Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2025.63.009932

Advantages and Limitations of 5-Aminolevulinic Acid (5-ALA) in Brain Tumors Resection, Review Study

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ARTICLE INFO

Received: October 22, 2025

Published: October 28, 2025

Citation: R.K. Prajapati, Sarvesh Chand, Dennis Sen and Nitendra Goundar. Advantages and Limitations of 5-Aminolevulinic Acid (5-ALA) in Brain Tumors Resection, Review Study. Biomed J Sci & Tech Res 63(4)-2025. BJSTR. MS.ID.009932.

ABSTRACT

Complete resection of malignant brain tumors, particularly high-grade gliomas, is a critical factor in improving patient outcomes. However, differentiating tumor tissue from healthy brain parenchyma intraoperatively remains a significant challenge.5-Aminolevulinic Acid (5-ALA) has emerged as a significant adjunct in neurosurgery, particularly in the resection of brain tumors. As a precursor in the heme biosynthetic pathway, 5-ALA is metabolized by malignant cells into protoporphyrin IX (PpIX), which fluoresces under blue light and enhance tumor visualization. This fluorescence provides real-time visual feedback to surgeons, allowing for enhanced delineation of tumor boundaries, thereby improving the extent of resection and minimizing damage to surrounding healthy tissue. Clinical studies have demonstrated that the use of 5-ALA-guided surgery can lead to improved outcomes, including increased rates of gross total resection and prolonged progression-free survival in patients with high-grade gliomas. Furthermore, the reduction in tumor residue after surgery correlates with lower recurrence rates, thus highlighting the potential for 5-ALA to enhance surgical precision and patient outcomes. This abstractreviews the application, efficacy, and limitations of 5-ALA in the surgical resection of brain tumors. However, further research is needed to fully understand its impact on long-term survival and to establish standardized protocols for its use in various tumor types.

Keywords: 5-Aminolevulinic Acid; 5-ALA; Neurosurgery; Brain Tumors; Fluorescence-Guided Surgery; Protoporphyrin Ix; Tumor Resection; Glioblastoma

Abbreviations: 5-ALA: 5-Aminolevulinic Acid; PpIX: Protoporphyrin IX; EMA: European Medicines Agency; FDA: Food and Drug Administration; Imri: Intraoperative MRI; FGS: Fluorescence-Guided Surgery; PDT: Photodynamic Therapy; GTR: Gross-Total Resection

Introduction

The maximal safe resection, without no neurological deficits after the surgery, is a cornerstone in the management of malignant brain tumors, particularly high-grade gliomas such as glioblastoma. The extent of tumor resection has been positively correlated with overall survival and progression- free survival in numerous studies [1]. However, achieving complete resection remains challenging due to the infiltrative nature of gliomas and the difficulty in distinguishing tumor tissue from normal brain parenchyma during surgery.5-Aminolevulinic acid (5-ALA) is a precursor in the heme biosynthesis pathway that has revolutionized fluorescence-guided neurosurgery. When administered orally, 5-ALA is selectively taken up by tumor cells and metabolized into protoporphyrin IX (PpIX), a fluorescent compound that accumulates in malignant cells due to impaired activity of ferro chelatase, the final enzyme in the heme pathway. Under violet-blue excitation light (approximately 400-410 nm), PpIX emits a strong red fluorescence, allowing surgeons to visualize tumor tissue intraoperatively [2].

The use of 5-ALA was first validated in a landmark Phase III randomized controlled trial, which demonstrated a significantly higher rate of complete resection and six-month progression-free survival in patients undergoing 5-ALA-guided surgery compared to standard white-light resection. Since then, 5-ALA has become a widely adopted tool in neurosurgical oncology, especially in Europe and parts of North America, and has received regulatory approval by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration

(FDA) for use in glioma surgery [3,4]. Despite its proven benefits, the effectiveness of 5-ALA varies depending on tumor type, grade, and metabolic activity. While its application is most established in high-grade gliomas, studies are ongoing to assess its utility in low-grade gliomas, brain metastases, meningiomas, and pediatric tumors [5]. Thus, 5-ALA fluorescence-guided surgery represents a significant advancement in the pursuit of safer, more complete tumor resections. Continued research into fluorescence mechanisms, imaging technologies, and expanded clinical indications will likely refine and enhance its role in neurosurgical oncology [6].

Methods and Results

Administered orally prior to surgery, 5-ALA is metabolized preferentially by tumor cells into protoporphyrin IX, a fluorescent compound that accumulates intracellularly. Under violet-blue light (400–410 nm), protoporphyrin IX emits a red fluorescence, enabling real-time identification of tumor margins. Numerous clinical trials, including the pivotal Phase III trial (Stummer, et al. [7]), have demonstrated that 5-ALA-guided surgery significantly increases the extent of resection and progression-free survival in patients with glioblastoma. Its utility in other tumors, such as meningiomas and metastases, is under investigation with variable results.

Discussion

The adoption of 5-ALA fluorescence-guided surgery (FGS) in neurosurgical oncology has significantly advanced real-time intraoperative tumor visualization, particularly in high-grade gliomas (HGGs). Retrospective analyses continue to reaffirm that 5-ALA enhances key surgical outcomes. For instance, a cohort study of 343 patients with glioblastoma multiforme (GBM) found 5-ALA use was associated with a markedly improved overall survival (17.47 vs. 10.63 months), increased gross-total resection (GTR) rates (47.4% vs. 22.9%), better postoperative performance status, and fewer new focal neurological deficits compared to conventional surgery [8]. Nevertheless, evidence in lower-grade gliomas is more nuanced. In a retrospective comparison of grade III gliomas, no significant difference in overall survival or extent of resection was found between 5-ALA and non-5-ALA groups. Notably, only in the subgroup achieving GTR with fluorescence guidance did survival benefit emerge, while the 5-ALA group also experienced worse neurological outcomes when GTR was not achievable. This underscores that the utility of 5-ALA may be predicated on obtaining sufficient fluorescence to guide resection safely [9]. Beyond gliomas, expanding applications warrant consideration. In invasive meningiomas, a 2025 prospective study showed that intraoperative 5-ALA fluorescence allowed additional resection of residual tumor tissue in 38.5% of cases-and in 45.5% of those with fluorescence-positive lesions.

Fluorescence-positive areas in bone and dura consistently harbored tumor infiltration, although brain parenchymal fluorescence was less predictive (33.3%) [10]. Moreover, in brain metastasis surgery, retrospective analysis of 80 cases reported that 57.5% displayed fluorescence, with a trend toward improved resectability (+12.1%) and significantly longer survival in fluorescence-positive tumors [11]. A 2022 systematic review failed to conclusively confirm that 5-ALA improves resection completeness or survival in metastases, citing variability in fluorescence across tumor types and limited high-quality evidence [12]. Emerging technological advances are enhancing the sensitivity and practicality of 5-ALA FGS. Innovations include the incorporation of angled endoscopic blue-light platforms, which facilitate visualization of fluorescent tumor tissue in deep or complex resection cavities not readily accessible under standard microscopy [13]. Additional enhancements, such as scanning fiber endoscopes, nanoparticle delivery systems, and pulsed-light illumination, are improving detection sensitivity and intraoperative workflow integration [14]. Combining 5-ALA with adjunctive intraoperative imaging modalities appears promising. A systematic review comparing 5-ALA and intraoperative MRI (iMRI) suggests a complementary effect, where combined use may extend resection margins beyond gadolinium-enhancing regions-without increasing permanent neurological deficits or compromising quality of life when employed alongside intraoperative monitoring [15].

Furthermore, novel adjunctive treatments such as photodynamic therapy (PDT) show compelling preliminary results. In a matched cohort for recurrent malignant glioma, the addition of intraoperative PDT immediately following 5-ALA-guided resection significantly improved 6-and 12-month survival, and progression-free survival, compared to resection alone, without adding substantial morbidity [16]. Strengths of 5-ALA FGS include enhanced intraoperative tumor visualization, improved GTR rates in GBM, better functional outcomes, and potential survival benefits. It also offers a low-risk adjunct in metastatic and meningioma surgeries, contingent upon fluorescence positivity. The increasing integration of advanced optical technology and imaging modalities further strengthens its intraoperative utility [17] Limitations include variable fluorescence, especially in non-GBM tumors, which may reduce efficacy in grade III gliomas, metastases, and infiltrative meningiomas. False positives in brain parenchyma and potential for neurological deficits-particularly in eloquent areas-necessitate cautious interpretation of marginal fluorescence and judicious use of neurophysiological monitoring. Additionally, the current evidence base in metastases and meningiomas remains preliminary, requiring stronger prospective, randomized data [18] Future directions should focus on larger-scale, prospective trials across diverse tumor entities to validate benefits of 5-ALA FGS.

Combining 5-ALA with iMRI and endoscopic or hyperspectral imaging may enhance resection precision. Early data integrating PDT suggests potential survival advantages and warrants further investigation. Advances in quantitative sensing devices and machine learning (e.g., hyperspectral classifiers for tissue type and tumor margins) hold promise for real-time, objective evaluation of fluorescence in the operating field.

Conclusion

5-ALA fluorescence-guided surgery represents a major advancement in neuro-oncology, enhancing intraoperative tumor visualization and enabling safer, more complete resections. The 5-ALA is a powerful tool in neurosurgery, especially for GBM. Its expanding applications, supported by technological innovation and multimodal strategies, herald continued evolution in maximizing safe, effective tumor resection across broader neurosurgical oncology indications. Continued research is warranted to expand its application to a broader range of brain tumors and refine fluorescence detection techniques.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2025.63.009932

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