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FLUORESCENT DYES IN MODERN NEUROSURGERY: TECHNOLOGICAL ADVANCES AND CLINICAL TRANSLATION

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ABSTRACT

Introduction and purpose: Over recent decades, neurosurgery has undergone major technological advancement toward increased precision and safety, including the development of fluorescence-guided surgery. Conventional white-light microscopy has limited ability to distinguish pathological from normal tissue or to assess vascular flow in real time. Fluorescent dyes enhance intraoperative visualization and support surgical decision-making. This review aims to summarize the properties, mechanisms of action, clinical applications, and safety profiles of fluorescent dyes used in contemporary neurosurgery.

Materials and methods: A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar (2000–2025) using keywords including fluorescence-guided surgery, fluorescent dyes, neurosurgery, 5-aminolevulinic acid, fluorescein, indocyanine green, ICG angiography, glioma surgery, brain tumor resection, aneurysm clipping, vascular neurosurgery, near-infrared imaging, intraoperative imaging, and optical navigation. Eligible studies were qualitatively analyzed and synthesized narratively.

Conclusion: Fluorescent dyes have become integral tools in modern neurosurgery, enhancing visualization of tumors and vascular structures beyond conventional white-light microscopy. 5-ALA, fluorescein, and indocyanine green each provide unique mechanisms of fluorescence, supporting tailored intraoperative decision-making. Overall, these agents are well-tolerated, with severe adverse events being rare. Future advancements are likely to focus on integrating fluorescence with machine learning, augmented reality, quantitative assessment, and novel imaging technologies, improving precision and objectivity. While their current clinical position is stable, ongoing technological evolution may expand applications and refine existing techniques, maintaining fluorescence-guided surgery as a cornerstone of precision neurosurgical practice.

KEYWORDS

Fluorescence-Guided Surgery, 5-Aminolevulinic Acid, Fluorescein, Indocyanine Green, Neurosurgery, Intraoperative Imaging

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Introduction

Over the past decades, medicine, including neurosurgery, has undergone a profound technological transformation driven by advances in imaging, navigation, intraoperative visualization, or artificial intelligence development [1–5].

From the introduction of the operative microscope to the integration of neuronavigation systems and intraoperative MRI, the discipline has progressively moved toward greater precision and safety. Surgical decision-making under conventional white-light microscopy ultimately relies on the surgeon's visual perception, which is inherently limited in its ability to differentiate pathological tissue from normal brain parenchyma or to provide real-time functional information about vascular flow. The intrinsic constraints of the human eye, particularly in detecting subtle differences in tissue characteristics, may compromise the completeness of resection or the accuracy of vascular assessment.

In response to these challenges, fluorescence-guided neurosurgery (FGS) has emerged as a powerful optical adjunct that enhances intraoperative visualization beyond the capabilities of white light alone. By exploiting the selective accumulation or intravascular distribution of fluorescent agents, this technique enables improved delineation of pathological tissue, real-time assessment of blood flow, enhanced identification of critical anatomical structures, and potentially greater extent of resection while preserving functional tissue.

Fluorescence imaging is based on the principle that certain molecules absorb light at a specific wavelength and subsequently emit light at a longer wavelength [6]. When combined with dedicated optical filters and camera systems integrated into surgical microscopes, this phenomenon enables selective

visualization of tissues, vessels, or metabolic processes that are otherwise indistinguishable under standard illumination [7]. This capability is particularly critical in neurosurgery, where operative interventions are performed within the highly complex and delicate structures of the central nervous system. The brain and surrounding intracranial anatomy tolerate minimal mechanical or ischemic insult, and even subtle inaccuracies may result in significant neurological morbidity. By augmenting visual discrimination at the microscopic level, fluorescence-guided techniques contribute to safer dissection planes, more accurate identification of pathological tissue, and improved preservation of eloquent structures, ultimately reducing the risk of complications while maximizing surgical efficacy.

The aim of this review is to provide an in-depth analysis of fluorescent dyes used in contemporary neurosurgery, including their physicochemical characteristics, mechanisms of action, and established clinical applications in neuro-oncology and vascular surgery. Additionally, we discuss safety considerations, technological constraints, and emerging innovations that may shape the next generation of fluorescence-guided operative techniques. By situating fluorescence imaging within the broader framework of surgical innovation and real-time decision support, this article seeks to clarify its current role and future potential in precision neurosurgery.

Methodology

A comprehensive literature search was conducted to identify relevant studies addressing the use of fluorescent dyes in neurosurgery. Electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were systematically searched. The time frame was selected to capture both the early clinical implementation of fluorescence-guided techniques and the most recent technological advancements. The search strategy incorporated combinations of the following keywords: *fluorescence-guided surgery*, *fluorescent dyes*, *neurosurgery*, *5-aminolevulinic acid*, *fluorescein*, *indocyanine green*, *ICG angiography*, *glioma surgery*, *brain tumor resection*, *aneurysm clipping*, *vascular neurosurgery*, *near-infrared imaging*, *intraoperative imaging*, and *optical navigation*. Boolean operators ("AND," "OR") were applied to refine the search and ensure comprehensive coverage of relevant topics. Eligible publications included original research articles, randomized controlled trials, prospective and retrospective cohort studies, systematic reviews, and meta-analyses. To ensure completeness, the reference lists of selected articles were manually screened for additional relevant studies not captured in the primary database search. Recent publications addressing emerging near-infrared probes, quantitative fluorescence techniques, and integration with artificial intelligence-based intraoperative systems were also included.

The collected literature was qualitatively analyzed with respect to mechanisms of action, physicochemical properties, clinical indications, surgical outcomes, safety profiles, and technological limitations. Given the heterogeneity of study designs and outcome measures, a formal meta-analysis was not performed. Instead, findings are presented in a narrative synthesis structured according to clinical application and dye characteristics.

Principles of fluorescence in neurosurgery

Fluorescence is a photophysical phenomenon based on a two-stage process involving excitation and emission. During excitation, a fluorophore absorbs light energy in the form of a photon, resulting in the transition of an electron from the ground state to a higher-energy excited state. This excited state is inherently unstable and persists only for a few nanoseconds. As the molecule relaxes back toward the ground state, part of the absorbed energy is released as emitted light. Because some energy is dissipated through non-radiative processes such as vibrational relaxation, the emitted photon possesses lower energy than the absorbed photon. Since photon energy is inversely proportional to wavelength, the emitted light has a longer wavelength than the excitation light. This phenomenon, known as the *Stokes shift*, forms the optical basis for fluorescence imaging. The separation between excitation and emission wavelengths allows selective detection of fluorescent signals using optical filters integrated into surgical microscopes [8].

These molecular transitions are commonly illustrated using Jablonski energy diagrams, which depict electronic states and the pathways of excitation, relaxation, and emission. After photon absorption, the excited molecule may return to the ground state through fluorescence emission or via alternative non-radiative pathways. In contrast to phosphorescence, fluorescence occurs rapidly and ceases almost immediately when excitation light is removed. Unlike bioluminescence, fluorescence requires continuous external illumination [9].

In conventional fluorescence imaging, excitation occurs through the absorption of a single photon, and each absorbed photon results in the emission of one lower-energy photon. However, under specific conditions,

a fluorophore can simultaneously absorb two or more lower-energy photons whose combined energy equals that required for excitation. In this multiphoton process, each absorbed photon has less energy than the emitted photon, enabling longer-wavelength (e.g., red) excitation to produce shorter-wavelength emission [8–12].

This principle underlies two-photon microscopy, which requires extremely high photon density to ensure near-simultaneous photon absorption. Such conditions are achieved using high-powered, pulsed lasers that concentrate photons temporally and spatially. The advantage of longer-wavelength excitation lies in its improved tissue penetration and reduced scattering compared with shorter-wavelength (blue) light. Additionally, lower-energy red light is less likely to induce phototoxic cellular damage [8–12].

In biological tissues, including the brain, scattering and absorption significantly influence imaging depth and resolution. Shorter wavelengths are more strongly scattered and absorbed by hemoglobin and other chromophores, limiting penetration depth. Therefore, near-infrared and red-spectrum excitation are advantageous for deeper tissue imaging and improved signal-to-background ratios [8–12].

In conventional optical microscopy, spatial resolution is constrained by the diffraction limit of light. With one-photon confocal imaging, typical lateral resolution approaches approximately 200 nm, while axial resolution is approximately 500 nm. These limits are determined by excitation wavelength and optical system characteristics.

Super-resolution techniques have been developed to overcome these constraints. One such approach, stimulated emission depletion (STED) microscopy, improves spatial resolution by selectively suppressing fluorescence in the periphery of the excitation spot. This is achieved by overlapping the primary excitation beam with a second, longer-wavelength laser shaped as a ring or "donut." The secondary laser forces excited fluorophores back to the ground state through stimulated emission before they can fluoresce, effectively reducing the size of the active fluorescent region. This controlled quenching process exploits the same electronic transitions depicted in Jablonski diagrams and enables resolution improvements beyond the classical diffraction limit [13].

Although advanced multiphoton and super-resolution techniques are primarily used in experimental or research settings rather than routine neurosurgery, the fundamental optical principles governing these technologies are directly relevant to fluorescence-guided surgery. Intraoperative imaging relies on controlled excitation, spectral separation, and efficient detection of emitted light within scattering biological tissue.

Understanding excitation wavelength, emission spectra, photostability, tissue penetration, and signal-to-background ratio is critical for optimizing clinical fluorescence applications.

5-aminolevulinic acid (5-ALA)

One of the main fluorophores that facilitates FGS in neurosurgical oncology is 5-aminolevulinic acid (5-ALA), widely used in intracranial malignancies, including gliomas, brain metastases, meningiomas, and spinal tumors. In high-grade gliomas (WHO grades III–IV), 5-ALA demonstrates strong accuracy in identifying malignant tissue. Its use in fluorescence-guided surgery has been linked to more complete tumor removal, clearer resection margins, and improved patient survival. Beyond neuro-oncology, 5-ALA is increasingly being investigated in other types of cancer, such as urothelial, gastric, prostate, and ovarian malignancies [14].

Unlike vascular dyes, 5-ALA does not fluoresce directly; it serves as a precursor in the heme biosynthesis pathway. 5-ALA is an endogenous compound naturally formed as part of the heme biosynthesis pathway. When administered orally as an exogenous prodrug, it exhibits remarkable ability to cross the blood–brain barrier and penetrate tumor tissue in the brain. To date, no other orally available agent has demonstrated the capacity to selectively accumulate within both the main tumor mass and the infiltrating malignant cells surrounding it. Once internalized by glioma cells, 5-ALA is converted into the fluorescent molecule protoporphyrin IX (PpIX). The accumulation of PpIX in tumor cells enables visualization of malignant tissue as violet-red fluorescence under blue light illumination at 405 nm. The selective retention of 5-ALA in glioma cells is thought to result from reduced activity of ferrochelatase, the enzyme responsible for incorporating iron into heme, and facilitated uptake via the ATP-binding cassette transporter ABCB6. Additional factors influencing the intensity of 5-ALA–induced fluorescence include tumor cell density, proliferative activity, neovascularization, and the permeability of the blood–brain barrier [15].

PpIX fluorescence has been established as a highly sensitive tool for intraoperative identification of high-grade glioma tissue. However, recent analyses have highlighted that fluorescence is not exclusively restricted to neoplastic cells. Single-cell sequencing using SCOPE-seq2 on human glioblastoma specimens demonstrated that nonneoplastic cells can also exhibit fluorescence, either through direct uptake of 5-ALA or

via PpIX transferred from surrounding tumor cells. Complementary studies in acute slice cultures from mouse glioma models confirmed that 5-ALA preferentially labels tumor tissue over nonneoplastic brain tissue, including tumor margins, and that this selective contrast is largely independent of blood–brain barrier disruption [16].

Clinical studies support the high diagnostic sensitivity of 5-ALA FGS. In a cohort of sixty-nine patients providing 275 tumor samples, PpIX fluorescence exhibited a sensitivity of 96.5%, a positive predictive value (PPV) of 95.4%, and overall diagnostic accuracy of 92.4%. Specificity, however, was relatively low at 29.4%, reflecting the possibility of fluorescence in nonneoplastic cells at the tumor periphery. Complete resection of contrast-enhancing tumor was achieved in 51.9% of cases, with smaller preoperative tumor volume and the use of intraoperative MRI predicting lower residual tumor burden. Postoperative assessments of the Karnofsky Performance Status (KPS) showed transient reductions at 48 hours and 2 weeks, but no significant differences compared with preoperative scores at 6 weeks, indicating that 5-ALA FGS does not produce long-term functional deficits when performed by trained surgeons [17].

The safety profile of 5-ALA is favorable. Drug-related adverse events occurred in 22% of patients, and serious adverse events potentially related to intraoperative neurological injury were observed in 4.3% of cases. Mortality was unrelated to FGS. Phototoxicity remains a notable consideration, requiring patients to avoid direct sunlight and intense indoor lighting for approximately 24 hours post-administration [18,19].

Additional factors influencing fluorescence intensity include tumor cell density, proliferative activity, neovascularization, and local blood–brain barrier permeability. Fluorescence can also be attenuated by coagulation or intraoperative bleeding, and its interpretation remains primarily qualitative, although emerging techniques in quantitative fluorescence assessment, including spectroscopic probes and camera-based intensity mapping, may improve objectivity in the future [17].

Despite these limitations, 5-ALA FGS remains the most clinically validated metabolic fluorophore for high-grade glioma surgery. Its high sensitivity and PPV enable accurate intraoperative delineation of tumor tissue, supporting maximal safe resection. Continued integration with advanced technologies, such as hand-held fiber-optic probes, augmented reality, three-dimensional exoscopes, and machine-learning–assisted visualization, is likely to further enhance the precision and clinical utility of 5-ALA in neurosurgical oncology, particularly for low-grade gliomas and recurrent tumors where its performance is currently less optimal [20,21].

Fluorescein

Despite neurosurgery, fluorescein is widely employed in standard ophthalmological practice, with applications spanning applanation tonometry, gonioscopy, and contact lens fitting, as well as in vascular imaging techniques such as retinal and iris angiography [22]. Its major neuro-oncological applications include fluorescence-guided resection of high-grade gliomas, delineation of brain metastases, identification of meningiomas, and assessment of spinal tumors. Additionally, fluorescein has been utilized intraoperatively for real-time evaluation of blood-brain barrier disruption and vascular perfusion, supporting surgical decision-making in complex cranial procedures [23,24].

Fluorescein sodium is a synthetic fluorescent dye that exhibits its characteristic green fluorescence due to a conjugated system of electrons, which allows the molecule to remain in an excited state for a prolonged period after absorption of light. When exposed to blue light in the range of 465–490 nm, fluorescein emits bright green fluorescence at approximately 520–530 nm, enabling real-time visualization of tissues [25].

In neurosurgical applications, the fluorescence of fluorescein primarily reflects areas of blood–brain barrier disruption rather than selective uptake by tumor cells. After intravenous administration, the negatively charged fluorescein molecules circulate in the plasma and extravasate into regions where the blood–brain barrier is compromised, such as contrast-enhancing gliomas, metastases, or other lesions with vascular permeability. Once in the tissue, fluorescein can interact electrostatically with hydrophilic components of cell membranes, enhancing its retention and brightness within the extracellular space [26,27].

The dye's physicochemical properties, including water solubility and rapid distribution, make it suitable for real-time intraoperative imaging. While often administered alone in neurosurgery, fluorescein's action in other settings can be potentiated by combination with agents such as local anesthetics, which stabilize cell membranes and reduce nerve excitability. In the surgical context, however, the primary mechanism remains fluorescence emission from extravasated dye in regions of blood–brain barrier compromise, providing surgeons with immediate visual cues for tumor margins or vascular structures [26,27].

Intravenous fluorescein has long been generally regarded as safe; concerns have been raised regarding potential cardiovascular effects following systemic administration. In a clinical series of 50 patients monitored

perioperatively, blood pressure measurements were recorded at five-minute intervals before and after fluorescein administration. Repeated-measures analysis demonstrated no statistically significant sustained or transient hemodynamic instability attributable to fluorescein. Minor adverse reactions were observed, including transient nausea without vomiting and moderate fluctuations in blood pressure. Sustained increases in blood pressure exceeding 10% of baseline values were noted in a subset of patients, while transient or sustained decreases of similar magnitude occurred in others. Importantly, hypotensive episodes responded to fluid resuscitation and did not require vasopressor support. These findings suggest that, although transient cardiovascular fluctuations may occur, clinically significant hemodynamic compromise is uncommon [28,29].

In contrast to 5-ALA, phototoxicity is not a typical adverse effect of fluorescein administration and occurs only rarely [30].

Beyond its systemic effects, recent investigations have highlighted photochemical properties of fluorescein that may have biological relevance. While fluorescein itself exhibits relatively low intrinsic toxicity, photoactivation can generate reactive molecular species, including singlet oxygen (^1O_2) and carbon monoxide (CO). In vitro studies using human hepatoblastoma (HepG2) cells demonstrated that irradiation of intracellular fluorescein significantly reduced cell viability in an oxygen-dependent manner. This reduction was accompanied by marked alterations in cellular metabolism, including decreased concentrations of Krebs cycle intermediates and evidence of cell cycle arrest. These findings indicate that fluorescein photochemistry can induce oxidative stress and metabolic disruption under experimental conditions [31].

Although the clinical relevance of these in vitro findings in neurosurgical settings remains uncertain, given the relatively controlled illumination parameters and short exposure times used intraoperatively, they suggest a theoretical mechanism that could contribute to rare adverse reactions. Notably, the generation of singlet oxygen and carbon monoxide may exert both cytotoxic and potentially therapeutic effects, raising the possibility that fluorescein photoreactivity could influence tumor microenvironments under specific conditions [31].

Taken together, available clinical data support a favorable safety profile for fluorescein sodium, particularly at contemporary low-dose regimens. Hemodynamic changes are generally mild and manageable, and severe systemic reactions remain rare. However, emerging evidence regarding fluorescein photochemistry underscores the importance of continued investigation into its biological interactions, especially as intraoperative illumination technologies evolve and exposure parameters become more standardized.

Indocyanine green (ICG)

Indocyanine green (ICG) is a tricarbocyanine dye that has been used in clinical medicine since 1956, when it received approval from the U.S. regulatory authorities for imaging of cardiac and hepatic circulation. Since then, it has become an established diagnostic agent across multiple medical specialties.

ICG is a water-soluble compound with a molecular weight of approximately 775 daltons. It is characterized by absorption in the near-infrared (NIR) spectrum, with peak absorption between 790 and 805 nm and a maximal emission around 835 nm. These spectral properties distinguish it from visible-spectrum fluorophores such as sodium fluorescein and confer several practical advantages [32,33].

Although indocyanine green emits only approximately 4% of the fluorescence intensity of sodium fluorescein, its near-infrared excitation and emission wavelengths allow superior tissue penetration. NIR light is less scattered and absorbed by biological chromophores, enabling visualization through ocular pigments, blood, and serous fluids. This property is particularly advantageous in imaging structures located beneath pigmented or vascularized tissues, such as the choroid in retinal diagnostics [32].

Clinically, indocyanine green angiography (ICGA) was initially established as an adjunct to intravenous fluorescein angiography in ophthalmology, particularly in the evaluation of retinal disorders with suspected choroidal involvement. Owing to its near-infrared (NIR) absorption and emission profile, ICG enables visualization of deeper vascular layers that remain partially obscured in visible-spectrum imaging. The ability of NIR light to penetrate ocular pigments, blood, and serous fluids underlies the diagnostic advantage of ICGA in choroidal pathology. Beyond ophthalmology, near-infrared imaging with indocyanine green has gained widespread application in general, visceral, reconstructive, and transplant surgery. While early implementations relied predominantly on qualitative visual assessment, recent studies have increasingly focused on quantitative fluorescence analysis. Systematic evaluations of quantitative ICG use demonstrate that the most common surgical fields include esophageal, reconstructive, and colorectal procedures, with principal clinical endpoints such as prediction of anastomotic leak, assessment of flap perfusion, and identification of anatomical structures. The most frequently analyzed quantitative parameter is fluorescence intensity over time, reflecting dynamic blood flow, followed by absolute fluorescence intensity and intensity-to-background ratios

for structural delineation. Importantly, the growing integration of robotic platforms and image-analysis algorithms suggests that objective fluorescence quantification may become increasingly standardized and clinically impactful [34].

In neurosurgery, ICG has been primarily adopted for intraoperative vascular imaging, particularly in aneurysm clipping, bypass surgery, and arteriovenous malformation resection. Similar to other surgical disciplines, its initial use was qualitative, based on real-time visual assessment of vessel patency and flow dynamics under the operating microscope. However, emerging approaches incorporate semi-quantitative and quantitative flow analysis derived from fluorescence intensity curves, enabling more objective evaluation of cerebral perfusion and bypass functionality. Given the critical dependence of neurosurgical outcomes on precise vascular assessment, the transition from purely visual interpretation to quantitative fluorescence metrics may represent an important step toward improved intraoperative decision-making [35.36,37].

ICG is generally regarded as a safe and well-tolerated fluorophore; however, adverse effects of it are less common compared to fluorescein. Large clinical series report a very low incidence of adverse events. In one cohort, mild adverse reactions occurred in 0.15% of patients, moderate reactions in 0.2%, and a severe reaction in 0.05%, with no reported deaths, showing the rarity of clinically significant complications [38].

Most reported adverse events are transient and include mild hypersensitivity reactions, flushing, nausea, or short-lived hemodynamic fluctuations. Severe anaphylactic reactions remain exceptional. Given that ICG contains iodine moieties, caution is traditionally advised in patients with iodine hypersensitivity, although cross-reactivity mechanisms remain incompletely defined [39].

Although ICG is cleared exclusively via hepatic uptake and biliary excretion, rather than renal elimination, concerns have been raised regarding its use in patients with advanced chronic kidney disease (CKD) and kidney transplant recipients. A recent scoping review evaluating patients with advanced CKD and renal allografts found no evidence of increased adverse events associated with ICG administration. Across the analyzed cohorts (including 250 transplant recipients and 74 CKD patients), no ICG-related adverse reactions were reported. Moreover, transplant function was preserved in 94% of patients following transplantation procedures in which ICG was used intraoperatively, and no increase in other complications attributable to ICG was observed. These findings support the notion that ICG is non-nephrotoxic and can be safely administered in patients with impaired renal function, provided standard precautions are observed [40].

Despite its well-established safety profile and intraoperative utility [41], indocyanine green presents several important limitations that preclude it from fully replacing conventional digital subtraction angiography (DSA). First, ICG imaging is inherently restricted to the surgical field visualized under the operating microscope. Only vessels directly exposed and illuminated can be assessed, which limits evaluation of deeper, obscured, or anatomically hidden vascular segments. In contrast, DSA provides comprehensive visualization of the entire cerebrovascular tree, including regions beyond the operative corridor [42]. Second, unlike DSA, ICG does not provide dynamic multi-phase angiographic information across the entire intracranial circulation, nor does it allow delayed imaging phases for detection of slow-filling residual aneurysms or distal embolic phenomena [43]. For these reasons, ICG videoangiography is best regarded as a complementary intraoperative tool rather than a definitive replacement for DSA, particularly in complex aneurysm surgery, bypass procedures, or cases with high risk of residual vascular pathology.

Comparison of fluorescent dyes in neurosurgery

Fluorescence-guided neurosurgery relies on the distinct optical and pharmacological properties of specific fluorophores to enhance intraoperative visualization of pathological tissue and critical structures. Among the most widely employed agents are **5-aminolevulinic acid (5-ALA)**, **fluorescein**, and **indocyanine green (ICG)**. Each dye offers unique advantages and limitations that influence their clinical application. A comparative summary of the characteristics, clinical applications, advantages, and limitations of the most commonly used fluorescent dyes in neurosurgery is presented in Table 1.

Table 1. Comparison of fluorescent dyes in neurosurgery. Created based on: [44].

Fluorophore	Characteristics	Applications in Neurosurgery	Advantages	Limitations / Safety
5 -ALA	Excitation: 375–440 nmEmission: 630–720 nm Administration: OralHalf-life: 1–3 h Latency period: 7–9 h	High-grade gliomas, Low-grade gliomas, Meningiomas, Brain metastases	- Most reliable fluorescence in high-grade gliomas- FDA approved for high-grade gliomas - Long fluorescence duration (hours) - Potential cytotoxic effects via photodynamic therapy	- Weak fluorescence in low-grade/recurrent tumors - Requires specialized blue-violet light filters - Photosensitivity post-administration
Fluorescein	Excitation: 460–500 nmEmission: 540–690 nm Administration: IV Half-life: 23.5 minLatency period: 2–4 h	Brain metastases, High-grade gliomas, Meningiomas	- Reliable fluorescence in metastases and dural invasion - Long fluorescence duration - Low cost	- Non-tumor-specific (accumulates in BBB disruption) - Possible false positives in edema/inflammation - Mild side effects: nausea, transient hypotension
ICG	Excitation: 750–800 nmEmission: 700–850 nm Administration: IV Half-life: 3–4 min Latency period: Seconds	AVMs, Aneurysms, Cavernous hemangiomas, Hemangioblastomas, High-grade gliomas, Meningiomas, Brain metastases	- Visualizes tumor vasculature - Near-infrared fluorescence allows deeper tissue penetration- Immediate fluorescence	- Limited to operative field under microscope- Does not replace DSA for complete vascular assessment - Very short half-life (fluorescence is transient) - Rare hypersensitivity reactions, caution in iodine allergy

It is important to emphasize that, despite their distinct mechanisms and specific limitations, the currently used fluorescent dyes in neurosurgery are generally considered safe when administered according to established protocols. Adverse events are uncommon and typically mild.

Discussion

Future of dyes in neurosurgery

It is worth noting that the fluorescent dyes currently used in neurosurgery have been known for many years, and their clinical application has evolved alongside advances in optical imaging technology rather than the introduction of entirely new compounds. The widespread adoption of 5-ALA, fluorescein, and indocyanine green reflects a gradual refinement of surgical visualization techniques, allowing previously established agents to gain new clinical significance. Improvements in surgical microscopes, filter systems, and digital imaging have significantly enhanced the ability to detect fluorescence signals, thereby increasing the practical utility of these dyes in modern neurosurgery.

On the one hand, the long-standing use of established fluorescent dyes highlights the stability of their position in modern neurosurgery. Their well-documented safety profiles, reproducible fluorescence characteristics, and widespread clinical acceptance have contributed to their continued dominance in intraoperative imaging. This stability, however, may also reduce the incentive to develop entirely new fluorophores, as current agents already provide clinically sufficient visualization in many scenarios.

Consequently, recent progress has been driven predominantly by technological rather than biochemical innovation. Advances in optical systems, digital image processing, and quantitative fluorescence analysis have significantly expanded the capabilities of existing dyes, suggesting that future developments are more likely to focus on optimizing the use of established fluorophores rather than replacing them with novel compounds.

It is also important to consider that the future role of fluorescent dyes in neurosurgery may be influenced by the development of alternative intraoperative imaging techniques. Improvements in methods such as intraoperative

ultrasound, neuronavigation systems, and advanced intraoperative imaging may reduce the need for fluorescence-guided visualization in selected clinical scenarios. For example, vascular procedures such as aneurysm clipping can be performed using intraoperative ultrasound alone, which in some cases may provide sufficient information without the need for fluorescent angiography. As these technologies continue to evolve, fluorescent dyes may become complementary rather than essential tools in certain neurosurgical applications [45].

Overall, the current position of fluorescent dyes in neurosurgery appears stable, supported by decades of clinical use and a well-established role in intraoperative imaging. Although it remains uncertain whether fluorescence-guided techniques will maintain their current importance in the long term, existing evidence suggests that they will continue to play a significant role in neurosurgical practice. Future developments are likely to focus primarily on technological advances, including machine learning-based analysis of fluorescence signals, augmented visualization systems, and quantitative fluorescence assessment, which may improve the objectivity and precision of intraoperative decision-making. At the same time, ongoing research into novel fluorophores with improved specificity and deeper tissue penetration may further expand clinical applications. Recent reviews indicate that continued technological refinement and development of new imaging approaches are expected to enhance fluorescence-guided surgery rather than replace it entirely [46].

Disclosure

Author's contribution:

All authors contributed to the article.

All authors have read and agreed with the published version of the manuscript.

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