid growth rate, and heterogeneity. Standard glioblastoma treatment includes microsurgical resection followed by adjuvant radiotherapy and chemotherapy [4,5].

In neuro-oncology, it is widely accepted that, compared to subtotal resection, total resection of high-grade malignant gliomas significantly improves overall survival and progression-free survival [6]. The median overall survival ranges from 14.6 to 20.5 months, with fewer than 5% of patients surviving five years from diagnosis [7]. Despite various treatment approaches, glioblastoma still has one of the lowest overall survival rates among all cancer types [8]. The use of stereotactic frames, neuronavigation systems, and intraoperative methods—including intraoperative ultrasound and intraoperative magnetic resonance imaging (iMRI)—enables the most precise possible tumor resection [9].

In June 2017, the U.S. Food and Drug Administration (FDA) approved oral 5-aminolevulinic acid (5-ALA) for use as an imaging agent in patients with gliomas as an adjunct for tumor visualization during surgery. It has proven to be a reliable intraoperative imaging agent, providing real-time guidance to neurosurgeons, which may allow for more complete resection of high-grade gliomas (HGG) [10].

Given the central role of maximal safe resection in glioblastoma management, fluorescence-guided surgery using 5-ALA has gained widespread attention for its ability to enhance intraoperative tumor visualization. Although its clinical utility is increasingly recognized, the literature remains fragmented regarding mechanistic underpinnings, comparative efficacy, off-label applications, and technical challenges.

This narrative review aims to synthesize current data on the use of 5-ALA in glioma surgery, with particular focus on its mechanism of action, clinical applications, limitations, and integration with other intraoperative technologies.

METHODS AND RESULTS OF SELECTION

A narrative literature review was conducted using the PubMed and Google Scholar databases. The search strategy included various combinations of the following keywords: *"5-ALA," "5-aminolevulinic acid," "glioblastoma," "neurosurgery,"* and *"high-grade glioma."* Studies were selected to explore the mechanism of action of 5-ALA, its clinical utility in fluorescence-guided glioma surgery, and the limitations associated with its use.

Only peer-reviewed articles published in English were considered. The selection included original research, systematic reviews, clinical trials, and relevant consensus statements. Given the narrative nature of this review, no formal inclusion or exclusion criteria were applied, and the time frame was not restricted. Although an effort was made to include recent and high-quality sources, the review does not claim to be exhaustive and may not cover all relevant studies.

MAIN BODY OF THE REVIEW

MECHANISM OF ACTION

5-aminolevulinic acid is administered orally to patients 2–4 hours before the induction of anesthesia. As a prodrug and precursor of protoporphyrin IX (PpIX), it is typically converted into heme by ferrochelatase in healthy individuals. [11]. The physiologically intact blood-brain barrier prevents 5-ALA from crossing. However, in high-grade gliomas, this barrier is disrupted, allowing for increased permeability. Additionally, cancer cells overexpress ABC membrane transporters, which enhance 5-ALA uptake [12]. Due to ferrochelatase deficiency, HGG accumulate PpIX instead of converting it into heme [13]. Furthermore, the externally administered tracer bypasses the regulatory inhibition of 5-ALA synthesis by heme, leading to further PpIX accumulation. [13]. Upon exposure to light in the 375–440 nm range, PpIX becomes excited and subsequently returns to its resting state, emitting red fluorescence detectable at wavelengths of 635–704 nm [13,14].

To enable fluorescence visualization in surgical microscopes, ion filters are integrated into the optical system. PpIX excitation occurs at 405 nm, which matches its peak absorption spectrum, leading to the emission of lower-energy photons at approximately 630 nm. Any 405 nm light that does not interact with PpIX is reflected by the tissue, producing two distinct spectral beams: blue light from non-tumorous areas and red fluorescence from the tumor. These return through the microscope's optical filter, which reduces violet-blue light intensity while allowing red fluorescence to pass through [15].

A slight overlap between excitation and emission spectra results in a small fraction of the excited light being re-emitted, giving healthy brain tissue a blue hue in contrast to the bright red fluorescence of gliomas [14]. During surgery, switching from conventional white light to blue light makes the tumor highly distinguishable, with 5-ALA serving as a neuro-navigation aid that theoretically facilitates the detection of all tumor cells [16].

Various intra- and extracellular factors can influence PpIX formation and cellular function. Conditions such as acidosis, hyperthermia, and hypoglycemia enhance PpIX accumulation, whereas hypoxemia has a mild inhibitory effect [17]. Additionally, residual tumor tissue tends to fluoresce more frequently in cases where MGMT methylation is present [18].

THE USE OF THE 5-ALA

In recent years, 5-ALA has become a widely utilized intraoperative imaging tool with diverse applications. Its sensitivity and specificity for detecting high-grade glioma tissue have been reported at 95% and 100%, respectively [19]. Research indicates that 5-ALA enhances both the extent and speed of tumor resection compared to traditional stereotactic navigation and contributes to prolonged progression-free and overall survival in contrast to surgeries without its use [20]. The growing interest in the neurosurgical field is also driven by its ability to provide real-time feedback on tumor localization, enabling continuous monitoring of the resection margin [21].

However, this method remains insufficiently sensitive for effectively identifying low-grade gliomas (LGG) or tumor margins with low cancer cell density. Although LGG cells accumulate more PpIX than normal brain tissue, only about 20% of LGGs exhibit fluorescence following 5-ALA administration [22].

Primary central nervous system lymphomas demonstrate strong fluorescence after 5-ALA administration. This observation confirms the accumulation of PpIX [23]. In such cases, histopathological evaluation remains essential for accurate diagnosis and proper adjuvant therapy, and patients may benefit from stereotactic biopsy of the lesions [24].

The application of 5-ALA in brain metastasis surgery has also been explored, though fluorescence detection in these tumors remains inconsistent. While fluorescence presence did not significantly impact the extent of resection, metastases that exhibited fluorescence correlated with longer progression-free and overall survival.

Beyond gliomas, 5-ALA-induced fluorescence is observed in certain rare tumors, including hemangioblastomas, ependymomas, and subependymomas. Hemangioblastomas, despite being well-defined, often contain cystic components and epithelial tumor layers that respond to PpIX fluorescence, aiding in their detection and facilitating complete resection. Similarly, fluorescence has been reported in both ependymomas and subependymomas that can exhibit significant fluorescence after 5-ALA administration. While its use in pediatric ependymomas is off-label, 5-ALA helps achieve complete resection, particularly in anaplastic cases. Strong fluorescence in spinal ependymomas aids in margin delineation, especially in hemorrhagic tumors [25].

The degree of tumor resection remains a crucial prognostic factor for survival in high-grade gliomas, and 5-ALA is the most effective available tool for achieving maximal safe resection while minimizing local and systemic side effects [25]. Randomized controlled trials have shown no significant difference in complication rates between patients receiving 5-ALA and those in control groups. For tumors situated near eloquent brain regions, additional surgical techniques, such as awake craniotomy, may be necessary to reduce the risk of functional deficits.

SAFETY OF USING 5-ALA

5-ALA is well tolerated by patients, and potential side effects are rare and manageable. Special caution should be exercised in cases where the tumor is located near eloquent brain areas. This is particularly important for patients with pre-existing deficits such as aphasia, paresis, or vision disturbances that do not respond to corticosteroid treatment. Studies indicate that using fluorescence-guided resection in such cases may increase the risk of neurological deficits. To mitigate this risk, preoperative or intraoperative imaging techniques are recommended to precisely determine the tumor's location relative to functionally important structures. These measures help in meticulous surgical planning and reduce the likelihood of damage to critical brain regions.

For 24 hours after 5-ALA administration, it is recommended to limit eye and skin exposure to intense light sources (surgical lamps, sunlight, high-intensity spotlights) [26]. The simultaneous use of phototoxic substances, such as tetracyclines, sulfonamides, fluoroquinolones, or St. John's wort extracts, is contraindicated. Additionally, during this period, the use of medications with potential hepatotoxic effects should be avoided [27].

For patients with cardiovascular diseases, a cautious approach is necessary, as literature data suggest that 5-ALA may lower both systolic and diastolic blood pressure.

Adverse reactions following the administration of this medicinal product for fluorescence-guided glioma resection can be categorized into two distinct groups. The first includes immediate reactions occurring after oral administration of 5-ALA, prior to anesthesia, which are considered active substance-specific side effects. The second category comprises adverse effects resulting from the combined influence of 5-ALA, anesthesia, and tumor resection, referred to as procedure-specific side effects.

The frequency of adverse reactions associated with this medicinal product is categorized based on occurrence rates. Reactions classified as very common occur in at least 1 in 10 patients. Common adverse effects are observed in at least 1 in 100 but less than 1 in 10 patients. Uncommon reactions occur in at least 1 in 1,000 but less than 1 in 100 cases. Rare side effects are reported in at least 1 in 10,000 but less than 1 in 1,000 patients. Finally, very rare reactions occur in fewer than 1 in 10,000 cases.

Adverse reactions are presented in order of decreasing seriousness in Table 1. They are categorized as substance-specific side effects and procedure-related side effects [38].

Table 1. Adverse Effects of 5-ALA Administration

Very common	Blood and lymphatic system disorders	Anaemia[2] Thrombocytopenia[2] Leukocytosis[2]
	Hepatobiliary disorders	Blood bilirubin increased[2] Alaninę aminotransferase increased[2] Aspartate aminotransferase increased[2] Gamma glutamyltransferase increased[2] Blood amylase increased[2]
Common	Nervous system disorders	Neurological disorders (e.g. hemiparesis, aphasia, convulsions, hemianopsia) [2]
	Vascular disorders	Thromboembolism[2]
	Gastrointestinal disorders	Vomiting[2] Nausea[2]

Uncommon	Nervous system disorders	Brain oedema[2]
	Cardiac disorders	Hypotension[1, 2]
	Skin and subcutaneous tissue disorders	Photosensitivity reaction[1] Photodermatosis[1]
	Gastrointestinal disorders	Nausea[1]
Very rare	Nervous system disorders	Hypesthesia[2]
	Gastrointestinal disorders	Diarrhoea[2]

[1]substance-specific side effects; [2]procedure-related side effects

LIMITATIONS OF THE TECHNIQUE

Despite its advantages, 5-ALA as an intraoperative imaging tool has certain limitations. Cases of false-positive fluorescence in biopsies taken near the tumor have been documented, with potential causes including reactive astrocytes, autofluorescence of normal brain tissue, or the presence of radiation necrosis [25, 28]. However, it is important to note that necrotic tissue itself does not exhibit fluorescence. False-negative results may arise due to factors such as a low density of tumor cells, structural obstructions affecting fluorescence visualization (e.g., blood in the surgical field), improper timing of 5-ALA administration, or extensive tumor necrosis.

Fluorescence is only visible on the exposed tumor surface, requiring optimal lighting conditions for accurate detection. Proper alignment between the microscope and the tissue is essential for generating clear images. In 5-ALA-guided surgery, the tumor cavity is often partially obscured or beyond the focal reach of the fluorescent microscope. Additionally, lateral walls may be challenging to visualize due to their steep angle relative to the light source and optics, potentially leading to incomplete resection in cases with deep and narrow surgical access [29].

Another limitation is the potential for photo-bleaching of 5-ALA-induced fluorescence due to prolonged exposure to light. The frequency of this phenomenon may vary depending on the surgical approach, as well as tumor location and shape. Spectrographic analyses have demonstrated that in patients previously treated with steroids, porphyrin fluorescence is not detectable in either normal brain tissue or peritumoral edematous regions following 5-ALA administration [28].

ALTERNATIVE METHODS

Combining intraoperative 5-ALA with other imaging technologies can significantly improve the extent of tumor resection. Currently, intraoperative ultrasound and intraoperative MRI are employed to evaluate residual tumor tissue during surgery. In most cases, iMRI findings prompt surgeons to re-examine the surgical field and remove any remaining tumor tissue. The integration of these tools with 5-ALA may offer particular advantages and enhance surgical outcomes [30].

Unlike 5-ALA, iMRI allows for the assessment of the entire brain simultaneously. However, its use requires a pause in the surgical procedure, making it more time-consuming. In contrast, 5-ALA provides real-time imaging, allowing for continuous visualization of tumor fluorescence. Additionally, the fluorescence extends beyond the conventional T1Gd contrast-enhancing region seen on MRI scans [31]. It is also important to note that iMRI can produce false-positive results due to nonspecific gadolinium enhancement, which may be a consequence of surgical manipulation. Recently, 5-ALA has been combined with advanced metabolic imaging techniques, such as whole-brain magnetic resonance spectroscopy, to improve the identification of infiltrative tumor margins in glioma patients [32].

5-ALA functions not only as a fluorescence-inducing agent but also contributes to tumor sensitization. Tumor-derived porphyrins from 5-ALA, particularly protoporphyrin IX (PPIX), have been shown to enhance tumor sensitivity to various external stimuli. When exposed to light, sound, radiation, or magnetism, these porphyrins can locally generate reactive oxygen species, initiating cellular mechanisms that lead to tumor cell death. In recent years, stimulus-responsive therapies have gained traction in glioblastoma treatment,

demonstrating promising antitumor effects [33]. Notably, photodynamic therapy (PDT) utilizing 5-ALA has already been introduced into clinical practice, as it is approved by both the FDA and EMA for fluorescence-guided resection [34].

Sodium fluorescein (SF) has emerged as the preferred fluorophore in many centers due to its favorable safety profile, ease of use, and cost-effectiveness. Unlike other markers, SF accumulates in the extracellular space where the blood-brain barrier is compromised. It is excited by light in the 460–500 nm range, emitting fluorescence between 540 and 690 nm. Surgical microscopes equipped with blue excitation light and corresponding emission filters allow for the differentiation of pathological tissue from healthy brain tissue, particularly at tumor margins where viable tumor cells are more prevalent [35].

The intensity of fluorescence has been observed to vary and correlate with tissue pathology, although it is highly time dependent [30]. The marker accumulates at tumor margins similarly to contrast-enhancing tumor boundaries seen in MRI imaging. However, instances of fluorescence in healthy brain parenchyma have also been documented [35]. Due to its unique mechanism of action, SF may spread beyond tumor margins as a result of direct surgical manipulation

Some studies propose the concurrent application of 5-ALA and SF to enhance the accuracy of glioma cell detection by improving both sensitivity and specificity [36]. However, fluorescence has been observed in certain regions of high-grade gliomas without the administration of any contrast agent [35], raising concerns about the precise mechanism underlying SF activity.

The combined use of 5-ALA and SF has been associated with improved overall survival, though factors such as patient selection and timing of administration may influence outcomes. These fluorophores are predominantly utilized in younger patients undergoing planned total resection, yielding comparable rates of gross total resection. From a financial perspective, SF presents a cost-effective alternative to 5-ALA. Nonetheless, 5-ALA remains the preferred option for cases requiring supramaximal resection due to its superior ability to highlight tumor infiltration beyond the contrast-enhancing margin [37].

Exploring alternative agents to 5-ALA could further enhance its efficacy and broaden its applicability to a wider range of tumors.

DISCUSSION

CLINICAL UTILITY OF 5-ALA IN HIGH-GRADE GLIOMAS

The incorporation of 5-aminolevulinic acid (5-ALA) into glioma surgery has demonstrated clear clinical benefits in the management of high-grade gliomas. Multiple studies have shown that the use of 5-ALA enhances the likelihood of achieving gross total resection, which correlates with improved progression-free and overall survival [19, 20]. The mechanism of selective fluorescence through the accumulation of protoporphyrin IX in tumor cells enables surgeons to distinguish malignant tissue intraoperatively, contributing to real-time decision-making and improved resection margins [13, 14, 15].

LIMITATIONS OF 5-ALA-GUIDED SURGERY

Despite its proven utility, several limitations restrict the broader applicability of 5-ALA. The sensitivity of fluorescence is significantly lower in low-grade gliomas, with only 20% of tumors showing detectable signals [22]. False-positive fluorescence can occur due to reactive astrocytes or radiation necrosis, while false-negative results may result from extensive necrosis, insufficient cell density, intraoperative bleeding, or prior steroid administration [25, 28]. Technical factors such as the requirement for direct visual access, optimal alignment with the optical axis, and the phenomenon of photobleaching further limit its effectiveness in deep or irregularly shaped surgical fields [28, 29].

Additionally, while fluorescence has been observed in other tumor types—such as hemangioblastomas, ependymomas, and CNS lymphomas—the diagnostic and therapeutic implications of these findings remain under investigation [23, 24, 25]. Some glioma surgeries have incorporated 5-ALA in combination with sodium fluorescein (SF), aiming to improve both sensitivity and specificity of tumor detection [35, 36]. Although early results suggest improved visualization and potential survival benefit, these approaches are typically limited to younger patients undergoing planned gross total resection and require further evaluation in controlled trials [37].

EMERGING COMBINED APPROACHES AND FUTURE INTEGRATION

Future directions include the integration of 5-ALA with neuronavigation systems, intraoperative MRI, and metabolic imaging techniques to improve surgical accuracy [21, 30, 31]. Moreover, photodynamic therapy using 5-ALA-derived porphyrins has shown preliminary promise in experimental settings and may represent

a novel therapeutic approach [33, 34].

In conclusion, 5-ALA remains a valuable adjunct in fluorescence-guided resection of high-grade gliomas. While limitations exist, particularly in low-grade and deep-seated tumors, ongoing advances in imaging integration and combined fluorescence approaches offer opportunities to further refine and personalize surgical strategies.

FUTURE RESEARCH DIRECTIONS

Based on the reviewed literature, further research should focus on several key areas. First, improving the diagnostic accuracy of 5-ALA in low-grade gliomas remains a critical challenge due to low fluorescence intensity in these tumors [22]. Investigating strategies to enhance PpIX accumulation in LGG, such as modulation of tumor metabolism or the use of adjuvant agents, may improve detection rates.

Second, the combination of 5-ALA with other intraoperative imaging modalities, including sodium fluorescein and intraoperative MRI, requires validation in prospective clinical studies to determine whether such dual-agent or multimodal approaches yield superior resection outcomes [30, 35, 36].

Third, the off-label use of 5-ALA in non-glioma tumors (e.g., CNS lymphomas, ependymomas) has shown isolated success [23, 24, 25], but systematic investigations are needed to clarify its diagnostic utility, safety, and role in surgical decision-making across tumor types.

Finally, the therapeutic applications of 5-ALA beyond visualization—particularly its role in photodynamic therapy—warrant continued exploration given the potential for selective tumor cell destruction via porphyrin-mediated reactive oxygen species generation [33, 34].

CONCLUSIONS

5-ALA remains a valuable adjunct in fluorescence-guided resection of high-grade gliomas. Its use is supported by evidence of improved surgical precision and patient outcomes. However, limitations related to tumor type, depth, fluorescence variability, and technical constraints must be acknowledged. Current literature supports its role in the standard surgical management of glioblastoma, while its use in low-grade and non-glioma tumors requires further clinical validation. Integration with other intraoperative imaging modalities and continued investigation into photodynamic applications may enhance its future clinical utility.

AUTHOR CONTRIBUTIONS

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ARTIFICIAL INTELLIGENCE DISCLOSURE

Artificial intelligence tools (e.g., ChatGPT, OpenAI) were used to assist with language editing, structural refinement, and the formulation of selected textual segments (e.g., background synthesis, objectives, conclusions). All AI-assisted content was critically reviewed, fact-checked, and finalized by the authors.

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