Review

ANNALS OF MEDICINE & SURGERY

OPEN

Fluorescence in neurosurgery: its therapeutic and diagnostic significance – a comprehensive review

Sameer A. Rauf, MBBS[a], Rubayyi Ahmed, MBBS[a], Tooba Hussain, MBBS[b], Muhammad Saad, MBBS[a], Hussain H. Shah, MBBS[b], Syed A. Jamalvi, MBBS[a], Fnu Yogeeta, MBBS[a], Muskan Devi, MBBS[a], Arun Subash, MBBS[b], Maryam Gul, MBBS[b], Shaheer Ahmed, MBBS[b], Md Ariful Haque, MBBS, MD, MPH[c,d,e,*]

Abstract

This review provides a comprehensive overview of the therapeutic and diagnostic implications of fluorescence imaging in neurosurgery. Fluorescence imaging has become a valuable intraoperative visualization and guidance tool, facilitating precise surgical interventions. The therapeutic role of fluorescence is examined, including its application in photodynamic therapy and tumor-targeted therapy. It also explores its diagnostic capabilities in tumor detection, margin assessment, and blood–brain barrier evaluation. Drawing from clinical and preclinical studies, the review underscores the growing evidence supporting the efficacy of fluorescence imaging in neurosurgical practice. Furthermore, it discusses current limitations and future directions, emphasizing the potential for emerging technologies to enhance the utility and accessibility of fluorescence imaging, ultimately improving patient outcomes in neurosurgery.

Keywords: diagnostic applications, fluorescence imaging, neurosurgery, photodynamic therapy, therapeutic applications

Introduction

Fluorescence imaging is a scientific technique employed across various disciplines to observe and analyze biological or chemical systems at the cellular or molecular level. It involves stimulating fluorescent molecules or probes within a sample using specific light wavelengths and detecting the emitted light at different wavelengths. This light, fluorescence, provides valuable information about the sample's characteristics[1].

The clinical applications of fluorescence are tumor visualization, vascular assessment, endoscopic procedures, infectious disease diagnosis, wound assessment, and image-guided surgery[2].

The principle of fluorescence imaging is based on the interaction between light and fluorescent molecules, known as fluorophores[3], to visualize and study biological or chemical systems at a cellular or molecular level. It involves the excitation of fluorophores within a sample using specific wavelengths of light, followed by detecting the emitted fluorescence at different wavelengths[4,5].

Intraoperative visualization and guidance are pivotal in neurosurgical procedures, offering numerous benefits that improve surgical outcomes and patient safety[4]. These techniques provide neurosurgeons with the ability to accurately and precisely navigate the complex structures of the brain. Surgeons can pinpoint specific areas using neuronavigational systems and other visualization technologies, minimizing the risk of damaging critical structures[6].

The enhanced safety provided by intraoperative visualization techniques is paramount in neurosurgery. These methods allow surgeons to better visualize and navigate around delicate and vital

HIGHLIGHTS

- Comprehensive review: explores the multifaceted applications of fluorescence imaging in neurosurgery.
- Therapeutic role: discusses the use of fluorescence in guiding therapeutic interventions such as photodynamic therapy (PDT) and tumor-targeted therapy.
- Diagnostic role: highlights fluorescence imaging's diagnostic significance in tumor detection, assessment of tumor margins, and evaluation of blood–brain barrier disruption.
- Clinical evidence: synthesizes relevant clinical and preclinical studies supporting the efficacy of fluorescence imaging in neurosurgery.
- Future considerations: addresses current limitations and future advancements in the field, including the development of novel fluorescent agents and integration with other imaging modalities.

[a]Liaquat National Medical College, [b]Dow University of Health Sciences, Karachi, Pakistan, [c]Department of Public Health, Atish Dipankar University of Science and Technology, [d]Voice of Doctors Research School, Dhaka, Bangladesh and [e]Department of Orthopaedic Surgery, Yan'an Hospital Affiliated to Kunming Medical University, Kunming, Yunnan, People's Republic of China

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Department of Public Health, Atish Dipankar University of Science and Technology, Dhaka 1230, Bangladesh. Tel.: +880 189 477 3747. E-mail: arifulhaque58@gmail.com (M.A. Haque).

Annals of Medicine & Surgery (2024) 86:4255–4261

Received 25 March 2024; Accepted 15 May 2024

Published online 23 May 2024

http://dx.doi.org/10.1097/MS9.0000000000002218

brain structures, reducing the chances of accidental injuries and complications. Real-time assessment is another crucial advantage of these techniques[7]. Intraoperative imaging modalities, such as intraoperative MRI or ultrasound, offer surgeons immediate feedback during the procedure. This enables them to assess the extent of tumor resection, identify residual tumor tissue, and make necessary real-time adjustments to the surgical approach, ensuring optimal surgical outcomes[8].

Fluorescence-guided resection is a therapeutic technique in neurosurgery that enhances tumor removal precision by visualizing tumor boundaries, reducing recurrence risk, and improving outcomes[9]. PDT utilizes fluorescence imaging to selectively destroy tumor cells by activating photosensitizing agents with specific light wavelengths, sparing healthy tissue[10]. Fluorescence imaging enables tumor-targeted therapies using fluorescent markers or molecules that bind to tumor cells or receptors, delivering therapeutic agents directly to the tumor site for enhanced treatment outcomes[11].

Intraoperative tumor detection is facilitated by fluorescence imaging, allowing for real-time visualization of tumors during surgery[12]. Assessment of tumor margins and residual disease is improved through fluorescence imaging, enabling surgeons to accurately identify the extent of tumor removal and determine if any residual disease remains[13]. Fluorescence imaging plays a role in studying blood–brain barrier disruption, providing insights into the permeability and integrity of the barrier in the context of neurosurgical procedures[14]. The following neurosurgical applications of fluorescence imaging are listed in Table 1.

This review aims to provide a concise and paraphrased overview of the applications of fluorescence imaging in neurosurgery. It aims to highlight the clinical significance and advantages of utilizing fluorescence imaging techniques in various neurosurgical procedures, including brain tumor surgery, vascular neurosurgery, epilepsy surgery, and spinal surgery. By exploring the therapeutic and diagnostic roles of fluorescence imaging, this review aims to underscore its importance in improving surgical precision, optimizing patient outcomes, and guiding decision-making in neurosurgical interventions.

Methodology

This narrative review discusses fluorescence imaging in neurosurgery. An extensive literature search was conducted using PubMed/MEDLINE and Google Scholar databases, with data included up to 2023. Our search strings included keywords such as “fluorescence imaging,” “neurosurgery,” “therapeutic applications,” “diagnostic applications,” “photodynamic therapy,” “tumor-targeted therapy,” “margin assessment,” and “blood-brain barrier evaluation.” We focused on articles that provided insights into applying fluorescence imaging techniques in neurosurgical practice, encompassing clinical and preclinical studies. Articles in languages other than English were excluded from the review. Articles that reviewed fluorescence in neurosurgery, specifically focusing on its therapeutic and diagnostic significance, were included. The titles and abstracts of the articles were screened, reviewed, and removed according to the inclusion criteria. Additionally, all references and citations were screened to ensure relevance to the topic under discussion.

Therapeutic role of fluorescence in neurosurgery

Photodynamic therapy

PDT is a minimally invasive treatment modality that utilizes photosensitive agents, often photosensitizers, and light to selectively destroy abnormal cells, such as tumor cells[19,20]. The mechanism of PDT involves three key components: a photosensitizer, light of a specific wavelength, and molecular oxygen[21]. Upon administration of the photosensitizer, it accumulates preferentially in tumor tissue. When exposed to light of the appropriate wavelength, the photosensitizer becomes activated and initiates a photochemical reaction, generating reactive oxygen species. These reactive oxygen species induce oxidative stress, resulting in cellular damage and ultimately leading to apoptosis or necrosis of the targeted cells[22].

Various fluorescent agents have been explored for their utility in PDT, with 5-aminolevulinic acid (5-ALA) being one of the most widely studied and utilized agents in neurosurgery[23]. 5-ALA is a prodrug metabolized within cells to produce a fluorescent protoporphyrin IX (PpIX) compound. PpIX preferentially accumulates in malignant glioma cells due to their altered metabolism and decreased capacity for PpIX conversion to heme. Upon exposure to blue light, PpIX fluoresces red, allowing for real-time visualization of tumor tissue during surgery[24].

Fluorescence-guided resection using PDT has demonstrated several clinical benefits in neurosurgical practice. By enabling real-time visualization of tumor margins, fluorescence-guided

Table 1

The neurosurgical application of fluorescence imaging.

Neurosurgery	Application
Brain tumor surgery	Fluorescence imaging is extensively utilized in brain tumor surgery to improve tumor visualization, distinguish tumor tissue from healthy tissue, and guide accurate tumor removal. This technology helps surgeons identify tumor boundaries, evaluate the extent of resection, and minimize damage to surrounding brain structures, ultimately leading to enhanced patient outcomes[15]
Vascular neurosurgery	Fluorescence imaging plays a significant role in visualizing and assessing blood vessels during vascular neurosurgery. It assists surgeons in identifying abnormal vessel structures, evaluating blood flow characteristics, and guiding interventions such as aneurysm clipping or arteriovenous malformation resection. By enhancing accuracy and ensuring safety, fluorescence imaging improves outcomes in vascular procedures[16]
Epilepsy surgery	In cases involving cortical dysplasia or epileptic foci, fluorescence imaging finds application in epilepsy surgery. Through fluorescence-guided techniques, surgeons can identify and remove abnormal cortical tissue, reducing the likelihood of recurrent seizures and improving seizure control in individuals with drug-resistant epilepsy[17]
Spinal surgery	Fluorescence imaging is also employed in spinal surgery to enhance visualization and precision. It aids in detecting spinal cord tumors, differentiation between tumor and normal spinal cord tissue, and precise removal of tumors. Additionally, fluorescence imaging assists in identifying spinal cord ischemia during complex spinal procedures, allowing for timely interventions to prevent neurological complications[18]

Table 2

The advantages and limitations of tumor-targeted therapy.

Advantages	Limitations
Precision: Targeted therapy enables precise delivery of drugs to tumor cells, minimizing damage to healthy tissue[31]	Resistance: Tumor cells can develop resistance to targeted therapies over time, reducing their effectiveness[34]
Reduced side effects: By specifically targeting tumor cells, these therapies often have fewer side effects than traditional chemotherapy[32]	Specificity: Identifying suitable targets for specific brain tumors can be challenging, limiting the applicability of targeted therapies[27]
Enhanced efficacy: Targeted drugs can more effectively halt tumor growth by interfering with specific molecular pathways unique to cancer cells[27]	Cost: Some targeted therapies can be expensive, posing financial challenges for patients[34]
Personalized treatment: Tailoring treatment to the individual characteristics of the tumor leads to more personalized and effective therapy[33]	Clinical trials: The availability of targeted therapies may be limited to clinical trial settings, restricting access for all patients[35]

resection allows for more accurate and complete removal of tumor tissue while minimizing damage to surrounding healthy brain parenchyma[25]. Studies have shown that the extent of resection significantly predicts patient outcomes in glioma surgery, with maximal safe resection associated with improved progression-free survival and overall survival. Additionally, fluorescence-guided resection has been shown to reduce the rates of residual tumors and the need for repeat surgeries, thereby improving patient morbidity and reducing healthcare costs[26].

Tumor-targeted therapy

Tumor-targeted therapy harnesses the specificity of fluorescent agents to selectively deliver therapeutic agents to tumor cells while minimizing systemic toxicity. These agents are utilized to track and guide the delivery of therapeutic drugs specifically to tumor cells, enhancing precision and effectiveness[27]. By incorporating fluorescent markers into drug formulations, neurosurgeons can visualize and monitor the distribution of drugs in real time, ensuring accurate targeting of tumor cells while minimizing damage to healthy tissue.

The fluorescent agents used in targeted drug delivery include:

1. Fluorescein: widely used for drug tracking and visualizing ocular damage following treatment[28].
2. Green fluorescent protein: produced inside cells, allowing for the identification of corneal layers and tracking protein production[29].
3. Various fluorescent dyes: excitable in visible to near-infrared wavelengths, enabling visualization and tracking of drug distribution within tissues and cells[29].
4. Nile red: used as a fluorescent dye in liposomal formulations for tracking and visualizing cell drug uptake in vitro and in vivo[30].

These fluorescent agents play a crucial role in enhancing the precision and effectiveness of targeted drug delivery systems by enabling real-time visualization, monitoring, and tracking of therapeutic agents within the body.

In neurosurgery, fluorescence is employed not only for tracking drug delivery but also for activating therapeutic agents. By utilizing fluorescence-guided techniques, surgeons can precisely identify tumor margins and selectively activate therapeutic agents within the tumor site. This targeted approach allows for tailored treatment, ensuring the therapeutic effects are concentrated on the tumor cells while sparing healthy surrounding tissue[27,28].

The following advantages and limitations are listed in Table 2 related to tumor-targeted therapy in neurosurgery.

Intraoperative monitoring and guidance

Fluorescence-guided surgery enables real-time visualization of different structures and types of tissue during surgical procedures. Surgeons can accurately identify surgical targets by utilizing fluorescence imaging techniques, enhancing precision and reducing the risk of damaging surrounding healthy tissue[36]. This real-time visualization provides crucial guidance throughout the surgery, allowing for more accurate and targeted interventions[37].

Fluorescence is vital in guiding tissue resection and preservation during surgical procedures. By using fluorescence-based techniques, surgeons can distinguish between tumor and healthy tissue with high molecular selectivity. This enables precise tissue resection, ensuring that the surgical margins are accurately defined and that as much tumor tissue as possible is removed while preserving critical structures[25]. Fluorescence in guiding tissue resection enhances the surgical outcome by improving the extent of resection and reducing the likelihood of leaving residual tumor cells[38].

Fluorescence-guided surgery has shown significant improvements in surgical outcomes and patient safety. By providing real-time visualization and guidance, fluorescence-based techniques enhance the accuracy and precision of surgical procedures, leading to improved outcomes such as the increased extent of tumor resection and reduced rates of residual tumor cells[39]. This targeted approach improves the efficacy of surgical interventions and enhances patient safety by minimizing damage to healthy tissue and critical structures. Fluorescence in surgery contributes to better patient outcomes, reduced complications, and improved safety during surgical procedures[25].

Diagnostic role of fluorescence in neurosurgery

Intraoperative tumor detection

Fluorescence imaging has numerous medical applications, including cancer detection and treatment, vascular imaging, intraoperative guidance during surgery, and monitoring physiological processes at the biomolecular level[40–42]. The use of fluorescent contrast agents for tumor identification and diagnostic purposes has revolutionized medicine. From its usage in cancer imaging to real-time visualization of tumor margins during surgery, fluorescent contrast agents are crucial in improving diagnostic accuracy and sensitivity and guiding treatment decisions[43–45].

Within clinical practice, different areas of focus for fluorescent diagnosis make it an asset in the medical world. Autofluorescence imaging has detected specific premalignant alterations previously undetectable under white light, such as low-grade dysplasias in

Barrett's esophagus[46]. The ability to detect these changes at the preliminary stage means it is ideal for early detection of cancers[47,48].

Autofluorescence in neurosurgery, similarly, plays a vital role. This passage discusses autofluorescence spectroscopy, a technique that examines the natural fluorescence emitted by tissues for characterizing different types of brain tumors and normal tissues. This method is affordable and easy to use, as it allows for the simultaneous evaluation of various molecules within tissues. Differences between normal and tumor tissues can be identified by analyzing the levels of certain molecules like collagen and lipids[49]. Endogenous cellular fluorophores also include various compounds such as nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, flavin adenine dinucleotide, lipofuscin, retinoids, in addition to collagen and elastin. Some of these fluorophores interact with cellular proteins, resulting in subtle alterations in fluorescence spectra. This result produces specific fluorescence patterns, which offer valuable information. This technique has been particularly beneficial in learning more about cellular activities and tissue compositions[50]. Integrating fluorescence and Raman signals can also differentiate between tumor and nontumor tissue with enhanced accuracy. It is a widely known fact in the medical community that fluorescence contributes significantly to the signal obtained during Raman measurements on biological tissue[51].

Detection of tumor margins and residual disease

Fluorescence-guided tumor resection has emerged as a promising technique for improving patient outcomes in various surgical procedures. Surgeons can visualize tumors and surrounding tissue more clearly during the procedure using fluorescent dyes, such as indocyanine green. This real-time visualization allows them to achieve greater precision and accuracy in tumor removal, resulting in increased complete resection rates. Complete resection of tumors has been associated with improved patient outcomes, including increased overall survival and a decreased risk of tumor recurrence. Furthermore, fluorescence-guided tumor resection can help spare healthy tissue and reduce the risk of damaging critical structures during surgery[52]. Numerous fluorescent biomarkers have been studied to enhance intraoperative guidance and detect residual tumor tissue. Among these biomarkers, 5-ALA is the most commonly utilized[53]. Based on the existing clinical evidence, it is compellingly indicated that utilizing ALA/PpIX fluorescence-guided resection has the potential to improve the precision and thoroughness of brain tumor removal significantly. This effect is particularly pronounced when the technique is applied quantitatively, enhancing the ability to precisely identify and remove tumor tissue during surgery[54].

Assessment of blood–brain barrier disruption

In experiments examining cerebral ischemia in animals, scientists have observed impairment in the integrity of the blood–brain barrier by employing fluorescent and radiolabeled markers. This method allows researchers to track and assess changes in blood–brain barrier function, providing valuable insights into the pathophysiology of cerebral ischemia and potential therapeutic interventions[55]. The utilization of in vivo near-infrared fluorescence imaging, employing fluorescently labeled albumin, stands as an ideal technique for investigating the involvement of plasma albumin extravasation in the pathophysiological mechanisms underlying cerebral ischemia, alongside various other central nervous system disorders. This method facilitates a comprehensive exploration of the dynamics of albumin extravasation, shedding light on its potential role in the progression and manifestation of these conditions within the central nervous systems[56].

Because of its versatility, sensitivity, and noninvasive nature, it is a powerful tool with significant potential and various applications in the medical field, enabling it to advance medical research, diagnosis, and therapy.

Overview of preclinical and clinical trials

Neurosurgery often involves delicate procedures to achieve maximal tumor resection while minimizing damage to healthy tissue. In recent years, fluorescence imaging has become a valuable adjunct to traditional neurosurgical techniques. This review aims to provide an in-depth analysis of preclinical and clinical studies investigating the use of fluorescence in neurosurgery, including their key findings, diagnostic accuracy, limitations, and challenges.

Numerous preclinical studies have demonstrated the potential of fluorescence imaging in neurosurgery. For instance, Cho *et al.*[57] conducted a study evaluating the diagnostic accuracy of delta-5-ALA and indocyanine green coadministration in rodent and human glioblastomas, showing promising results in tumor visualization and delineation. Similarly, Acerbi *et al.*[58] explored the use of the fluorescein-guided technique in resecting high-grade gliomas, demonstrating high rates of complete tumor removal based on postoperative MRI scans. These preclinical studies highlight the efficacy of fluorescence imaging in enhancing tumor visualization and resection.

Clinical studies have further validated the utility of fluorescence imaging in neurosurgery. Stummer *et al.*[59] conducted a randomized controlled multicenter phase III trial assessing the use of 5-ALA for resection of malignant gliomas, reporting improved extent of resection and progression-free survival. Cordova *et al.*[60] conducted a phase II trial evaluating the impact of 5-ALA on the extent of resection and survival outcomes in glioblastoma patients, demonstrating significant associations between the extent of resection, progression-free survival, and overall survival. These clinical studies provide robust evidence supporting the efficacy and safety of fluorescence imaging in neurosurgery.

Diagnostic accuracy

Fluorescence imaging has shown promising diagnostic accuracy in neurosurgery. Preclinical and clinical studies have consistently demonstrated its ability to enhance tumor visualization, improve the extent of resection, and reduce the risk of recurrence. Cho *et al.*[57] reported high diagnostic accuracy following the coadministration of 5-ALA and indocyanine green in rodent and human glioblastomas, highlighting its potential for accurate tumor delineation. Similarly, Acerbi *et al.*[58] found that the fluorescein-guided technique resulted in high rates of complete tumor removal based on postoperative MRI scans, underscoring its diagnostic utility.

Limitations and challenges

Despite its promise, fluorescence imaging in neurosurgery faces several limitations and challenges. Systemic adverse effects, such as nausea, vomiting, and cardiovascular responses, have been reported with the use of 5-ALA at high doses[59]. Additionally, the interpretation of fluorescence images can be subjective and may require specialized training. Furthermore, the cost and availability of fluorescence imaging systems pose barriers to the widespread use of fluorescence imaging.

Technical considerations and limitations

Despite its potential benefits, fluorescence imaging in neurosurgery is not without technical limitations. One key challenge is the need for specialized equipment, including fluorescent dyes and imaging systems, which may not be readily available in all medical centers[59]. Additionally, fluorescence signals can be affected by tissue autofluorescence and background noise, potentially reducing the accuracy of tumor detection[60]. Moreover, the interpretation of fluorescence images can be subjective and dependent on the surgeon's experience, highlighting the need for standardized protocols and training[58].

Standardization and validation of fluorescence-guided techniques

Standardization and validation are crucial aspects of implementing fluorescence-guided techniques in neurosurgery. While numerous studies have demonstrated the efficacy of fluorescence imaging in improving tumor visualization and resection, there is a lack of standardized protocols for drug administration, imaging parameters, and data interpretation[57]. Furthermore, the validation of fluorescence-guided techniques often relies on subjective endpoints, such as the extent of resection, which may vary between studies[58]. To address these issues, multicenter trials with standardized protocols and objective outcome measures are needed to validate the efficacy and safety of fluorescence-guided techniques in neurosurgery[60].

Cost-effectiveness and accessibility

Cost-effectiveness and accessibility are significant barriers to the widespread adoption of fluorescence imaging in neurosurgery. The initial investment required for purchasing fluorescence imaging systems and fluorescent dyes can be substantial, particularly for more minor medical centers with limited resources[61]. Moreover, the ongoing costs associated with maintenance, training, and consumables may further limit accessibility[58]. Additionally, reimbursement policies may vary between healthcare systems, impacting patients' and providers' affordability of fluorescence-guided techniques[57].

Fluorescence imaging holds great promise as a valuable tool in neurosurgery, offering enhanced tumor visualization and improved surgical outcomes. Preclinical and clinical studies have provided compelling evidence supporting its efficacy and safety. However, systemic adverse effects and cost constraints must be addressed to facilitate broader adoption. Continued research and technological advancements are needed to realize the full potential of fluorescence imaging in neurosurgery.

Future consideration

In neurosurgery, fluorescence imaging has become a valuable tool for enhancing visualization and surgery outcomes. Fluorescence in oncological neurosurgery is a developing field, and with advancements in this field, the standards of extensive and safe resection have been raised. To enhance surgical outcomes, integrating fluorescence agents with intraoperative imaging has become a common practice[62]. One notable application of this approach is seen in high-grade glioma surgery, where the combination of fluorescence-guided techniques with contrast-enhanced ultrasound has proven to be a safe, efficient, quick, and cost-effective method for tumor resection, surpassing alternative modalities such as computed tomography and MRI[63]. In conjunction with artificial intelligence, fluorescence imaging has also demonstrated notable benefits in achieving extended yet safe tumor resection. One such example was when fluorescence imaging was combined with deep convolutional neural networks to provide rapid and precise diagnosis of glioma during surgery[64].

Fluorescence imaging is increasingly being utilized in cerebrovascular surgeries as well. A notable advancement in this field is the intraoperative application of multispectral fluorescence (MFL) imaging, which employs indocyanine green as a fluorescent agent. MFL imaging enables real-time visualization of blood vessel perfusion, and research indicates that this innovative technology offers advantages in terms of efficiency compared to the traditional gold standard method, digital subtraction angiography (DSA)[65,66]. Unlike DSA, MFL imaging does not require interruption of the ongoing procedure, resulting in significant time savings. Furthermore, studies demonstrate that the accuracy of information regarding blood flow and vessel patency obtained through MFL imaging correlates well with that of DSA[67].

Conclusion

In conclusion, fluorescence in neurosurgery offers a wide range of benefits in both therapeutic and diagnostic approaches. It enlightens surgical precision by helping identify tumors, demarcation, and target drug delivery, ultimately leading to better patient outcomes. While all of these advantages, some limitations, like technical limitations and standardized issues, challenge its efficacy. Overall, fluorescence imaging is a futuristic tool with the potential to shape personalized treatment approaches and advancement in patient care through collaboration among clinicians and surgeons.

The take-home message of this review is that while fluorescence imaging in neurosurgery holds transformative potential, offering enhanced precision and diagnostic capabilities, addressing ongoing technical and cost-related challenges through continued research and collaboration is imperative to realize its impact on personalized patient care fully.

Limitations

While this review provides valuable insights, several limitations must be acknowledged. First, the literature search was confined to English-language publications, potentially overlooking relevant studies in other languages. Second, despite efforts to utilize comprehensive databases, there remains a possibility of missing pertinent studies that could have enriched the discussion. Moreover, the review primarily concentrates on the joint role of fluorescence in neurosurgery, potentially neglecting other relevant aspects. Lastly, information bias cannot be entirely ruled out, as interpretations of the included studies may have been influenced by subjective perspectives.

Ethical approval

This paper did not involve patients; therefore, no ethical approval was required.

Consent

This paper did not involve patients; therefore, no consent was required.

Sources of funding

No funding was acquired for this paper.

Author contribution

S.A.R.: conceptualization; data curation; formal analysis; methodology; writing – original draft. R.A.: data curation; investigation; methodology; resources; software; writing – original draft. T.H.: data curation; investigation; methodology; resources; software; writing –original draft. M.S.: methodology; investigation; resources; writing – review and editing. H.H.S.: methodology; investigation; resources; writing – review and editing. S.A.J.: methodology; investigation; resources; writing – review and editing. F.Y.: methodology; investigation; resources; writing – review and editing. M. D.: methodology; investigation; resources; writing – review and editing. A.S.: methodology; investigation; resources; writing – review and editing. M.G.: methodology; investigation; resources; writing – review and editing. S.A.: methodology; investigation; resources; writing – review and editing. M.A.H.: data curation; formal analysis; methodology; project administration; resources; visualization; writing – review and editing.

Conflicts of interest disclosure

There are no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Sameer Abdul Rauf.

Data availability statement

It will be available upon reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

[1] Ettinger A, Wittmann T. Fluorescence live cell imaging. Meth Cell Biol 2014;123:77–94.
[2] Sieroń A, Sieroń-Stołtny K, Kawczyk-Krupka A, *et al*. The role of fluorescence diagnosis in clinical practice. OncoTargets Ther 2013;6:977–82.
[3] Rao J, Dragulescu-Andrasi A, Yao H. Fluorescence imaging in vivo: recent advances. Curr Opin Biotechnol 2007;18:17–25.
[4] Dunst S, Tomancak P. Imaging flies by fluorescence microscopy: principles, technologies, and applications. Genetics 2019;211:15–34.
[5] Fixler D. Fluorescence imaging for biomedical analysis. Optics Encyclopedia 2007. doi:10.1002/9783527600441.oe1005
[6] Schulz C, Waldeck S, Mauer UM. Intraoperative image guidance in neurosurgery: development, current indications, and future trends. Radiol Res Pract 2012;2012:197364.
[7] Schulz C, Woerner U, Luelsdorf P. Image-guided neurosurgery for secondary operative removal of projectiles after missile injury of the brain. Surg Neurol 2008;69:364–8.
[8] Spetzger U, Laborde G, Gilsbach JM. Frameless neuronavigation in modern neurosurgery. Minim Invas Neurosurg 1995;38:163–6.
[9] Nagaya T, Nakamura YA, Choyke PL, *et al*. Fluorescence-guided surgery. Front Oncol 2017;7:314.
[10] Nair LV, Nazeer SS, Jayasree RS, *et al*. Fluorescence imaging assisted photodynamic therapy using photosensitizer-linked gold quantum clusters. Acs Nano 2015;9:5825–32.
[11] He J, Li C, Ding L, *et al*. Tumor targeting strategies of smart fluorescent nanoparticles and their applications in cancer diagnosis and treatment. Adv Mater 2019;31:1902409.
[12] Belykh E, Martirosyan NL, Yagmurlu K, *et al*. Intraoperative fluorescence imaging for personalized brain tumor resection: current state and future directions. Front Surg 2016;3:55.
[13] Voskuil FJ, de Jongh SJ, Hooghiemstra WTR, *et al*. Fluorescence-guided imaging for resection margin evaluation in head and neck cancer patients using cetuximab-800CW: a quantitative dose-escalation study. Theranostics 2020;10:3994–4005.
[14] Hawkins BT, Egleton RD. Fluorescence imaging of blood-brain barrier disruption. J Neurosci Meth 2006;151:262–7.
[15] Zhang DY, Singhal S, Lee JYK. Optical principles of fluorescence-guided brain tumor surgery: a practical primer for the neurosurgeon. Neurosurgery 2019;85:312–24.
[16] Zhao X, Belykh E, Cavallo C, *et al*. Application of fluorescein fluorescence in vascular neurosurgery. Front Surg 2019;6:52.
[17] Bhatia S, Ragheb J, Johnson M, *et al*. The role of optical spectroscopy in epilepsy surgery in children. Neurosurg Focus 2008;25:E24.
[18] De la Garza-Ramos R, Bydon M, Macki M, *et al*. Fluorescent techniques in spine surgery. Neurol Res 2014;36:928–38.
[19] Friesen SA, Hjortland GO, Madsen SJ, *et al*. 5-Aminolevulinic acid-based photodynamic detection and therapy of brain tumors (review). Int J Oncol 2002;21:577–82.
[20] Kennedy JC, Marcus SL, Pottier RH. Photodynamic therapy (PDT) and photodiagnosis (PD) using endogenous photosensitization induced by 5-aminolevulinic acid (ALA): mechanisms and clinical results. J Clin Laser Med Surg 1996;14:289–304.
[21] Lee CN, Hsu R, Chen H, *et al*. Daylight photodynamic therapy: an update. Molecules (Basel, Switzerland) 2020;25:5195.
[22] Donnelly RF, McCarron PA, Tunney MM. Antifungal photodynamic therapy. Microbiol Res 2008;163:1–12.
[23] Pogue BW, Gibbs-Strauss S, Valdés PA, *et al*. Review of neurosurgical fluorescence imaging methodologies. IEEE J Select Topics Quant Electr 2010;16:493–505.
[24] Wachowska M, Muchowicz A, Firczuk M, *et al*. Aminolevulinic acid (ALA) as a prodrug in photodynamic therapy of cancer. Molecules 2011;16:4140–64.
[25] Sun R, Cuthbert H, Watts C. Fluorescence-guided surgery in the surgical treatment of gliomas: past, present and future. Cancers 2021;13:3508.
[26] Wong LS, St George J, Agyemang K, *et al*. Outcomes of fluorescence-guided vs white light resection of glioblastoma in a single institution. Cureus 2023;15:e42695.
[27] Veselov VV, Nosyrev AE, Jicsinszky L, *et al*. Targeted delivery methods for anticancer drugs. Cancers 2022;14:622.
[28] Zingale E, Romeo A, Rizzo S, *et al*. Fluorescent nanosystems for drug tracking and theranostics: recent applications in the ocular field. Pharmaceutics 2022;14:955.
[29] Chen Z, Mok H, Pflugfelder SC, *et al*. Improved transduction of human corneal epithelial progenitor cells with cell-targeting adenoviral vectors. Exp Eye Res 2006;83:798–806.
[30] Genicot G, Leroy JL, Soom AV, *et al*. The use of a fluorescent dye, Nile red, to evaluate the lipid content of single mammalian oocytes. Theriogenology 2005;63:1181–94.
[31] Li J, Wang Q, Xia G, *et al*. Recent advances in targeted drug delivery strategy for enhancing oncotherapy. Pharmaceutics 2023;15:2233.

[32] Shuel SL. Targeted cancer therapies: clinical pearls for primary care. Can Fam Phy 2022;68:515–8.
[33] Saeed RF, Awan UA, Saeed S, *et al*. Targeted therapy and personalized medicine. Cancer Treat Res 2023;185:177–205.
[34] Curigliano G, Criscitiello C. Successes and limitations of targeted cancer therapy in breast cancer. Progr Tumor Res 2014;41:15–35.
[35] Fougner V, Hasselbalch B, Lassen U, *et al*. Implementing targeted therapies in the treatment of glioblastoma: Previous shortcomings, future promises, and a multimodal strategy recommendation. Neuro-oncol Adv 2022;4:vdac157.
[36] Wang LG, Gibbs SL. Improving precision surgery: a review of current intraoperative nerve tissue fluorescence imaging. Curr Opin Chem Biol 2023;76:102361.
[37] Teatini A, Pelanis E, Aghayan DL, *et al*. The effect of intraoperative imaging on surgical navigation for laparoscopic liver resection surgery. Sci Rep 2019;9:18687.
[38] Smith BL, Hunt KK, Carr D, *et al*. Intraoperative fluorescence guidance for breast cancer lumpectomy surgery. NEJM Evid 2023;2: EVIDoa2200333.
[39] Muto J, Mine Y, Nishiyama Y, *et al*. Intraoperative real-time near-infrared image-guided surgery to identify intracranial meningiomas via microscope. Front Neurosci 2022;16:837349.
[40] PubMed. (n.d.). Indocyanine green fluorescence angiography during laparoscopic low anterior resection: results of a case-matched study. Accessed 18 March 2024. https://pubmed.ncbi.nlm.nih.gov/27553790/
[41] PubMed. (n.d.). Diffusion of technology: trends in robotic-assisted colorectal surgery. Accessed 18 March 2024. https://pubmed.ncbi.nlm.nih.gov/28347491/
[42] PubMed. (n.d.). Biomedical applications of fluorescence imaging in vivo. Accessed 18 March 2024. https://pubmed.ncbi.nlm.nih.gov/15679261/
[43] PubMed Central (PMC). Optical contrast agents and imaging systems for detection and diagnosis of cancer - PMC. (n.d.). Accessed date 18 March 2024. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2902964/#:~:text=Imaging%20visible%20and%20near%2Dinfrared,appearance%20of%20the%20surgical%20field
[44] PubMed. (n.d.). Real-time identification of liver cancers by using indocyanine green fluorescent imaging. Accessed 18 March 2024. https://pubmed.ncbi.nlm.nih.gov/19326450
[45] PMC. (n.d.). PubMed Central (PMC). The role of fluorescence diagnosis in clinical practice. Accessed 18 March 2024. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3735341/
[46] PMC. (n.d.). Autofluorescence endoscopy for detection of high-grade dysplasia in short-segment Barrett's esophagus. Accessed 18 March 2024. https://pubmed.ncbi.nlm.nih.gov/14595307/
[47] ScienceDirect.Com|Science. Early detection of lung cancer with laser-induced fluorescence endoscopy and spectrofluorometry – ScienceDirect. (n.d.). Health and Medical Journals, Full Text Articles and Books. Accessed 18 March 2024. https://www.sciencedirect.com/science/article/abs/pii/S0012369215378922
[48] PubMed. (n.d.). Fluorescence detection and diagnosis of non-melanoma skin cancer at an early stage. Accessed 18 March 2024. https://pubmed.ncbi.nlm.nih.gov/19226578/
[49] PubMed. (n.d.). Fluorescence spectroscopy as a highly potential single-entity tool to identify chromophores and fluorophores: study on neoplastic human brain lesions. Accessed 19 March 2024. https://pubmed.ncbi.nlm.nih.gov/23733026/
[50] Scientific Reports. (n.d.). Quantitative non-invasive cell characterization and discrimination based on multispectral autofluorescence features. Nature; Springer Nature. Accessed 19 March 2024. https://www.nature.com/articles/srep23453
[51] PubMed. (n.d.). Raman spectroscopy for the detection of cancers and precancers. Accessed 19 March 2024. https://pubmed.ncbi.nlm.nih.gov/23014644/
[52] PubMed. (n.d.). Fluorescence-guided surgery. Accessed 19 March 2024. https://pubmed.ncbi.nlm.nih.gov/29312886/
[53] PubMed. (n.d.). Fluorescence-guided resection of high-grade gliomas: a systematic review and meta-analysis. Accessed 19 March 2024. https://pubmed.ncbi.nlm.nih.gov/25131747/
[54] PubMed. (n.d.). Fluorescence-guided resection of brain tumor: review of the significance of intraoperative quantification of protoporphyrin IX fluorescence. Accessed 19 March 2024. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227178/
[55] PubMed. (n.d.). Differential passage of [14C]sucrose and [3H]inulin across rat blood-brain barrier after cerebral ischemia. Accessed 19 March 2024. https://pubmed.ncbi.nlm.nih.gov/11907803/
[56] PubMed. (n.d.). Near-infrared fluorescence imaging with fluorescently labeled albumin: a novel method for non-invasive optical imaging of blood-brain barrier impairment after focal cerebral ischemia in mice. Accessed 19 March 2024. https://pubmed.ncbi.nlm.nih.gov/19427539/
[57] Cho SS, Sheikh S, Teng CW, *et al*. Evaluation of diagnostic accuracy following the co administration of delta-aminolevulinic acid and second window indocyanine green in rodent and human glioblastomas. Mol Imag Biol 2020;22:1266–79.
[58] Acerbi F, Broggi M, Eoli M, *et al*. Is fluorescein-guided technique able to help in resection of high-grade gliomas? Neurosurg Focus 2014;36:E5.
[59] Stummer W, Pichlmeier U, Meinel T, *et al*. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 2006;7: 392–401.
[60] Cordova JS, Gurbani SS, Holder CA, *et al*. Semi-automated volumetric and morphological assessment of glioblastoma resection with fluorescence-guided surgery. Mol Imag Biol 2016;18:454–62.
[61] Esteves Susana, Marta Alves, Marta Castel-Branco, *et al*. A pilot cost-effectiveness analysis of treatments in newly diagnosed high-grade gliomas: the example of 5-aminolevulinic acid compared with white-light surgery. Neurosurgery 2015;76:552–62; discussion 562.
[62] Orillac C, Stummer W, Orringer DA. Fluorescence guidance and intraoperative adjuvants to maximize extent of resection. Neurosurgery 2021;89:727–36.
[63] Della Pepa GM, Sabatino G, la Rocca G. "Enhancing vision" in high grade glioma surgery: a feasible integrated 5-ALA + CEUS protocol to improve radicality. World Neurosurg 2019;129:401–3.
[64] Shen B, Zhang Z, Shi X, *et al*. Real-time intraoperative glioma diagnosis using fluorescence imaging and deep convolutional neural networks. Eur J Nucl Med Mol Imag 2021;48:3482–92.
[65] Nickele C, Nguyen V, Fisher W, *et al*. A pilot comparison of multispectral fluorescence to indocyanine green videoangiography and other modalities for intraoperative assessment in vascular neurosurgery. Operat Neurosurg (Hagerstown, Md) 2019;17:103–9.
[66] Anas Z, Hasan SFS, Moiz MA, *et al*. The role of hydrogels in the management of brain tumors: a narrative review. Annals of Medicine and Surgery. 2024;10–97
[67] Greuter L, Croci DM, Zumofen DW, *et al*. Augmented reality fluorescence imaging in cerebrovascular surgery: a single-center experience with thirty-nine cases. World Neurosurg 2021;151:12–20.