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REVIEW

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Advances in laser-based diagnostic modalities for intraoperative tissue diagnosis in neurosurgery: current practices and future perspectives

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Abstract

This review assesses laser-based diagnostic modalities for intraoperative tissue diagnosis in neurosurgical oncology, emphasizing their utility in delineating tumor margins. Technologies such as optical coherence tomography, photoacoustic imaging, and confocal microscopy are scrutinized for their capability to enhance intraoperative discernment of neoplastic versus healthy tissue. We discuss the technical advancements, limitations related to depth penetration and resolution, and innovative approaches to mitigate these challenges. Economic and regulatory considerations pertinent to the clinical adoption of these technologies are also examined. The review highlights current clinical trials and research initiatives aiming to validate and standardize these applications. It concludes by highlighting the importance of ongoing research, cross-disciplinary cooperation, and professional training to integrate laser-based diagnostics into neurosurgical practice, with the ultimate goal of optimizing patient outcomes in brain tumor resection.

Introduction

Primary and metastatic brain tumors pose significant diagnostic and therapeutic challenges. Traditional imaging modalities have been essential in the diagnosis, surgical planning, and postoperative monitoring of these tumors. Recently, laser-based diagnostic technologies have emerged as valuable tools, offering real-time, high-resolution data that can guide surgical interventions. The physics underlying these laser technologies generally involves the absorption and scattering of laser light by tissue, yielding data that can be analyzed for diagnostic purposes. While lasers are traditionally associated with therapeutic applications, their diagnostic potential is increasingly acknowledged, especially in obviating the need for time-consuming frozen section biopsies during neurological surgery. Despite the inherent limitations of light-based imaging, such as challenges with deep anatomical structures due to the physics of light absorption and reflection, laser technologies hold promise for improving both surgical efficiency and tumor resection accuracy. This review will explore the advancements, limitations, and applications of laser-based diagnostic technologies, focusing specifically on their role in brain tumor diagnosis and surgical guidance.

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Current technologies in laser diagnostics

Diagnosis of brain tumors primarily relies on magnetic resonance imaging (MRI) with and without contrast; computed tomography (CT) is an alternative for those who cannot undergo MRI [1]. The standard for tissue status assessment during neurosurgical tumor resection remains excisional biopsy with frozen section analysis, a method limited by its time-consuming nature and lack of real-time diagnostic capability [2]. Prognosis following surgical intervention is intrinsically linked to the completeness of tumor resection. Incomplete resection can lead to tumor recurrence and poorer long-term outcomes [3]. These modalities aim to address the limitations of conventional imaging techniques and excisional biopsy, paving the way for more effective and precise neurosurgical procedures by allowing real-time diagnosis and improved surgical guidance.

Hyperspectral imaging (HSI)

HSI provides real-time, high-resolution spectral imaging, achieving an 80% accuracy rate in delineating glioblastoma margins [4]. It surpasses traditional MRI in both spatial and spectral resolution while remaining cost-effective [5, 6]. In the preoperative phase, the system is calibrated and mounted onto the surgical microscope. During surgery, HSI captures spectral data controlled via a remote computer, offering surgeons precise guidance for tissue resection. This intraoperative assistance can enhance the likelihood of a successful, complete tumor removal, ultimately improving patient prognosis [7].

Photoacoustic imaging (PAI)

Photoacoustic imaging (PAI) leverages laser-induced ultrasound signals and integrates with multispectral optical tomography (MSOT) for nuanced tissue characterization, including angiogenesis and blood saturation [8, 9]. During neurosurgery, an ultrasound probe captures these signals, providing real-time images that assist in delineating tumor from healthy tissue. However, its utility is primarily restricted to superficial brain tumors, with diminished effectiveness in deeper tissues [8].

Laser-induced fluorescence (LIF)

In the realm of surgical resection of brain tumors, laser-induced fluorescence (LIF) stands out as a promising modality. Guided by various light wavelengths, LIF employs their differential absorptive properties to delineate tumor borders intraoperatively [10]. Research led by Kustov et al. demonstrated the effectiveness of LIF, particularly when using red-shifted wavelengths for enhanced penetration into brain tissues [10]. The fluorophore of choice in LIF is 5-aminolevulinic acid (5-ALA), known for its capability to cross the blood–brain barrier and yield protoporphyrin IX, a fluorescent substance [11].

Near-infrared radiation (NIR) spectroscopy

Near-infrared radiation (NIR) spectroscopy also shows promise in delineating tumor margins. Investigations led by Butte et al. revealed NIR's utility in displaying microvessel involvement and precisely defining tumor borders [12]. The technique works by shining NIR light into the tissue and measuring the reflected or transmitted light. The unique optical properties of tumorous tissue, such as altered blood supply and metabolic profiles, result in distinct patterns of light absorption and scattering. These patterns are analyzed in real time, allowing for immediate identification of tissue type. This modality is gaining attention for its cost-effectiveness and clinical feasibility [13].

Optical coherence tomography (OCT)

Optical coherence tomography (OCT) leverages low-coherence interferometry to differentiate between solid tumors, diffusely invaded brain tissue, and adjacent normal brain parenchyma with high spatial resolution [14]. By splitting a light source into a sample and reference arm, and recombining the scattered and reflected light, OCT generates cross-sectional images with micrometer-scale resolution. This allows for 'optical biopsies,' offering histology-level detail without tissue resection [15]. Its high soft tissue contrast surpasses established oncological imaging modalities in anatomical detail, aiding in early cancer diagnosis [16]. The technology's rapid image acquisition and adaptability to miniaturized probes position it as a novel intraoperative tool for detecting residual tumors and guiding neurosurgical resections [14, 16]. Notably, OCT requires no labeling and delivers quantitative, depth-resolved tumor information, setting it apart from other optical modalities like spectroscopy, fluorescence, and DOT [16].

Fluorescence and diffuse reflectance spectroscopy

For intraoperative diagnosis, minimally invasive optical techniques such as fluorescence spectroscopy (FRS) and diffuse reflectance spectroscopy (DRS) are garnering attention. FRS illuminates tissue with specific wavelengths to excite endogenous fluorophores like amino acids and enzyme cofactors. The emitted light, captured and analyzed, reveals dynamic biochemical compositions, cellular structures, and metabolic statuses within tumors [17–19]. DRS, on the other hand, shines white light onto tissue and measures back-scattered light, providing insights into tissue biochemistry, such as hemoglobin concentration, and morphological features like scatter size and shape [20]. Combining FRS and DRS has shown promise in differentiating brain tumors from normal tissue. Lin et al. utilized steady-state autofluorescence and diffuse reflectance to effectively distinguish normal cortex from brain tumors [21]. In animal studies, Butte et al. demonstrated that gliomas and normal cortex could be differentiated using indocyanine green, BLZ-100, and a charge-coupled device camera [12].

In summary, advancements in laser and optical technologies are progressively filling the gaps in real-time, intraoperative tumor diagnostics. These modalities show promise in improving surgical precision, thereby potentially impacting long-term patient outcomes (Fig. 1).

Limitations and challenges

Technical limitations

Optical imaging technologies such as OCT and PAI indeed offer advancements in the realm of intraoperative diagnosis but come with their own set of technical limitations. Limitations include depth penetration, scattering, and absorption of laser light, which can impair their effectiveness, particularly for deeper-seated brain tumors [22]. Factors like tissue heterogeneity, blood flow, and ambient light conditions can also influence the accuracy of these modalities, necessitating meticulous calibration and control. Various methodologies have been proposed to mitigate these limitations, such as utilizing imaging probes with long wavelengths like near infrared II (NIR-II) to enhance tissue penetration, reduce scattering, and ultimately improve image quality [23].

Cost and accessibility

Although some of these techniques are lauded for their cost-effectiveness, the initial investment in specialized equipment and training can be substantial. Also, for modalities that require contrast agents or specialized fluorophores, additional costs are incurred. Even though efforts are underway to develop lower-cost systems that maintain comparable accuracy to commercial systems [24, 25], the financial burden remains a potential challenge. Moreover, the expertise level of the surgeons in using these tools can influence their widespread adoption. With technologies like confocal laser microscopy, an inexperienced user might misinterpret artifacts as hypercellularity, thus affecting the diagnostic outcome [26]. Therefore, it is important for medical training programs to include curricula that ensure proficiency in the use and interpretation of these emerging tools.

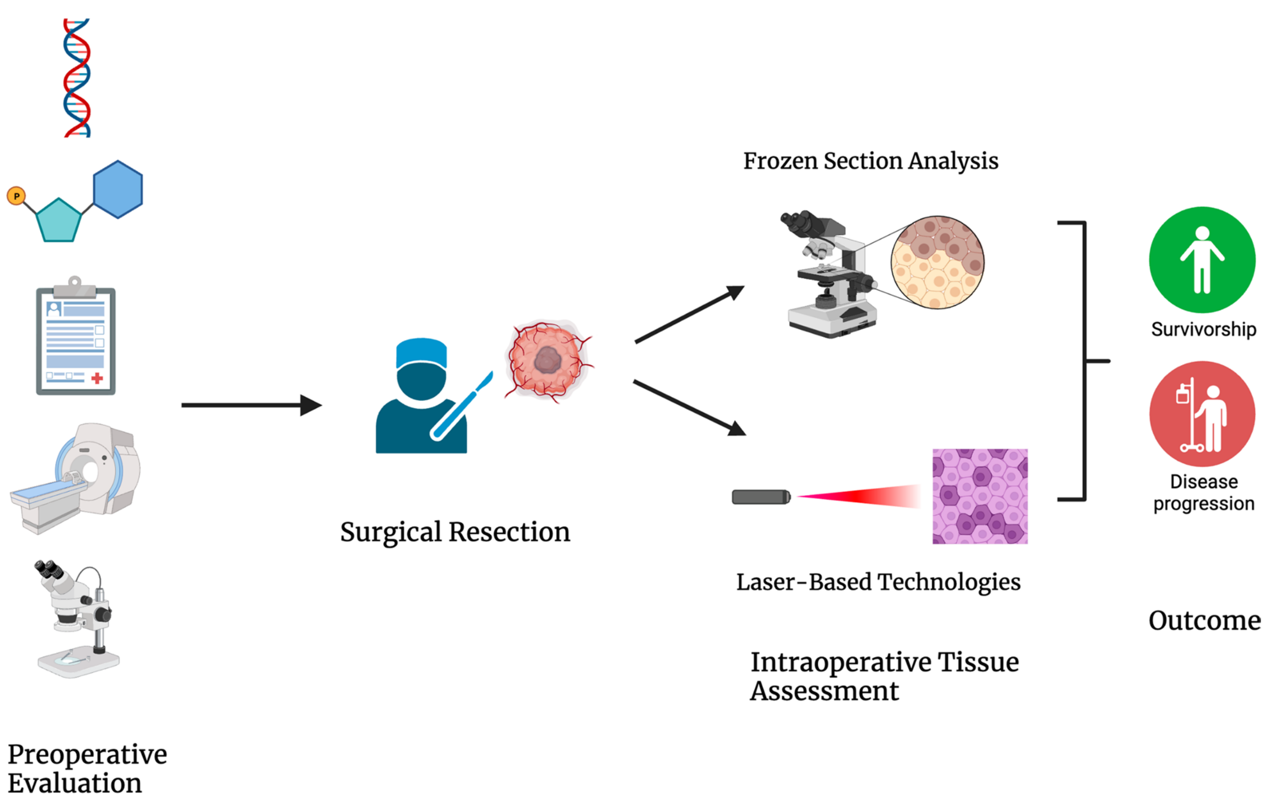

Fig. 1 Neurosurgical workflow diagram demonstrating the application of laser-based technologies for intraoperative tissue analysis and tumor margin differentiation. Created with BioRender.com

Safety concerns

These technologies aim to improve the safety of surgical procedures, but they are not without their own safety concerns. For instance, increased light intensity is required for deeper imaging but can result in thermal tissue damage if not properly administered. Standard safety parameters have been established to avoid such issues [27]. While the American National Standards Institute provides a maximum permissible exposure (MPE) for laser radiation to the eye and skin, tissue-specific limits for organs like the brain are yet to be standardized [28]. Methods such as the use of tissue-mimicking phantoms can help in safety testing, device design optimization, and calibration [29]. As in the case of laser-induced fluorescence (LIF) using 5-aminolevulinic acid (5-ALA), concerns include potential allergic reactions, toxicity, and the unknown long-term effects of repeated use.

Standardization and validation

A significant challenge for these technologies is the lack of standardized protocols and validation studies. Temporal drift, influenced by factors like aging components or temperature changes, affects instrument accuracy and requires regular calibration and data quality validation. Tools like Raman spectroscopy can be quantitatively validated once set to specific calibrations [30]. Despite some in vivo and ex vivo experiments validating aspects of these technologies, large-scale, multi-center trials are essential for their clinical standardization and validation [31].

Research and development

Laser-based advanced diagnostic modalities can be very complex and require the coordinated efforts of interdisciplinary teams, including neurosurgeons, radiologists, oncologists, physicists, engineers, clinical researchers, and technologists, to name a few.

Radiology plays an important role in the multidisciplinary collaboration between oncology and neurosurgery for the management of brain tumors. It not only integrates traditional imaging methods like MRI, CT, and PET scans with new laser diagnostic technologies but also specializes in imaging fusion and brain shift analysis. The latter is important for real-time surgical adjustments, compensating for tissue shifts during procedures to maintain surgical accuracy. Image fusion software combines various imaging modalities, offering a multidimensional view that informs surgical planning and intraoperative decision-making.

In their capacity for protocol and guideline creation, radiologists standardize the use of these technologies, ensuring their safe and effective incorporation into clinical workflows. Radiologists also play an integral part in postoperative evaluations to assess treatment efficacy and monitor for tumor recurrence, allowing clinicians to adapt ongoing treatment plans. These coordinated efforts between radiologists, oncologists, and neurosurgeons can result in more accurate diagnoses, enhanced surgical planning, and better postoperative outcomes for patients with brain tumors.

Advancements in laser-based diagnostic technologies are under active investigation for their utility in neurological applications. Ongoing clinical trials are evaluating hyperspectral imaging for intraoperative diagnosis of low-grade gliomas, employing a broad electromagnetic spectrum for enhanced sample analysis [32–34]. Similarly, the CONVIVO system, a type of confocal microscopy, and Raman spectroscopy are also in trials, where their intraoperative tissue analysis capabilities are compared against standard histopathology [35, 36]. In addition to emerging technologies, established methods like laser speckle contrast imaging (LSCI) are studied for their ability to visualize cerebral vasculature intraoperatively, specifically in comparison to indocyanine green angiography (ICGA) [37].

Emerging technologies demonstrate potential in advancing the diagnosis and treatment of brain tumors. Surface-enhanced Raman spectroscopy, which employs nanostructured metals for signal amplification, shows promise for high-sensitivity brain tumor diagnostics [38–40]. Multiphoton microscopy offers advantages like improved resolution and tissue penetration and is considered for clinical applications, often alongside other modalities like Raman spectroscopy and fluorescence lifetime imaging microscopy (FLIM) [41–45].

FLIM itself has shown feasibility in real-time neurosurgical diagnostics and the detection of metastatic disease in cerebrospinal fluid [46–48]. Laser-induced breakdown spectroscopy, analyzed in conjunction with spiking neural networks, also offers potential in tissue composition analysis [49]. Elastic light scattering spectroscopy (ESS) and light sheet microscopy (LSM) are under investigation for their utility in brain tissue analysis and three-dimensional imaging, respectively, with LSM's new application in 3D imaging of solvent-cleared organs (3DISCO) showing promise in tissue histopathology [50–56]. These technologies are in varying stages of research and hold potential for future clinical implementation.

Conclusion

As it stands, the application of laser-based diagnostic technologies in the context of brain tumor diagnosis and surgical guidance is an evolving field. Although conventional imaging modalities like CT and MRI have been the cornerstone of neurological diagnostics, they have limitations, particularly during real-time intraoperative guidance. Laser technologies offer a compelling alternative by providing real-time, high-resolution imaging data. However, their use remains predominantly experimental, and most are either in the clinical trial phase or still confined to pre-clinical research.

Despite their promise, laser-based diagnostic technologies are not without challenges. The physics of light absorption and reflection complicates the imaging of deep anatomical structures, and thus, further research is needed to overcome these technical hurdles. Moreover, cost and regulatory factors may present barriers to widespread clinical adoption.

Going forward, randomized controlled trials with larger patient populations are essential to better assess the clinical utility, safety, and cost-effectiveness of these laser-based systems. Moreover, interdisciplinary collaborations between radiologists, neurosurgeons, and engineers will be crucial for the iterative refinement and validation of these technologies. Future research should also focus on the integration of laser-based diagnostics with existing imaging modalities to create multimodal systems that capitalize on the strengths of each technique.

In conclusion, while laser-based diagnostic technologies hold promise for improving the diagnosis and surgical treatment of brain tumors, their development is still in relatively early stages. Rigorous clinical evaluation and ongoing technical innovation will be required for their successful transition from the research laboratory to the operating room.

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K.P. led the conceptualization of the review paper, managed project administration and coordinated the review process, involved in original draft preparation, literature search, and analysis, participated in the review and editing of the manuscript. G.M., S.R., A.P., A.A., J.C., A.R., J.Z. were responsible for original draft preparation, literature search, and analysis. D.R. participated in the review and editing of the manuscript. B.L.W. contributed to the conceptualization of the review and participated in the review and editing of the manuscript. All authors read and approved the final manuscript.

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