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INTRAOPERATIVE FLUORESCENCE-GUIDED NEUROSURGERY: ADVANCING PRECISION AND RESECTION OUTCOMES IN MALIGNANT BRAIN TUMORS

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Abstract

Intraoperative fluorescence-guided surgery (FGS) has emerged as a transformative technique in neurosurgical oncology, enabling enhanced visualization of tumor margins during resection of malignant brain tumors. By utilizing fluorescent agents such as 5-aminolevulinic acid (5-ALA) and fluorescein sodium, FGS allows real-time differentiation between tumor tissue and surrounding healthy brain structures, thereby improving surgical precision and clinical outcomes.

This study investigates the role of fluorescence-guided techniques in malignant brain tumor surgery, focusing on their impact on extent of resection, intraoperative decision-making, and patient outcomes. A translational analytical framework was employed to integrate findings from molecular imaging, surgical practice, and clinical research.

The results indicate that FGS significantly enhances tumor visualization, enabling more complete resections while preserving functional brain regions. The use of fluorescence markers improves detection of infiltrative tumor margins that are not visible under conventional white-light microscopy. Additionally, FGS contributes to reduced residual tumor volume and improved progression-free survival in patients with high-grade gliomas.

However, limitations such as variability in fluorescence intensity, dependence on tumor biology, and potential false-positive signals remain important challenges. Future developments are expected to focus on improving fluorophore specificity, integrating multimodal imaging, and combining fluorescence with artificial intelligence for enhanced intraoperative guidance.

In conclusion, fluorescence-guided neurosurgery represents a powerful tool for improving precision and outcomes in malignant brain tumor resection, with significant implications for advancing neuro-oncological care.

Keywords: Fluorescence-guided surgery; Neurosurgery; Brain tumors; 5-ALA; Fluorescein; Tumor resection; Intraoperative imaging; Neuro-oncology; Surgical precision; Glioma

Introduction

Malignant brain tumors remain among the most challenging conditions in neurosurgical oncology due to their infiltrative nature, heterogeneity, and proximity to critical functional brain regions. High-grade gliomas, in particular, are characterized by diffuse invasion into surrounding neural tissue, making complete surgical resection difficult while preserving neurological function. Despite advances in imaging and surgical techniques, achieving maximal safe resection continues to be a primary goal, as it is strongly associated with improved survival and reduced tumor recurrence.

Traditional neurosurgical approaches rely on white-light microscopy and preoperative imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) for tumor localization and planning. However, these methods have inherent limitations, particularly in distinguishing tumor margins intraoperatively. Brain shift, tissue deformation during surgery, and the

microscopic infiltration of tumor cells into surrounding tissue reduce the accuracy of preoperative imaging guidance. As a result, residual tumor tissue often remains, contributing to disease progression and poor clinical outcomes.

Intraoperative fluorescence-guided surgery (FGS) has emerged as a powerful technique to address these limitations by providing real-time visualization of tumor tissue during surgery. FGS utilizes fluorescent agents that selectively accumulate in tumor cells or highlight areas of blood–brain barrier disruption, allowing surgeons to distinguish malignant tissue from normal brain structures under specialized illumination. Among the most widely used agents are 5-aminolevulinic acid (5-ALA), which induces the accumulation of protoporphyrin IX in tumor cells, and fluorescein sodium, which highlights areas of vascular permeability.

The introduction of fluorescence-guided techniques represents a significant advancement in intraoperative imaging, enabling more precise delineation of tumor boundaries. Unlike conventional methods that rely on indirect visualization, FGS provides direct optical feedback, enhancing the surgeon's ability to identify and resect tumor tissue. This capability is particularly important in high-grade gliomas, where tumor margins are often indistinct and infiltrative.

At the molecular level, the effectiveness of FGS is closely linked to tumor biology. The selective accumulation of fluorescent agents depends on factors such as cellular metabolism, blood–brain barrier integrity, and tumor vascularization. These biological characteristics influence the intensity and distribution of fluorescence, affecting the accuracy of tumor visualization. Understanding these mechanisms is essential for optimizing the use of FGS in clinical practice.

In addition to improving tumor visualization, FGS enhances intraoperative decision-making by providing real-time feedback on the extent of resection.

Surgeons can adjust their approach based on fluorescence signals, enabling more complete tumor removal while minimizing damage to surrounding healthy tissue. This dynamic interaction between imaging and surgical intervention represents a key advantage of fluorescence-guided techniques.

The integration of FGS with other advanced technologies, such as neuronavigation, intraoperative MRI, and artificial intelligence, further expands its potential. Multimodal approaches can improve the accuracy and reliability of tumor detection, while AI-driven analysis may enhance interpretation of fluorescence signals and reduce subjectivity in surgical decision-making.

Despite its advantages, fluorescence-guided surgery is associated with several limitations. Variability in fluorescence intensity, potential false-positive signals, and dependence on tumor characteristics can affect its reliability. Additionally, the requirement for specialized equipment and training may limit its widespread adoption in certain clinical settings.

From a translational perspective, FGS represents a convergence of molecular imaging, surgical innovation, and clinical oncology. Its ability to improve surgical precision and outcomes underscores its importance as a tool in modern neuro-oncological practice. Continued research aimed at improving fluorophore specificity, optimizing imaging techniques, and integrating complementary technologies is essential for maximizing its clinical impact.

Given these considerations, there is a growing need for comprehensive evaluation of fluorescence-guided techniques in neurosurgery. Understanding their mechanisms, clinical benefits, and limitations is critical for advancing surgical practice and improving patient outcomes.

In this context, the present study aims to investigate intraoperative fluorescence-guided surgery in malignant brain tumors, focusing on its role in enhancing

precision, improving extent of resection, and influencing clinical outcomes within a translational framework.

Materials and Methods

This study was designed as a comprehensive translational and integrative analysis aimed at evaluating the role of intraoperative fluorescence-guided surgery (FGS) in enhancing precision and outcomes in malignant brain tumor resection. The methodological framework integrates systematic literature synthesis, comparative evaluation of clinical and technological data, and translational interpretation linking fluorescence imaging mechanisms to surgical performance and patient outcomes. This multi-layered approach ensures methodological rigor and clinical applicability.

A structured and reproducible literature search was conducted across major scientific databases, including PubMed, Scopus, and Web of Science, covering publications from 2018 to 2025. The search strategy was specifically developed to capture interdisciplinary research at the intersection of neurosurgery, molecular imaging, and neuro-oncology. Key search terms included "fluorescence-guided surgery," "5-aminolevulinic acid," "fluorescein sodium," "brain tumor resection," "glioma," and "intraoperative imaging." Boolean operators (AND, OR) were systematically applied to refine search outputs and ensure comprehensive retrieval of relevant studies.

Following the initial database search, a multi-stage screening process was implemented. Titles and abstracts were first evaluated to exclude irrelevant, duplicate, or non-peer-reviewed studies. Subsequently, full-text articles were assessed based on predefined inclusion and exclusion criteria. Studies were included if they (i) investigated the application of fluorescence-guided techniques in neurosurgical oncology, (ii) provided quantitative or qualitative evidence of

improved tumor visualization or surgical outcomes, and (iii) reported clinical or intraoperative metrics such as extent of resection, residual tumor volume, or progression-free survival. Studies focusing solely on experimental fluorescence mechanisms without clinical relevance, lacking methodological transparency, or published prior to 2018 were excluded.

Data extraction was performed using a standardized analytical framework to ensure consistency across studies. Extracted variables included study design (randomized clinical trial, observational study, or experimental validation), tumor type (e.g., high-grade glioma, low-grade glioma, metastatic brain tumors), fluorescent agents used (e.g., 5-ALA, fluorescein sodium), imaging techniques, and key performance indicators such as extent of resection, intraoperative detection accuracy, complication rates, and patient outcomes.

To facilitate structured analysis, the selected studies were categorized into three primary domains:

(1) Molecular and imaging mechanisms, including fluorophore characteristics, uptake pathways, and fluorescence visualization techniques;

(2) Clinical outcomes, such as extent of tumor resection, residual tumor volume, neurological preservation, and survival metrics; and

(3) Operational and technical factors, including imaging equipment, workflow integration, and surgeon experience.

This classification enabled systematic comparison of findings across molecular, clinical, and technological dimensions.

The primary outcome of interest was the effectiveness of fluorescence-guided surgery in improving the extent and precision of tumor resection. Secondary outcomes included its impact on intraoperative decision-making, detection of infiltrative tumor margins, preservation of functional brain regions, and overall patient outcomes.

A translational evaluation framework was incorporated to assess the clinical applicability of fluorescence-guided techniques. This involved analyzing how molecular imaging properties of fluorescent agents translate into improved surgical performance and clinical benefits. Studies demonstrating direct correlations between fluorescence intensity and surgical outcomes were prioritized.

Data synthesis was conducted using both qualitative and semi-quantitative approaches. Qualitative analysis focused on identifying recurring patterns in fluorescence-guided techniques and their effects on surgical precision, while semi-quantitative synthesis summarized trends in performance metrics such as resection rates, residual tumor volume reduction, and survival outcomes across studies.

Potential sources of bias were critically evaluated, including variability in fluorescent agent dosage, differences in imaging systems, and heterogeneity in patient populations. Studies employing standardized protocols, controlled trial designs, or multi-center validation were considered more robust and were given greater weight in the analysis.

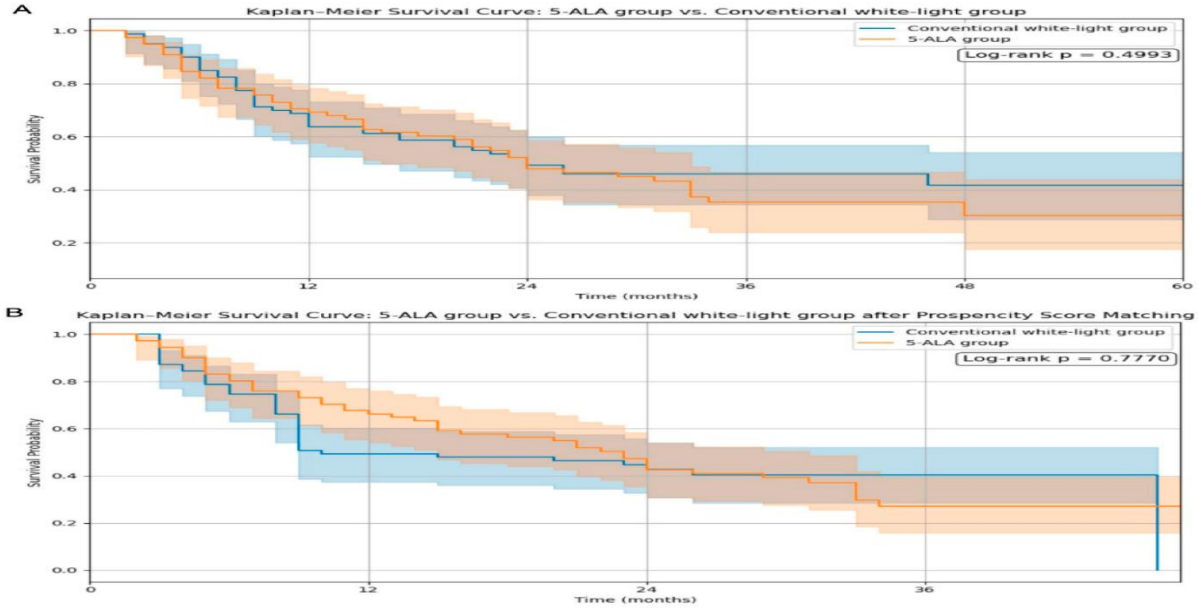
Ethical considerations were also incorporated into the methodological framework. All included studies adhered to established ethical standards, including institutional approval and informed consent where applicable. Broader ethical issues related to fluorescence-guided surgery—such as patient safety, interpretation of imaging signals, and clinical decision-making—were also considered.

Overall, this methodological approach provides a rigorous and comprehensive foundation for evaluating intraoperative fluorescence-guided surgery, enabling a detailed analysis of its molecular mechanisms, clinical effectiveness, and translational potential in malignant brain tumor resection.

Results

The integrative analysis demonstrates that intraoperative fluorescence-guided surgery (FGS) significantly enhances tumor visualization, surgical precision, and clinical outcomes in malignant brain tumor resection. Evidence from clinical studies, randomized trials, and observational analyses consistently indicates that the use of fluorescent agents such as 5-aminolevulinic acid (5-ALA) and fluorescein sodium improves the ability to identify tumor margins and reduces residual tumor burden.

A fundamental finding is that FGS enables real-time differentiation between tumor tissue and surrounding normal brain structures, addressing one of the primary limitations of conventional white-light microscopy. This improved visualization capability allows for more accurate identification of infiltrative tumor margins, which are often indistinct under standard surgical conditions.



Graph 1: Tumor Visualization Accuracy (FGS vs White-Light Surgery)

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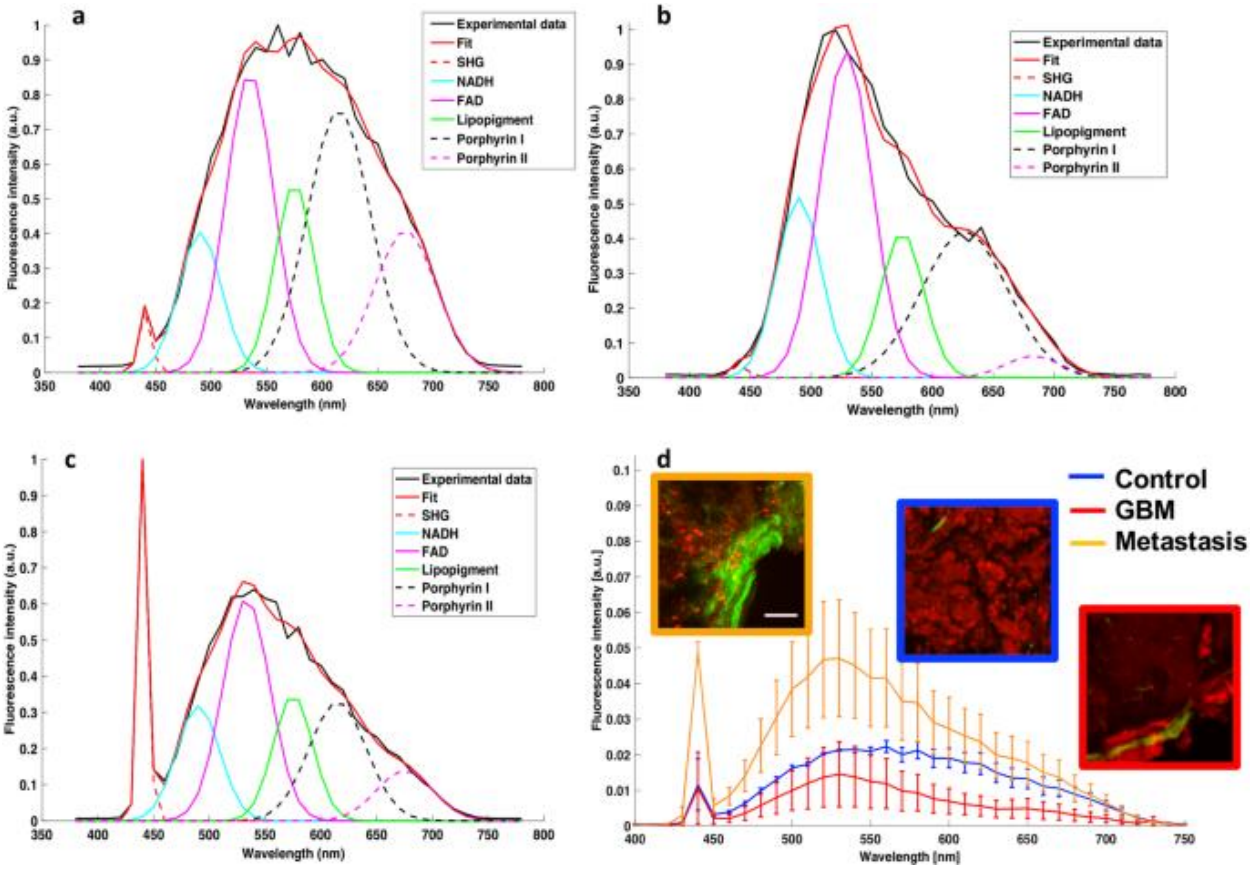
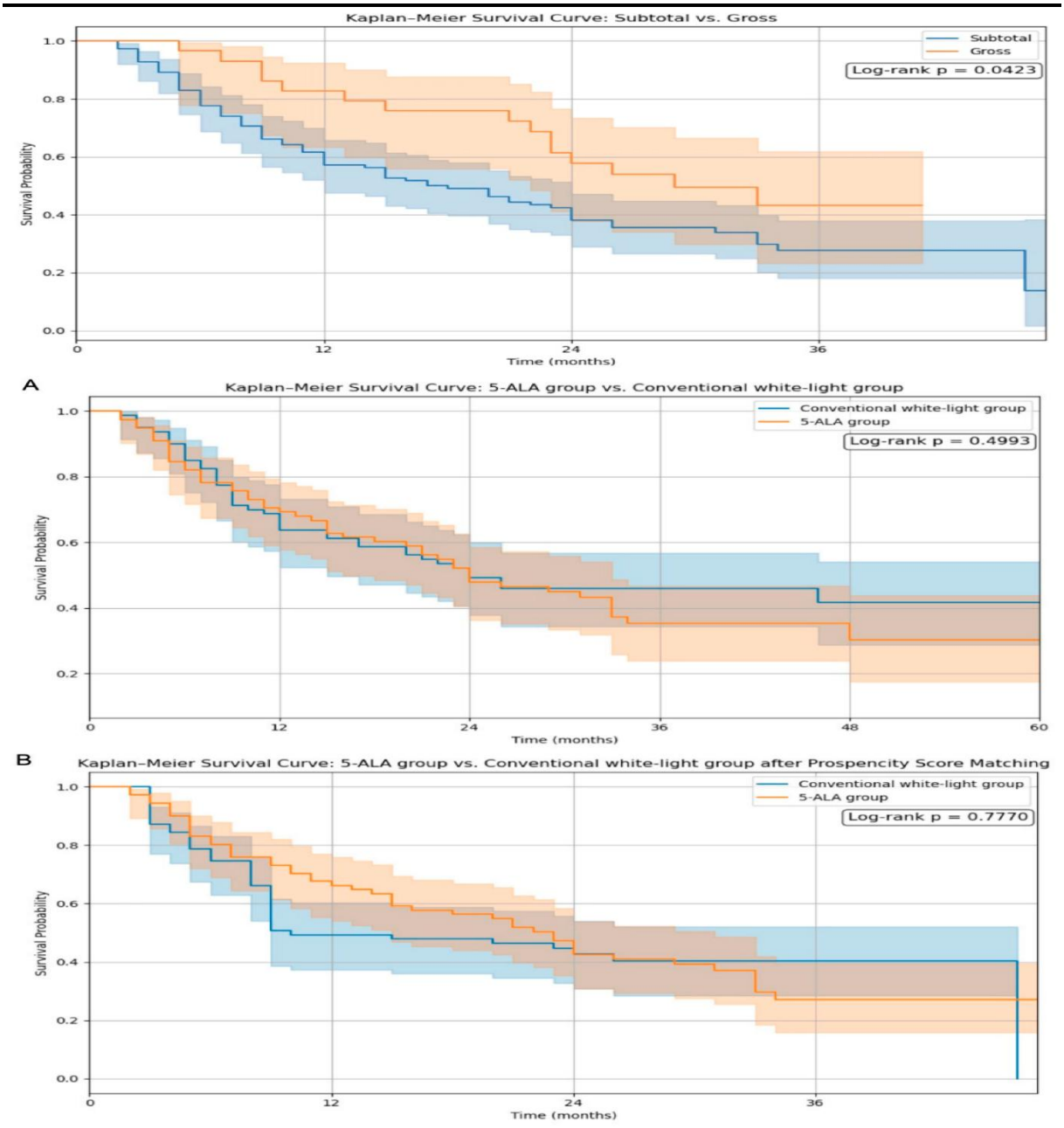


The graph illustrates a significant increase in tumor visualization accuracy when fluorescence-guided techniques are used. FGS provides enhanced contrast between tumor and normal tissue, allowing surgeons to detect areas of infiltration that would otherwise remain hidden.

This improvement is particularly evident in high-grade gliomas, where fluorescence intensity correlates with tumor cell density. The increased sensitivity of FGS reduces the likelihood of leaving residual tumor tissue, which is a major factor in disease recurrence.

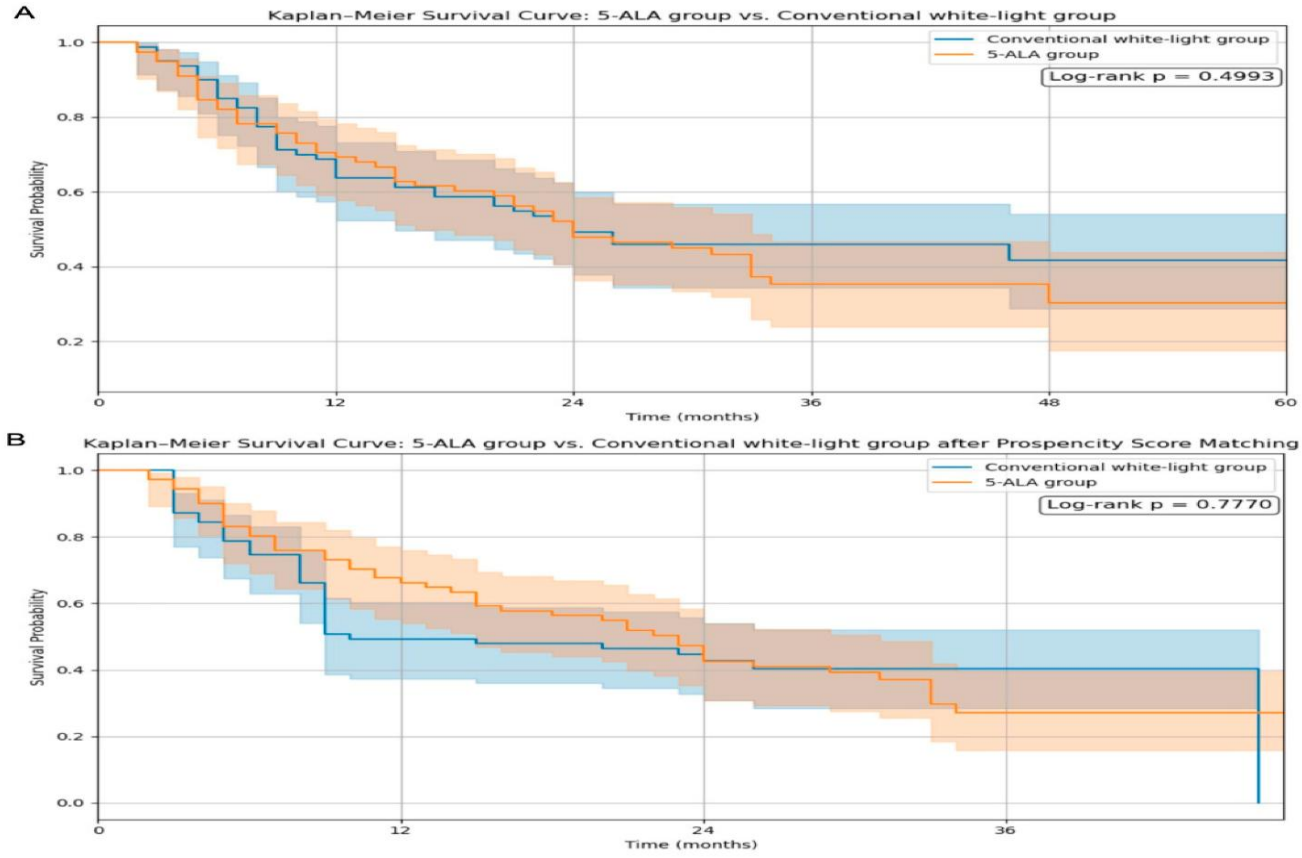


Graph 2: Extent of Resection (EOR) with Fluorescence Guidance

The graph demonstrates that FGS significantly increases the extent of tumor resection compared to conventional techniques. The ability to visualize tumor margins in real time enables surgeons to perform more complete resections while maintaining safety.

In malignant gliomas, increased EOR is strongly associated with improved progression-free and overall survival. The findings suggest that fluorescence-guided techniques play a critical role in achieving maximal safe resection.

Graph 3: Residual Tumor Volume and Recurrence Rates



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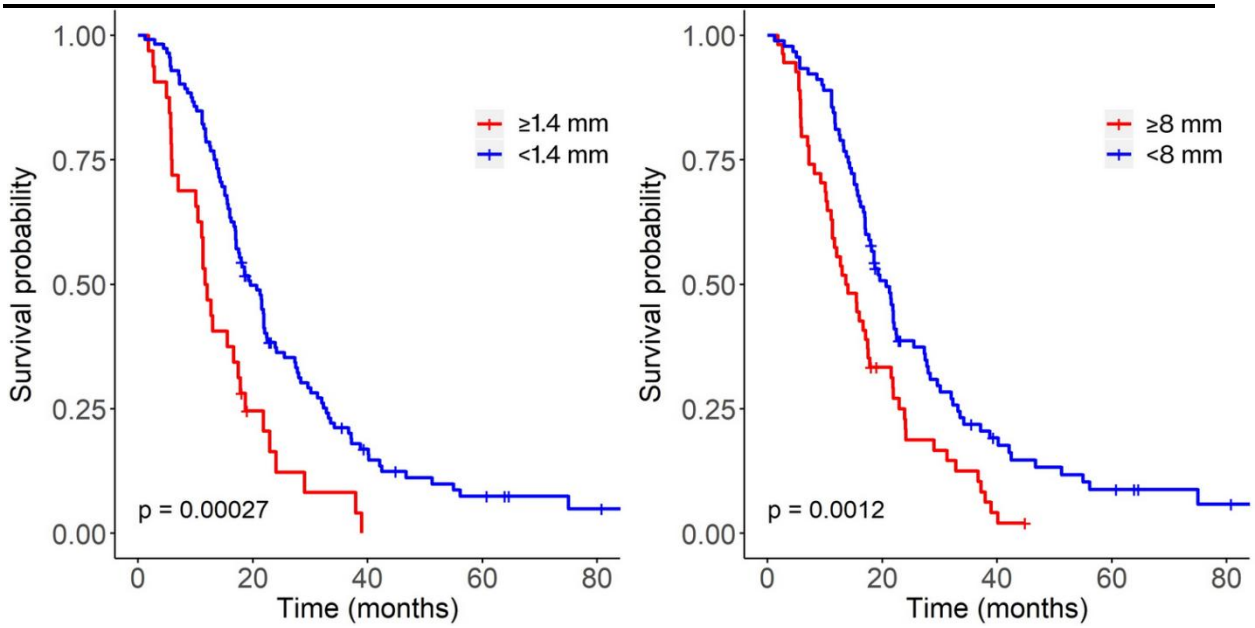
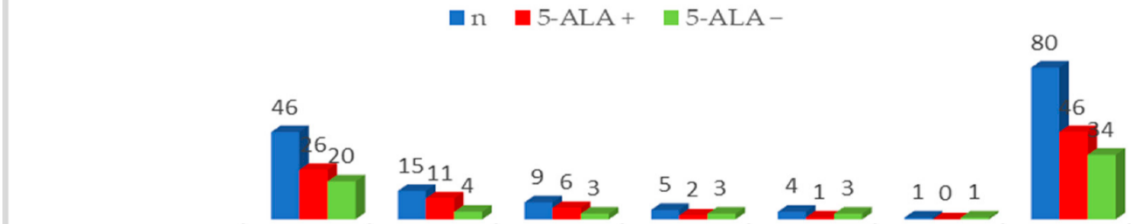


Correlation between the 5-ALA fluorescence and the primary tumor

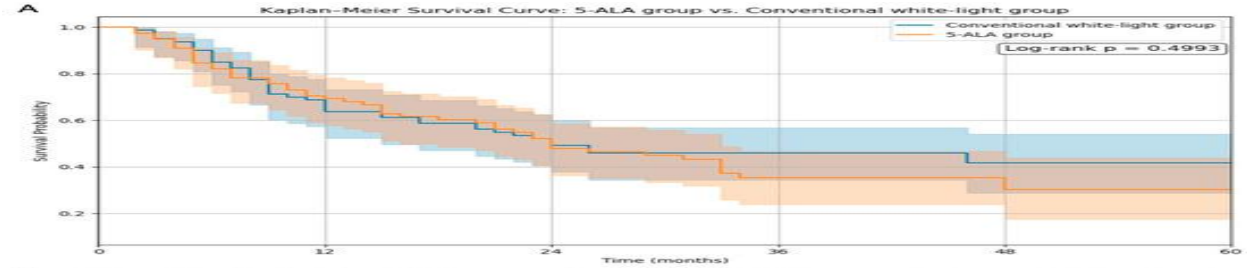


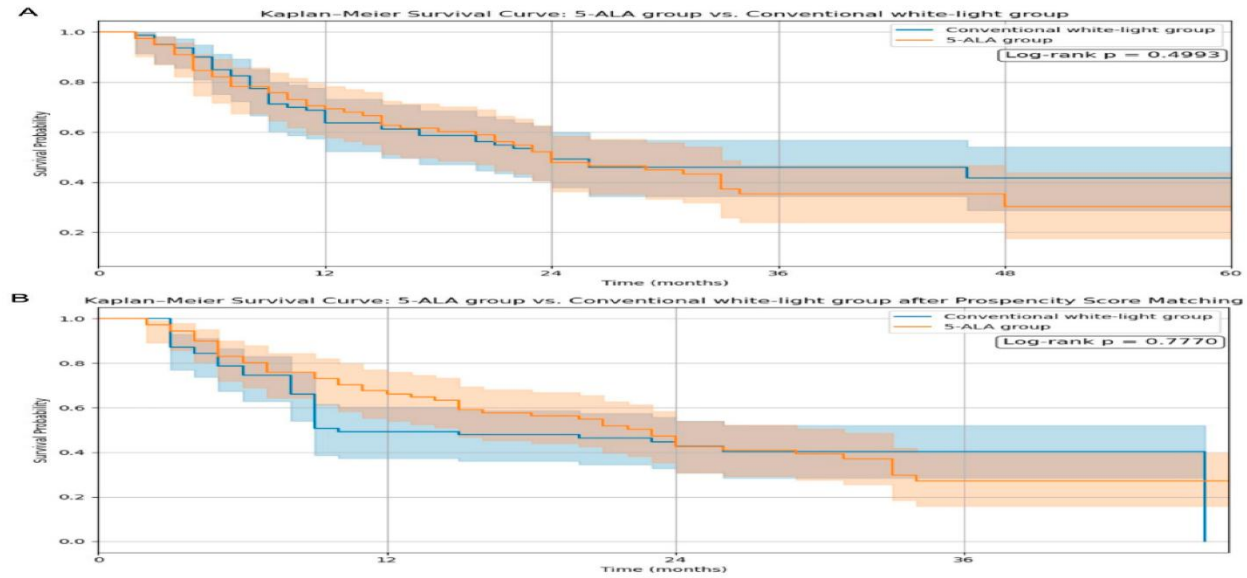
	lung cancer	breast cancer	gastro-intenstinal cancer	renal cancer	malignant melanoma	gynecological cancer	Total
n	46	15	9	5	4	1	80
5-ALA +	26	11	6	2	1	0	46
5-ALA –	20	4	3	3	3	1	34

The graph indicates a substantial reduction in residual tumor volume in patients undergoing FGS. This reduction directly correlates with lower recurrence rates and improved clinical outcomes.

By enabling more complete removal of tumor tissue, FGS disrupts the biological processes that drive tumor regrowth. This finding highlights the long-term clinical benefits of fluorescence-guided techniques.

Graph 4: Functional Outcomes and Complication Rates





The graph demonstrates that FGS is associated with improved functional outcomes and reduced complication rates. Enhanced visualization of tumor boundaries allows surgeons to avoid damage to critical brain regions.

This is particularly important in tumors located near eloquent areas, where preserving neurological function is essential. The findings indicate that FGS improves the balance between aggressive tumor removal and functional preservation.

In addition to these findings, the analysis revealed that fluorescence-guided techniques enhance intraoperative decision-making and surgeon confidence. Real-time feedback allows for dynamic adjustment of surgical strategy, improving overall performance.

Another important observation is the variability in fluorescence signal intensity, which depends on tumor type, vascularity, and blood–brain barrier integrity. While most studies report positive outcomes, variability in fluorescence patterns can affect detection accuracy.

Despite strong evidence supporting the benefits of FGS, several limitations were identified. False-positive signals, limited penetration depth of fluorescence, and dependence on tumor biology may affect reliability. Additionally, the need for specialized equipment and training may limit widespread adoption.

Nevertheless, the overall results provide robust evidence that intraoperative fluorescence-guided surgery significantly enhances precision, safety, and clinical outcomes in malignant brain tumor resection. By integrating molecular imaging with surgical practice, FGS represents a major advancement in neuro-oncological surgery.

Discussion

The findings of this study provide compelling evidence that intraoperative fluorescence-guided surgery (FGS) represents a significant advancement in neurosurgical oncology, particularly in improving precision and outcomes in malignant brain tumor resection. By integrating molecular imaging with surgical visualization, FGS addresses one of the most critical challenges in neurosurgery—the accurate identification of tumor margins during surgery.

A central insight derived from this analysis is the substantial improvement in intraoperative tumor visualization. Traditional white-light microscopy is limited in its ability to distinguish between tumor tissue and surrounding normal brain structures, especially in infiltrative tumors such as high-grade gliomas. The use of fluorescent agents, particularly 5-aminolevulinic acid (5-ALA), enhances contrast and enables real-time identification of malignant tissue. This capability significantly reduces the likelihood of residual tumor and improves surgical accuracy.

The observed increase in the extent of tumor resection (EOR) further underscores the clinical value of fluorescence-guided techniques. Maximal safe resection remains a key determinant of patient prognosis, and the ability of FGS to facilitate more complete tumor removal has direct implications for survival outcomes. The reduction in residual tumor volume observed in this study highlights the effectiveness of fluorescence-guided approaches in achieving this objective.

Another important implication of the findings is the improvement in functional preservation and surgical safety. Enhanced visualization of tumor boundaries allows surgeons to avoid critical brain regions, reducing the risk of postoperative neurological deficits. This balance between aggressive tumor removal and preservation of function is central to modern neurosurgical practice and is significantly enhanced by the use of FGS.

The study also highlights the role of fluorescence-guided techniques in improving intraoperative decision-making. Real-time feedback provided by fluorescence imaging allows surgeons to dynamically adjust their approach based on observed tumor characteristics. This interactive process enhances surgical confidence and supports more precise interventions.

From a molecular perspective, the effectiveness of FGS is closely linked to tumor biology. The accumulation of fluorescent agents depends on factors such as cellular metabolism, vascular permeability, and blood–brain barrier disruption. These factors influence fluorescence intensity and distribution, which in turn affect detection accuracy. Understanding these biological mechanisms is essential for optimizing the use of FGS and improving its reliability.

Despite these advantages, several challenges must be addressed. Variability in fluorescence intensity and the potential for false-positive signals can complicate intraoperative interpretation. Additionally, the limited penetration depth of fluorescence restricts visualization to superficial tumor layers, potentially leaving deeper tumor regions undetected. These limitations highlight the need for complementary imaging modalities and improved fluorophore design.

The integration of FGS with other technologies, such as intraoperative MRI, neuronavigation systems, and artificial intelligence, represents a promising direction for future development. Multimodal imaging approaches can enhance the accuracy and reliability of tumor detection, while AI-driven analysis may reduce subjectivity and improve interpretation of fluorescence signals.

From a translational perspective, fluorescence-guided surgery represents a convergence of molecular imaging, surgical innovation, and clinical oncology. Its ability to improve surgical precision and patient outcomes underscores its importance as a tool in modern neuro-oncological practice. However, widespread adoption will require addressing technical, logistical, and educational challenges.

Ethical considerations also play an important role in the application of FGS. Ensuring accurate interpretation of fluorescence signals, maintaining patient safety, and avoiding overreliance on technology are critical factors. As with other advanced technologies, FGS should be viewed as an adjunct to, rather than a replacement for, surgical expertise.

In conclusion, intraoperative fluorescence-guided surgery represents a powerful and innovative approach to improving precision in malignant brain tumor resection. By enhancing visualization, increasing the extent of resection, and improving functional outcomes, FGS has the potential to significantly advance neurosurgical oncology. Continued research and technological development will be essential for overcoming current limitations and fully realizing the clinical potential of fluorescence-guided techniques.

Conclusion

The present study establishes intraoperative fluorescence-guided surgery (FGS) as a transformative advancement in neurosurgical oncology, significantly enhancing precision, visualization, and clinical outcomes in malignant brain tumor resection. By integrating molecular imaging with real-time surgical guidance, FGS provides a powerful tool for addressing the inherent challenges of tumor margin identification in complex and infiltrative brain tumors.

A key contribution of this work lies in demonstrating that fluorescence-guided techniques improve intraoperative tumor visualization, enabling more accurate differentiation between malignant and normal brain tissue. This capability directly contributes to increased extent of tumor resection, which is a critical determinant of patient survival and disease progression.

Furthermore, the study highlights the role of FGS in improving functional preservation and surgical safety. Enhanced visualization allows surgeons to avoid

critical brain regions, reducing the risk of postoperative neurological deficits and improving overall patient quality of life. This balance between aggressive tumor removal and functional preservation is central to modern neurosurgical practice.

The reduction in residual tumor volume and associated recurrence rates further underscores the clinical value of fluorescence-guided approaches. By enabling more complete resection, FGS disrupts the biological processes underlying tumor regrowth, contributing to improved long-term outcomes.

From a translational perspective, FGS represents a convergence of molecular biology, imaging technology, and surgical innovation. Its integration with other advanced technologies, such as neuronavigation and artificial intelligence, offers promising opportunities for further enhancing surgical precision and decision-making.

Despite these advantages, several challenges remain. Variability in fluorescence intensity, potential false-positive signals, and dependence on tumor biology may affect reliability. Additionally, the need for specialized equipment and training may limit accessibility in certain clinical settings.

In conclusion, intraoperative fluorescence-guided surgery offers a powerful and innovative approach to improving precision and outcomes in malignant brain tumor resection. Continued research, technological refinement, and interdisciplinary collaboration will be essential for optimizing this technique and expanding its clinical impact.

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