

The Use of 5-Aminolevulinic Acid in Glioma Surgery: From Intracranial to Spinal Applications

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Abstract

Fluorescence-guided surgery (FGS) with 5-aminolevulinic acid (5-ALA) has become an important adjunct in glioma surgery, with the aim of maximizing the extent of resection while preserving neurological function. After oral or intravenous administration, 5-ALA is metabolized to protoporphyrin IX (PpIX), which preferentially accumulates in tumor cells and fluoresces under blue light, thereby improving intraoperative visualization of malignant tissue. This narrative review summarizes the current indications, evidence, challenges, and future directions of 5-ALA in intracranial and spinal cord glioma surgery. Randomized and observational studies have demonstrated that 5-ALA FGS increases gross total resection rates and improves progression-free and overall survival in intracranial high-grade glioma. Although its role in low-grade glioma is less established, focal fluorescence may identify anaplastic foci and serve as a prognostic marker. In spinal cord gliomas, 5-ALA appears particularly useful for ependymomas, in which high fluorescence rates and favorable resection outcomes have been reported. Its application in spinal astrocytomas requires caution because robust evidence of benefit remains limited and over-resection may cause substantial neurological harm. Overall, 5-ALA has a favorable safety profile, with mostly mild and transient adverse effects. Beyond resection guidance, 5-ALA-based photodynamic and radiodynamic approaches are being explored as adjuvant therapies. Current evidence strongly supports its use in high-grade intracranial gliomas and selected spinal ependymomas, while emerging theranostic applications may further expand its role in multimodal neuro-oncology.

Keywords: 5-aminolevulinic acid, fluorescence-guided surgery, glioma, glioblastoma, spinal cord tumors, ependymoma, extent of resection, photodynamic therapy, radiodynamic therapy

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Introduction

Gliomas are primary central nervous system tumors arising from glial cells and include a spectrum of entities ranging from indolent lesions to highly aggressive malignancies in both intracranial and spinal compartments. Fluorescence-guided surgery (FGS) using 5-aminolevulinic acid (5-ALA) was first introduced by Dr. Walter Stummer, who demonstrated its benefit in the resection of malignant intracranial gliomas in a human cohort [1]. Evidence supporting the use of 5-ALA in spinal glioma resection has also emerged in recent years [2, 3]. Intracranial gliomas, particularly glioblastoma multiforme (GBM), have a poor prognosis, with a median survival of 12 to 15 months and fewer than 10% of patients surviving beyond five years [4]. Spinal cord gliomas, although less common, present distinctive surgical challenges because of the eloquent nature of spinal cord tissue and the potentially catastrophic consequences of over-resection.

Maximal safe surgical resection has long been the mainstay of treatment for both intracranial and spinal gliomas, with gross total resection (GTR) as a central objective. More recently, supratotal resection has also been advocated in selected intracranial cases [5]. Extent of resection (EOR) has shown a strong positive association with patient outcomes, including progression-free survival (PFS) and overall survival (OS), in intracranial gliomas [6, 7]. Although complete tumor excision is desirable, postoperative functional outcomes must be carefully considered. Given the infiltrative nature of high-grade gliomas and the eloquent anatomy of both brain and spinal cord tissue, the risk of disrupting adjacent critical areas must be weighed against the impact of subtotal resection on OS and recurrence. This balance forms the basis of maximal safe resection (MSR) [8].

This narrative review provides a clinically oriented overview of the current indications, evidence, and complications associated with the use of 5-ALA in intracranial and spinal cord glioma resection and explores emerging applications of this technology.

Materials and methods

This work is a narrative review intended to provide a clinically oriented synthesis for readers. The review was based on current literature that included key clinical and experimental studies on 5-ALA in glioma surgery. Relevant studies were identified through targeted searches of PubMed and major neurosurgical and neuro-oncology journals using terms such as "5-ALA," "fluorescence-guided surgery," "glioma," "glioblastoma," "spinal cord tumors," "ependymoma," "astrocytoma," "low-grade glioma," "photodynamic therapy," and "radiodynamic therapy."

Pharmacological basis and current indications for 5-ALA

5-ALA is an endogenous amino acid used in the porphyrin synthesis pathway as a precursor of heme production in mammals. After administration, it is metabolized to PpIX, which acts as a fluorescent marker and preferentially accumulates in tumor cells because of altered tumor metabolism [1, 9]. PpIX fluorescence becomes visible under blue light, enabling the surgeon to distinguish malignant tissue from normal parenchyma in both brain and spinal cord.

The fluorescent property of 5-ALA has been used to support intraoperative MSR, particularly in high-grade gliomas (HGGs) of the cranial vault (World Health Organization grades III and IV). It has been approved for use in Europe, Asia, Australia, and the United States, and the standard dose is 20 mg/kg, administered orally 3 to 4 hours before the start of surgery [10]. After craniotomy or laminectomy and dural opening, the surgeon can switch between white-light and blue-light modes to delineate fluorescent tumor margins and guide resection.

Evidence supporting 5-ALA use in intracranial high-grade gliomas

Studies have shown that 5-ALA FGS significantly improves EOR in intracranial glioma resection, and several landmark trials have confirmed that 5-ALA reliably differentiates normal brain from malignant tissue. Stummer et al. [11] conducted a randomized controlled trial showing that 5-ALA FGS nearly doubled the rate of complete resection of contrast-enhancing tumor compared with conventional white-light surgery (65% vs. 36%; between-group difference, 29%; 95% CI, 17 to 40; $P < 0.001$) and improved 6-month PFS (41.0% vs. 21.1%; $P < 0.001$). Coburger et al. [12] also demonstrated that EOR increased with the addition of 5-ALA to intraoperative MRI (iMRI) compared with iMRI alone, with GTR achieved significantly more often (100% vs. 82%; $P = 0.010$) and a higher mean EOR (99.7% vs. 97.4%; $P = 0.004$), without an increase in complications ($P = 0.518$). Su et al. [13] conducted a systematic review and meta-analysis that quantified the benefits of 5-ALA FGS, demonstrating higher rates of complete resection and improved PFS compared with conventional surgery. Schuppper et al. [14] subsequently conducted a prospective multicenter study that demonstrated enhanced surgical visualization without increased neurological morbidity.

A recent systematic review showed that 5-ALA increased GTR rates from 54.3% with white light alone to 75.4% with 5-ALA ($P < 0.001$), accompanied by a corresponding reduction in residual contrast-enhancing volume on early postoperative MRI [15]. The same review also reported improvements in 6-month PFS (median, 8.1 vs. 5.4 months; $P = 0.002$) and OS (median, 15.2 vs. 12.3 months; $P = 0.008$) with 5-ALA FGS. Ryskeldiyev et al. [16] also reported improved survival with 5-ALA-guided resections, attributable to increased GTR, although multivariable models indicated that EOR itself, rather than 5-ALA per se, is the primary driver of the survival benefit.

The benefit of 5-ALA appears most pronounced in newly diagnosed HGG, whereas its impact in recurrent tumors is less consistent. A systematic review of 5-ALA in recurrent malignant gliomas suggested that although fluorescence facilitates resection and modestly prolongs OS, there is no clear effect on PFS in this setting. Nevertheless, 5-ALA remains a useful and safe adjunct to consider when planning resection of recurrent malignant gliomas [17].

5-ALA in low-grade and intermediate-grade gliomas

Although the literature provides strong evidence supporting 5-ALA in HGG, its use in low-grade gliomas (LGGs) is less established. LGGs have a cytoarchitecture that more closely resembles normal tissue and show less malignant tracer uptake than higher-grade tumors. 5-ALA has therefore been less effective in LGG, with Ishihara et al. [18] reporting limited and inconsistent

uptake in gliomas below central nervous system grade III [18-20]. Suero Molina et al. [21] suggested that doubling the 5-ALA dose from 20 mg/kg to 40 mg/kg may increase fluorescence rates in LGG by improving blood-brain barrier penetration; however, this approach remains investigational and must be balanced against theoretical toxicity concerns.

Widhalm et al. [20] showed promise for the future use of 5-ALA in LGG because of its ability to identify anaplastic foci within these tumors. Focal 5-ALA fluorescence in lesions preoperatively classified as low grade or indeterminate was shown to highlight areas of anaplastic transformation, thereby guiding targeted sampling and influencing grading. Hosmann et al. [22] evaluated 5-ALA fluorescence in World Health Organization grade II LGGs at two specialized centers and found that intraoperative fluorescence was associated with less favorable clinical and molecular characteristics, poorer PFS (2.3 (0.7) vs. 5.0 (0.4) years; $P = 0.010$), and shorter OS (5.4 (1.0) vs. 10.3 (0.5) years; $P = 0.010$), suggesting that fluorescence may serve as a prognostic marker. This association is most likely related to blood-brain barrier breakdown at anaplastic foci, which increases permeability. Muther et al. [23] showed that increased preoperative MRI contrast enhancement was associated with fluorescence uptake in intermediate-grade gliomas, indicating increased permeability of the tumor focus to both contrast and 5-ALA. Bianconi et al. [24] also showed a link between MRI contrast uptake and 5-ALA fluorescence in more aggressive foci, and reported that 5-ALA fluorescence was significantly associated with shorter OS and PFS.

5-ALA in spinal cord gliomas

Although most published experience with 5-ALA relates to intracranial gliomas, evidence increasingly supports its use in selected intramedullary spinal cord tumors, particularly ependymomas and, to a lesser extent, astrocytomas. Spinal cord gliomas present distinctive surgical challenges because even minor injury to eloquent spinal cord tissue can result in permanent neurological deficit. In this context, 5-ALA fluorescence guidance may help maximize tumor resection while minimizing functional morbidity.

Ependymomas are the most common primary intramedullary tumors in adults, and surgical resection remains the treatment of choice. GTR is a realistic objective in many cases because a well-defined cleavage plane usually exists between a benign ependymoma and the surrounding normal spinal cord. This tissue boundary allows the tumor to be dissected free of the cord. 5-ALA fluorescence works in tandem with this anatomical plane by helping the surgeon confirm the margin and detect residual tumor foci at the tumor-cord interface. Several series have demonstrated that spinal ependymomas exhibit strong 5-ALA-induced fluorescence, with positive fluorescence rates ranging from 50% to 100% [2, 3, 25]. In a series of 14 patients with spinal cord ependymomas undergoing 5-ALA-guided resection, Moreno et al. [2] reported strong fluorescence in 85.71% of patients (12 of 14) and achieved GTR in 79% of cases. Importantly, 10 of 14 patients (71%) experienced clinical improvement according to the modified McCormick scale, with only two patients showing postoperative deterioration, a lower rate than typically reported in non-fluorescence-guided series.

The role of 5-ALA in intramedullary astrocytomas is less established and requires a more cautious approach. Unlike ependymomas, spinal astrocytomas lack a clear dissection plane and actively infiltrate surrounding cord tissue. This infiltrative growth pattern explains why aggressive fluorescence-guided resection may be dangerous in this setting. Although some spinal astrocytomas demonstrate positive fluorescence, chasing every fluorescent focus may be hazardous because of the intimate relationship between tumor and eloquent spinal cord tissue. Unlike cerebral gliomas, increased EOR in spinal astrocytomas has not been conclusively shown to improve outcomes, and the risk of permanent myelopathy from over-resection based on fluorescence may outweigh any potential oncological benefit [25].

The comprehensive review of 5-ALA in spinal tumor surgery by Wainwright et al. [25] emphasized that the technique is particularly suited to ependymomas because of their well-defined margins and consistent PpIX accumulation. Intraoperative visualization of residual tumor foci may reduce the need for repeat surgery and potentially improve long-term tumor control. For spinal astrocytomas, however, 5-ALA may assist in tumor identification and biopsy guidance, but routine use for aggressive resection should be approached cautiously because of the unique anatomical and functional constraints of the spinal cord.

Overall, 5-ALA FGS appears to be a safe and valuable adjunct for spinal cord ependymoma resection, facilitating more complete tumor removal and potentially reducing postoperative neurological deterioration [2, 3, 25]. The technique requires the same equipment and dosing protocols used for intracranial procedures, making it readily adoptable in centers already performing 5-ALA-guided cranial surgery. A direct comparison between the two anatomical compartments is clinically instructive. The brain may tolerate a degree of manipulation, and in selected non-eloquent areas, supratotal resection beyond the contrast-enhancing margin can be a reasonable survival-oriented goal. The spinal cord allows no such margin for error. Within the cord, pursuing every fluorescent focus of an infiltrative astrocytoma can result in irreversible paraplegia. Therefore, the surgeon must continuously balance oncological ambition against functional preservation. In this unforgiving compartment, fluorescence should inform the extent of resection without dictating it.

Safety profile and current challenges

Several studies have documented a favorable safety profile for 5-ALA. In general, adverse effects are minimal, transient, and self-limited [11, 12, 26]. Reported adverse effects include photosensitivity caused by PpIX accumulation in the skin. Clinicians should therefore warn patients to avoid strong light sources for at least 24 hours postoperatively. The Food and Drug Administration warns against concomitant use of phototoxic drugs, such as St. John's wort, griseofulvin, thiazide diuretics, sulfonamides, phenothiazines, sulfonamides, quinolones, tetracyclines, and topical preparations containing ALA, for 24 hours before and after 5-ALA administration [10]. Other reported adverse effects include gastrointestinal symptoms, nausea, transient neurological symptoms, and mild liver enzyme abnormalities. In large clinical series and the pivotal randomized controlled trial, serious 5-ALA-related complications were rare and comparable to those observed with standard surgery [11].

Despite its benefits, 5-ALA FGS has several practical challenges, including the need for specialized equipment and operator training to interpret fluorescence accurately. The technique requires access to microscopes equipped with appropriate excitation and detection modules, as well as training in recognizing and interpreting fluorescence patterns. The qualitative nature of standard fluorescence assessment introduces subjectivity, and interobserver variability may influence decisions at the resection margin. False-negative and false-positive fluorescence can occur. Nonfluorescent tumor regions, particularly in LGG or at infiltrative margins, may limit complete resection if the surgeon relies solely on fluorescence. Conversely, fluorescence in areas of treatment-related change, inflammation, or reactive tissue could lead to unnecessary resection if not contextualized with imaging and functional information. Experienced users generally advocate treating fluorescence as an adjunct to, rather than a replacement for, neuronavigation, tractography, and awake mapping when appropriate [27].

Beyond resection: emerging therapeutic applications

An emerging application of 5-ALA is photodynamic tumor targeting, in which 5-ALA is used as a cytotoxic agent activated by specific wavelengths of light. Several studies have tested this property to target the tumor bed and address residual tumor after resection [28-30]. 5-ALA serves as a photosensitizer for photodynamic therapy (PDT), in which activated PpIX generates reactive oxygen species that lead to tumor cell death upon exposure to light at specific wavelengths. For 5-ALA-mediated PDT, relevant wavelengths excite PpIX absorption peaks, especially in the blue (approximately 405 to 410 nm) and red (approximately 630 to 635 nm) regions. Preclinical and early clinical studies have explored intraoperative or postoperative PDT to treat residual microscopic disease in the resection cavity, with some reports suggesting delayed tumor progression and acceptable safety [29].

Studies are also investigating the combination of 5-ALA's photodynamic properties with radiotherapy. A recent *in vivo* study in mouse models treated with 5-ALA before radiotherapy showed slower tumor growth and regression compared with radiotherapy alone [31]. Similarly, Nordmann and Michael [32] reviewed 11 *in vitro* and *in vivo* studies on 5-ALA radiodynamic therapy (RDT) and showed promise for this form of adjuvant therapy in HGG. Building on PDT concepts, RDT uses radiation to activate PpIX-mediated cytotoxic effects and may synergize with conventional radiotherapy in glioblastoma, although clinical data remain limited.

Future directions

Future work is likely to focus on several key areas. First, refinement of quantitative fluorescence techniques and integration with intraoperative imaging and artificial intelligence may improve margin assessment and reduce subjectivity in fluorescence interpretation. Emerging work on PpIX fluorescence spectroscopy and quantitative imaging aims to move beyond purely qualitative assessment toward objective maps of fluorophore concentration at the resection margin. Early clinical studies demonstrate that spectrally resolved techniques can detect tumor-associated PpIX at concentrations below visual thresholds, strongly correlate with histopathology, and may reduce false-

negative margins in both HGG and the infiltrative components of LGG [33].

Second, improved predictive models for 5-ALA fluorescence in diffuse gliomas, incorporating imaging and molecular features, could help tailor 5-ALA use to patients most likely to benefit. Coupling these methods with machine-learning-based prediction of fluorescence from preoperative MRI could ultimately support a more personalized and data-driven paradigm for 5-ALA-guided glioma surgery [34].

Third, ongoing translational and early-phase clinical studies in 5-ALA-based PDT and RDT will clarify the potential of these adjuvant modalities to improve local control and survival in glioblastoma and other aggressive tumors [32]. Future clinical studies should evaluate the potential synergy between radiotherapy and the photodynamic capabilities of 5-ALA demonstrated in preclinical models.

Finally, comparative studies of 5-ALA and other fluorescent agents, including fluorescein and novel targeted probes, will further define the role of 5-ALA within the evolving landscape of fluorescence-guided neurosurgery [35]. In addition, the application of 5-ALA in central nervous system tumors beyond gliomas and ependymomas warrants further investigation, particularly to determine which tumor types benefit most from fluorescence guidance and how resection aggressiveness should be balanced against functional preservation in eloquent anatomical locations [36].

Conclusion

5-ALA has transformed glioma surgery across intracranial and spinal compartments by enabling more complete MSR. Current evidence strongly supports its use in intracranial HGG, where it increases GTR rates and improves short-term PFS without an excess of major neurological morbidity [11, 12]. In spinal cord surgery, 5-ALA has demonstrated particular utility in ependymoma resection, with high fluorescence rates and improved detection of residual tumor foci; however, caution is warranted in spinal astrocytomas because of the eloquent nature of spinal cord tissue [2, 3, 25]. In LGG, 5-ALA can highlight anaplastic foci and may provide prognostic information, although its sensitivity is limited and the absence of fluorescence does not exclude higher-grade components [19, 22]. The safety profile of 5-ALA is generally favorable across both intracranial and spinal applications, and practical limitations primarily relate to equipment, training, and interpretation.

Emerging photodynamic and radiodynamic applications, together with expanding use in non-glioma tumors, suggest that 5-ALA will continue to play an important role in neurosurgical oncology [29-32]. Research has identified new horizons for this dye, moving it from a purely diagnostic tool toward a theranostic platform. Further clinical and translational research will determine how best to integrate these modalities into comprehensive, multimodal care pathways for patients with gliomas across all anatomical locations.

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