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Review

ADVANCES IN INTRAOPERATIVE PROBE TECHNOLOGY FOR REAL-TIME TUMOR DELINEATION: A TEN-YEAR REVIEW FOR SURGICAL ONCOLOGY

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ABSTRACT

Introduction: Achieving a "clean surgical margin" in oncologic surgery is a fundamental goal for preventing local recurrence and improving patient survival. The persistence of high rates of positive surgical margins (PSMs) highlights the inadequacy of traditional visual and tactile assessment methods, driving the need for more precise, real-time intraoperative guidance technologies. The clinical consequences of PSMs, including high re-excision rates that delay essential adjuvant therapies, underscore the urgency for such innovation.

Methods: This review aims to comprehensively analyze the major intraoperative probe technologies that have transformed the practice of oncologic surgery over the last decade: radioguided surgery (RGS), fluorescence-guided surgery (FGS), advanced intraoperative ultrasound (IOUS), and spectroscopic probes. The physical principles, technological evolution, clinical applications, advantages, and limitations of each modality are comparatively analyzed.

Results: Key trends examined include the transition from simple count-based detection to imaging in RGS; the paradigm shift in FGS from non-specific agents to biologically targeted and activatable "smart" probes; the revitalization of IOUS through integration with surgical navigation and functional techniques; and the potential of spectroscopy to provide in-situ "optical biopsy," which is heavily dependent on artificial intelligence (AI) for interpretation. It is emphasized that no single technology is the optimal solution for every clinical scenario; rather, the future lies in the intelligent orchestration of multimodal systems where AI serves as the central interpretive engine for comprehensive decision support.

Conclusions: The development and integration of these technologies are transforming surgical decision-making from a subjective assessment to an approach guided by real-time, biologically relevant data, holding the promise to reduce PSM rates and shape the future of oncologic surgery.

Keywords: Surgical Oncology; Margins of Excision; Surgery, Computer-Assisted; Fluorescence Guided Surgery; Artificial Intelligence.

INTRODUCTION

The foundational principle of oncologic surgery is the complete removal of malignant tissue (1) while preserving maximal healthy tissue and function (2,3). The status of the surgical margin, the tissue at the edge of the resected specimen, is one of the most powerful predictors of local recurrence (4). Failure to achieve a 'clean' or negative margin results in a positive surgical margin (PSM), a critical failure point that significantly increases the risk of local disease recurrence and can diminish survival outcomes (5,6). The clinical consequences are substantial. In breast-conserving surgery (BCS), for example, an estimated 20% to 40% of patients require a second operation due to PSMs (4,7). These re-excisions delay essential adjuvant therapies, increase patient anxiety, and can compromise cosmetic results (4). This challenge extends across specialties. In neuro-oncology, maximizing the extent of resection (EOR) is paramount for improving outcomes in patients with gliomas (2), while in head and neck, colorectal, and gynecological cancers, incomplete resection remains a primary driver of poor prognosis (5,8,9).

This persistent problem highlights a fundamental inadequacy in the conventional surgical paradigm, which has historically relied on direct visualization and tactile feedback (1)—methods that are inherently subjective and often insufficient, particularly with the rise of minimally invasive techniques that limit palpation (10). Early attempts to augment these senses involved vital dyes for lymphatic mapping; however, these agents lack tumor-specific biological targeting and instead rely on passive lymphatic drainage patterns (11,12). Intraoperative pathology, through frozen-section analysis or cytology, offers microscopic assessment but is hindered by significant time delays of 20 to 55 minutes, resource intensity, and the potential for sampling errors, making it an imperfect and not universally available solution (1,7,13).

This "clinical pull" for more accurate, real-time feedback has spurred a technological inflection point, leading to the development and maturation of a diverse array of intraoperative technologies. Radioguided surgery (RGS) represents one of the earliest and most established of these modalities, leveraging gamma-detecting probes to localize tissues labeled with radionuclides (5,12,14). More recently, fluorescence-guided surgery (FGS) has gained significant momentum, utilizing fluorescent agents that accumulate in or are activated by tumors,

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rendering them visible under specific light wavelengths (3,10,15,16). In parallel, intraoperative ultrasound (IOUS) provides real-time, high-resolution anatomical imaging, addressing challenges in tumor localization and resection without requiring exogenous contrast agents (9,17). Concurrently, other optical and molecular technologies like optical coherence tomography (OCT), Raman spectroscopy, and intraoperative mass spectrometry are emerging, offering cellular and molecular-level data to guide resection with unprecedented detail (1,7,13). The maturation of these tools, often used in combination with advanced imaging like intraoperative MRI (2,6), is reshaping modern surgical practice. While numerous reviews have expertly detailed these technologies in isolation (9,10,12,14,15,17), a comprehensive, cross-modal synthesis that critically compares their principles, capabilities, and clinical evidence is lacking. This review aims to bridge that gap by providing a structured analysis of the principal intraoperative technologies, equipping the oncology community with an integrated perspective to navigate this rapidly evolving landscape and advance the goal of precision surgical oncology.

RESEARCH FINDINGS

Study Design

The Evolution of Radiation-Detecting Probes

Radioguided surgery (RGS) has been a foundational technique in surgical oncology for decades, centered on the use of gamma-detecting probes to localize tissues pre-labeled with a gamma-emitting radiopharmaceutical (12,16). Over the last decade, the technological trajectory of RGS has been marked by a clear evolution from simple, non-spatial count-based detection toward high-resolution intraoperative imaging, driven by a clinical demand for greater spatial context to improve surgical precision (16,18).

Gamma Probes for Sentinel Lymph Node Biopsy (SLNB)

The most established and widely practiced application of RGS is sentinel lymph node biopsy (SLNB), a standard-of-care procedure for staging cutaneous melanoma and early-stage breast cancer (19,20). The technique involves injecting a radiotracer, typically Technetium-99m (Tc-99m), which migrates to the primary draining lymph node. Intraoperatively, a surgeon utilizes a handheld gamma probe to home in on the area with the highest count rate, thereby identifying the "hot" sentinel node for excision (21). Early probes relied on scintillation detectors, but the field has seen significant advances with the adoption of semiconductor detectors made from materials like cadmium zinc telluride (CZT), which offer superior spectroscopic resolution at room temperature (22,23). These detectors convert the 140 keV gamma photons from Tc-99m into an electronic signal, which is then translated into an audible count rate and a numerical display (24). The ultimate success of the procedure, however, remains highly dependent on the probe's fundamental performance characteristics—its sensitivity to detect a signal and its spatial resolution to distinguish that signal from background radiation (25).

Intraoperative Imaging: Portable Gamma Cameras (PGCs)

While a simple gamma probe provides essential localization data, it lacks spatial information. This limitation has fueled the development of portable gamma cameras (PGCs), which represent a significant technological leap by offering a real-time, two-dimensional scintigraphic image of radiotracer distribution (18,26). This transition from non-spatial detection to intraoperative imaging provides crucial anatomical context, aiding surgeons in planning incisions and navigating complex surgical fields (16). However, this advancement introduces an engineering trade-off: the added imaging capability often comes at the cost of increased size and weight, which can limit maneuverability within the surgical wound (25). To balance these factors, a synergistic workflow has emerged where a PGC is used for initial, wide-field localization, followed by a smaller, nimbler conventional probe for final, precise pinpointing of the target node (27).

New Frontiers in RGS

Probes for PET-Guided Surgery

Perhaps the most exciting research frontier in RGS is the development of probes for use with positron emission tomography (PET) radiotracers, such as [18F] FDG or agents targeting prostate-specific membrane antigen (PSMA) (10,28). This would allow surgeons to precisely resect metabolically active or molecularly specific lesions identified on preoperative PET scans (29,30). This pursuit, however, presents a significant physics challenge. The high-energy 511 keV photons produced by PET tracers are far more penetrating than the 140 keV photons of Tc-99m, demanding detectors with thicker crystals and more substantial shielding, which can make probes bulky (23). A recent systematic review confirmed that many PET-guided procedures are still performed with conventional gamma probes not optimized for these high energies, highlighting a critical hardware gap (29). Innovations are underway to address this, including the development of probes with novel detector materials, such as the LaBr3(Ce) crystal, capable of high spectral and spatial resolution for differentiating multiple isotopes simultaneously (31).

Beta-Emitting Probes

Another emerging area is the use of beta-emitting radionuclides for radioguidance. Beta particles have a much shorter range in tissue compared to gamma photons, meaning that any detected signal must originate from a source in very close proximity to the probe (23). This property offers the potential for extremely high-resolution localization with minimal background interference. Radionuclides like Yttrium-90, already used therapeutically, could be adapted for intraoperative detection to enable highly precise, targeted resections (32). However, this technology has not yet reached routine clinical practice and faces challenges related to detector design and logistical implementation (5).

Fluorescence-Guided Surgery (FGS): Lighting the Way to Tumor Resection

Fluorescence-guided surgery (FGS) has emerged as one of the most dynamic and rapidly evolving areas of intraoperative guidance, with a market size projected to grow significantly in the coming years (33). The technique leverages the emission of light from fluorescent molecules (fluorophores) to make tumors "glow," allowing for real-time visual demarcation from surrounding healthy tissue (15).The field's progress is characterized by a fundamental shift from using non-specific, passively accumulating agents to developing sophisticated, biologically targeted probes that actively seek out and identify cancer cells based on their molecular properties (3,34,35).

Principles of Optical Imaging: Autofluorescence vs. Exogenous Agents

Optical imaging in surgery can be broadly divided into two approaches. The first relies on tissue autofluorescence, where endogenous molecules within the tissue (like collagen and NADH) naturally fluoresce when excited by light of a specific wavelength. While this method is label-free, the differences in autofluorescence signals between cancerous and normal tissues are often subtle, leading to low signal-to-background ratios (SBR) (10). The more common and clinically advanced approach involves the administration of an exogenous fluorescent agent. These agents are designed to preferentially accumulate in malignant tissue, creating a high-contrast signal that can be detected by a dedicated camera system or a handheld probe. The goal is to maximize the SBR, making the tumor stand out brightly against a dark background of normal (10).

Near-Infrared (NIR) Probes and Agents

The core tension in FGS lies in the trade-off between the shallow *tissue penetration depth* of light and the clinical need for high *signal specificity*. Light in the near-infrared (NIR) spectrum (approximately 700-900 nm) offers the best compromise, as it has deeper tissue penetration (though still typically <1 cm) and lower tissue autofluorescence compared to visible light (34). The evolution of NIR agents reflects a concerted effort to overcome this trade-off by dramatically improving signal specificity to compensate for limited depth.

Non-Specific Agents: The Role and Evolution of ICG

The first and most widely used agent is Indocyanine Green (ICG), a dye approved by the U.S. Food and Drug Administration (FDA) for other indications for over 50 years (36). ICG is inexpensive and has an excellent safety record. It is used in oncology for applications like SLN mapping and visualizing tumor perfusion (37). However, the primary limitation of ICG is its lack of tumor specificity. It accumulates in tumors largely due to the Enhanced Permeability and Retention (EPR) effect, where leaky tumor blood vessels and poor lymphatic drainage cause the molecule to be retained (38). This passive mechanism means ICG can also leak out of the tumor, reducing the SBR and making precise margin delineation difficult (37). A recent innovation to improve ICG's utility is the "second window ICG" (SWIG) technique, particularly in glioma surgery. This involves administering a high dose of ICG approximately 24 hours before surgery, allowing for a long plateau period of fluorescence that can better delineate tumor boundaries (39).

Targeted Probes

The major advancement of the last decade has been the development of probes that are no longer passive bystanders but are actively involved in biological targeting, representing a convergence of probe engineering with molecular biology (1,36,40,41) These probes involve conjugating a fluorophore to a molecule, such as an antibody, peptide, or small molecule, that binds to a specific receptor or protein overexpressed on the surface of cancer cells (42). A compelling example is ICG-p28, which links ICG to the tumor-targeting peptide p28. The p28 peptide is known to preferentially penetrate cancer cells without significant toxicity. In preclinical animal models of breast cancer, image-guided surgery using ICG-p28 resulted in a dramatic reduction in the amount of residual tumor DNA at the surgical margin compared to surgery with ICG alone or conventional palpation. This translated into a significantly lower tumor recurrence rate, with 92% specificity (43).

Activatable Probes

This even more sophisticated strategy involves probes that are designed to be optically silent or "off" until they encounter a specific feature of the tumor microenvironment, at which point they are switched "on" and become fluorescent (44). This mechanism dramatically increases the SBR by minimizing background signal from non-target areas. This is the principle behind the Lumicell Imaging System, which uses the agent LUM015. LUM015 is a protease-activated agent that is administered intravenously before surgery. It becomes fluorescent only when it is cleaved by proteases, such as cathepsins, which are known to be highly active and overexpressed in many cancers (7). Another example is VGT-309, which is also activated by cathepsins and uses ICG as its fluorescent component (45). The progression from passive (ICG) to targeted to activatable probes represents a deliberate and increasingly successful strategy to maximize the signal-to-background ratio, thereby overcoming the inherent limitations of optical imaging.

Case Study: The Lumicell System and Real-Time Cavity Assessment

The Conventional specimen-focused assessment is described as "inherently flawed" because the residual tumor is in the patient, not on the specimen (7). The Lumicell system addresses this by moving assessment to the patient's bedside. Post-excision, a sterile handheld probe scans the lumpectomy cavity, providing immediate feedback on residual fluorescence to guide targeted re-excision.

Nanoparticle-Based Probes

Another area of active research is the use of nanoparticles as platforms for fluorescent probes. Quantum dots (QDs), which are semiconductor nanocrystals, are of particular interest due to their bright, tunable fluorescence and high photostability (41) Like ICG, they can accumulate in tumors via the EPR effect. However, a significant barrier to their clinical translation is the potential for long-term toxicity, as many QDs are made with heavy metal cores like cadmium, which can be cytotoxic. While more biocompatible nanoparticles based on silica are being developed, concerns about potential organ injury persist, and extensive safety validation is required before they can be widely used in humans (46).

For a practicing surgeon, FGS is currently the premier technology for real-time assessment of superficial margins, particularly in breast and brain surgery. The workhorse agent remains ICG, but its non-specificity is a key limitation. In the next 2-3 years, surgeons should watch for the FDA approval and clinical adoption of the first targeted and activatable fluorescent agents. These "smart probes" will dramatically improve tumor contrast and expand the application of FGS to a wider range of cancer types by targeting specific molecular markers (1).

Advanced Intraoperative Ultrasound (IOUS): Beyond Anatomic Localization

Intraoperative ultrasound (IOUS) is a well-established technology that has been used for decades to provide real-time anatomical imaging during surgery ((9). However, its role has been revitalized and expanded over the last ten years through a powerful trend of integration and data fusion (47). Rather than revolutionary changes in the ultrasound transducer itself, the most significant advancements have come from combining IOUS with surgical navigation systems, functional contrast agents, and other imaging modalities. This synergistic approach is

transforming IOUS from a simple localization tool into a dynamic guidance system that can improve resection rates and patient outcomes (17).

The Challenge of Intraoperative Dynamics: The Brain Shift Problem

The central tension in IOUS is the conflict between its primary strength, providing *real-time anatomical updates*, nd its primary weakness---the often-poor *tissue contrast* of standard B-mode ultrasound. This tension is most evident in neurosurgery. A fundamental limitation of relying solely on preoperative imaging (e.g., MRI or CT) for surgical guidance is that the anatomy is not static. Once a surgical procedure begins, tissues shift, deform, and are resected. This is particularly problematic in neurosurgery, where the phenomenon of "brain shift" can occur after a craniotomy. The brain can sag or swell, causing its position to deviate significantly from the preoperative MRI data on which the surgical navigation plan was based (47). This can render the navigation system inaccurate, potentially leading to incomplete tumor resection or injury to critical brain structures (2).

Navigated Ultrasound (nUS): Correcting for Real-Time Changes

IOUS has emerged as a versatile, multifaceted, and cost-effective alternative to more expensive and cumbersome solutions like intraoperative MRI (iMRI) (48). The key innovation has been the development of navigated ultrasound (nUS). In an nUS system, the ultrasound probe is co-registered with the surgical navigation system. This allows the surgeon to acquire real-time ultrasound images and see them displayed directly on the preoperative MRI scans (17). By touching the probe to the brain surface or within the resection cavity, the surgeon can instantly update the navigation system to account for brain shift, effectively re-registering the patient's current anatomy to the surgical plan (48). This ability to track the tumor and surrounding structures in real time has been shown to improve surgical outcomes. Meta-analyses have demonstrated that the use of IOUS is associated with a higher incidence of gross total resection (GTR) in patients with gliomas (49). By providing an up-to-date map of the surgical field, nUS helps surgeons resect tumors more aggressively and confidently.

Functional Ultrasound Techniques

While nUS addresses the problem of anatomical shift, traditional B-mode (grayscale) IOUS can suffer from relatively low spatial resolution and poor image quality, making it difficult to distinguish tumor from surrounding edema, gliosis, or normal brain parenchyma (47). This is the core weakness that has driven the development of functional ultrasound. To overcome this, recent advancements have focused on adding layers of functional, biological information to the anatomical ultrasound image.

Contrast-Enhanced Ultrasound (CEUS)

CEUS involves injecting intravascular microbubble contrast agents to enhance the visualization of tumor vascularity, aiding in boundary delineation and the detection of residual disease, with high diagnostic accuracy in applications like liver metastases (41,50,51). A complementary technique, elastosonography, provides information on tissue stiffness. By measuring deformation under probe compression, it can differentiate stiffer malignant tumors from healthy tissue via a color-coded map (52), with high-resolution variants like optical coherence micro-elastography (OCME) showing high accuracy for margin assessment in breast specimens (2,53).

The Power of Synergy: Multimodal IOUS Approaches

The true power of modern IOUS lies in its ability to be combined with other intraoperative guidance technologies. A prime example of this synergy is the combination of CEUS with the fluorescent agent 5-aminolevulinic acid (5-ALA) for glioma resection. A retrospective study of 230 glioblastoma patients found that using both CEUS and 5-ALA together resulted in a higher EOR than using either modality alone (Della Pepa et al., 2020). Similarly, combining radiofrequency localization with IOUS has been shown to be an effective method for locating non-palpable breast cancers (54). This highlights a key trend in the field: the future of intraoperative guidance is likely not a single "magic bullet" technology, but rather the intelligent fusion of multiple complementary systems to provide the surgeon with a rich, multi-layered view of the surgical field.

Spectroscopic Probes: Towards In-Situ "Optical Biopsy"

The most nascent but potentially transformative class of intraoperative tools are probes based on spectroscopy (55,56). These technologies represent a fundamental conceptual leap, moving beyond imaging to perform real-time, in-situ molecular analysis. The goal of this "optical biopsy" is to provide a diagnostic "fingerprint" of the tissue at the probe tip, differentiating cancerous from healthy tissue based on its intrinsic biochemical composition, without the need for external labels like dyes or radiotracers (57). This approach has the potential to bring the diagnostic power of the pathology lab directly into the operating room (56).

Radiofrequency (RF) Spectroscopy

One of the first spectroscopic technologies to achieve commercialization for margin assessment is the MarginProbe device. This system is based on radiofrequency (RF) spectroscopy. The handheld probe emits a low-power electric field and measures the tissue's response (reflection and absorption) across a range of radiofrequencies. Because cancerous tissue has different dielectric properties (e.g., higher cell density, different water content, altered membrane capacitance) compared to normal tissue, it generates a distinct RF signature. An algorithm analyzes this signature and provides the surgeon with a binary "positive" or "negative" reading for the margin being assessed (58). While the device has been evaluated in prospective clinical trials and has been shown to reduce the absolute rate of re-operation by approximately 6%, its adoption has been somewhat limited. The trials also reported a false-negative rate of 25%, meaning the device failed to identify one in four positive margins (58). A recent systematic review and meta-analysis of intraoperative margin assessment techniques found that RF spectroscopy had a lower pooled sensitivity and specificity compared to other methods like cytology and optical spectroscopy (4).

Vibrational Spectroscopy: A Molecular Fingerprint

The defining tension for spectroscopy is the immense promise of *label-free, real-time molecular diagnostics* versus the profound *data complexity* that makes the raw output uninterpretable to a human. At the forefront of research in optical biopsy are techniques based on vibrational spectroscopy, primarily Raman spectroscopy and Fourier-transform infrared (FTIR) spectroscopy. These powerful analytical methods provide a detailed molecular fingerprint of the tissue, but in doing so, they intensify the reliance on artificial intelligence for interpretation (59).

Principles of Raman and FTIR Spectroscopy

Raman spectroscopy involves illuminating the tissue with a monochromatic laser. Most of the light is scattered without a change in energy (Rayleigh scattering), but a tiny fraction (about 1 in 10 million photons) is scattered with a shift in energy (Raman scattering). This energy shift corresponds directly to the vibrational modes of the molecules in the tissue (e.g., C-H bonds in lipids, amide bonds in proteins). The resulting Raman spectrum is a highly specific plot of these vibrational modes, providing a rich biochemical profile of the tissue (60). FTIR spectroscopy, conversely, measures the absorption of infrared light by the tissue. As with Raman, the specific frequencies of light that are absorbed correspond to the vibrational modes of the molecules present.

The AI Imperative for Spectral Interpretation

The clinical potential of these techniques is immense, but this modality's clinical utility is uniquely and completely dependent on the development of sophisticated machine learning and artificial intelligence (AI) algorithms (61). A single spectrum can contain hundreds or thousands of data points. No human can interpret this raw data in the time-pressured environment of the operating room. Therefore, the AI is not merely an add-on; it *is* the diagnostic component. These algorithms are trained on large datasets of spectra from known tissue types (e.g., normal brain vs. glioma) and learn to recognize the subtle patterns that differentiate them. The AI model then translates the complex spectrum from the probe into a simple, actionable output for the surgeon, such as "tumor" or "normal."

Clinical and Preclinical Evidence

Early ex-vivo studies have demonstrated the feasibility and accuracy of this approach. One study analyzing fresh brain tissue biopsies used AI algorithms to extract information from 60 different Raman peaks. The system was able to distinguish glioma tissue from healthy brain tissue with an accuracy of 83% and a precision of 82% (57,62). In another study, an FTIR-based system analyzed fresh gynecological tissue samples and, using a principal component analysis-linear discriminant analysis (PCA-LDA) model, was able to classify them as malignant or benign with up to 96% accuracy. Critically, the entire process, from sample placement to classification, was completed in less than 5 minutes (61). Handheld Raman probes have shown high sensitivity and specificity in differentiating tumor from normal brain tissue, and recent developments include fiber-optic probes compatible with endoscopic surgery for pituitary adenomas (61). Furthermore, stimulated Raman histology (SRH) is an innovative application that provides rapid, high-resolution tissue images comparable to traditional histopathology, but in a fraction of the time, aiding swift intraoperative diagnosis (56).

Comparative Analysis and Clinical Integration

The last decade has produced a diverse toolkit of intraoperative probe technologies **(Figure 1)**. A critical synthesis of these technologies, **summarized (in Table 1)**, reveals that the optimal choice is highly context-dependent, as no single probe is superior for all scenarios (56). The following comparative analysis explores the inherent trade-offs that clarify the specific clinical applications for each modality.

Comparative Analysis of Probe Modalities

The inherent trade-offs of each technology become clear when examined through the lens of specific clinical challenges. For a surgeon tasked with localizing a deep, non-palpable sentinel node in a melanoma patient, the superior tissue penetration of a conventional gamma probe is non-negotiable, making it the ideal tool despite its lack of spatial imaging (11,12). This technology is the established standard of care, with high sensitivity (>95%) for SLNB. However, the introduction of Portable Gamma Cameras (PGCs) addresses the primary limitation of the conventional probe by providing a crucial layer of 2D visual information, which has been shown to improve preoperative node detection rates and offer spatial context that a simple count-based probe cannot (25). This advantage, however, illustrates a classic engineering trade-off, as the added imaging capability comes at the cost of reduced maneuverability and increased bulk, which can be challenging in a confined surgical field (26).

In contrast, for assessing a superficial margin on the tumor bed during breast-conserving surgery, where deep penetration is not a primary concern, the high-resolution visual feedback of a targeted or activatable Fluorescence-Guided Surgery (FGS) system offers unparalleled precision. Agents like LUM015, which are activated by the tumor microenvironment, achieve an extremely high signal-to-background ratio, enabling the detection of residual disease with high sensitivity and specificity (100% and 85%, respectively, for residual breast cancer in one study) (7). This biologically driven approach stands in stark contrast to label-free technologies like RF Spectroscopy. While the MarginProbe device offers the advantage of immediate, agent-free feedback, its clinical utility is hampered by lower diagnostic accuracy. A recent meta-analysis reported a pooled sensitivity of approximately 65% and a specificity of 68%, and clinical trials have noted a significant false-negative rate of around 25%, limiting its reliability for definitive margin assessment (4,58).

For deep-seated gliomas, where "brain shift" can render preoperative MRI-based navigation inaccurate by several millimeters, navigated ultrasound (nUS) becomes the essential tool for re-establishing anatomical reality—a task for which both RGS and FGS are unsuited (47,48). By providing real-time anatomical updates, nUS has been shown in meta-analyses to significantly increase the rate of gross total resection in high-grade gliomas, with one study reporting a GTR rate of 64% (49). Finally, for the most challenging cases where visual and anatomical cues are ambiguous, **spectroscopic probes** represent the frontier of "optical biopsy." By analyzing the molecular fingerprint of tissue in situ, techniques like Raman spectroscopy have demonstrated high ex-vivo accuracy (90% sensitivity, 95% specificity for glioma) in differentiating tumor from normal brain, holding the promise of providing definitive molecular evidence to guide the final resection (56,62). However, this technology is uniquely dependent on sophisticated artificial intelligence for interpretation and is currently limited by a penetration depth of mere microns (59).

The Rise of Multimodal Approaches

The inherent and complementary trade-offs of each technology are the primary driver for the development of multimodal strategies that combine the strengths of different systems. This trend represents a clear evolutionary trajectory in surgical guidance, moving from subjective methods and passive agents toward the integration of multiple, objective data streams to create a comprehensive, real-time decision support system for the surgeon **(Figure 2)**.

The combination of contrast-enhanced ultrasound (CEUS) with 5-ALA fluorescence for glioma resection is a prime example of this synergy in action. In this approach, the surgeon benefits from

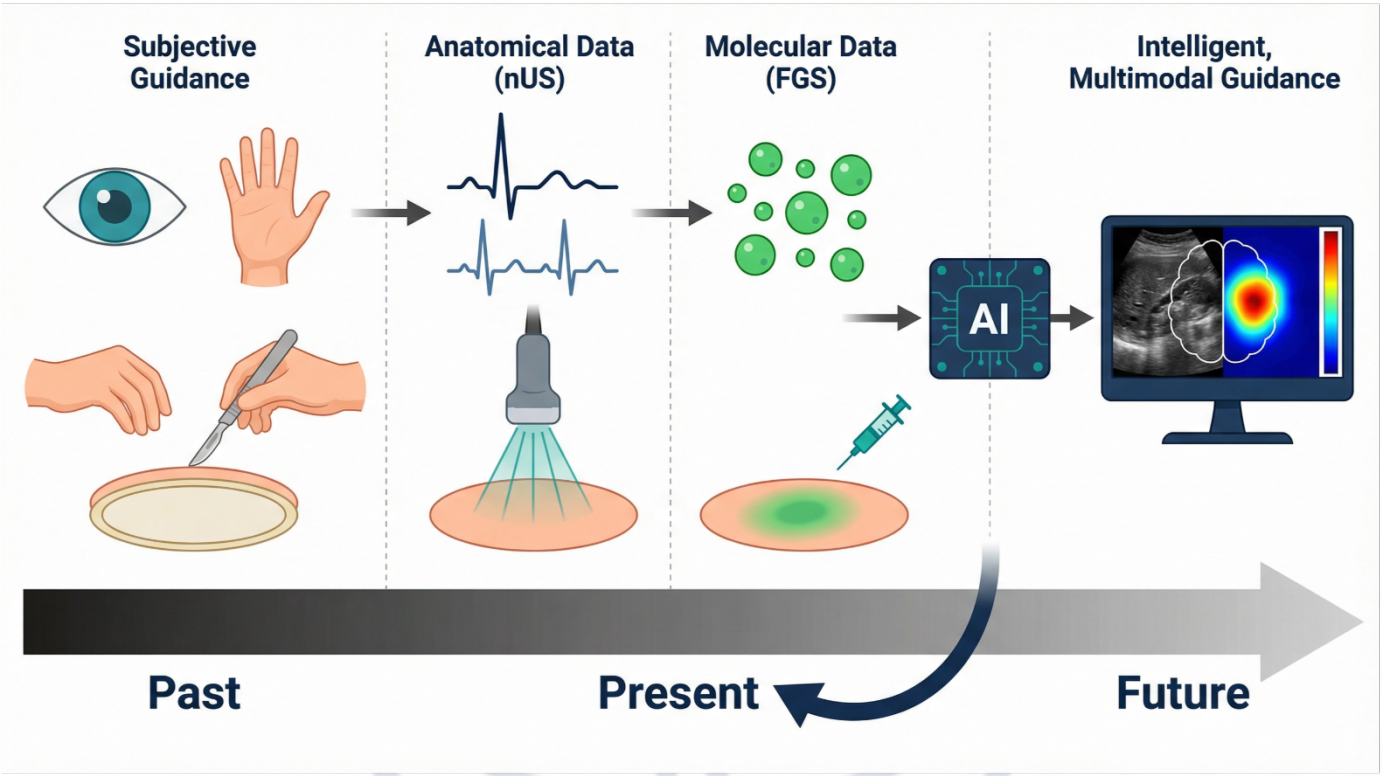

Figure 2. The Evolutionary Trajectory of Intraoperative Guidance. Surgical guidance has progressed from subjective methods (left) toward integrated, multimodal systems using biologically active probes (right). The convergence of data streams (e.g., anatomical from nUS, molecular from FGS), interpreted by artificial intelligence (AI), creates a comprehensive decision support system for the surgeon. The figure is an original illustration created by the authors (Created with BioRender.com).

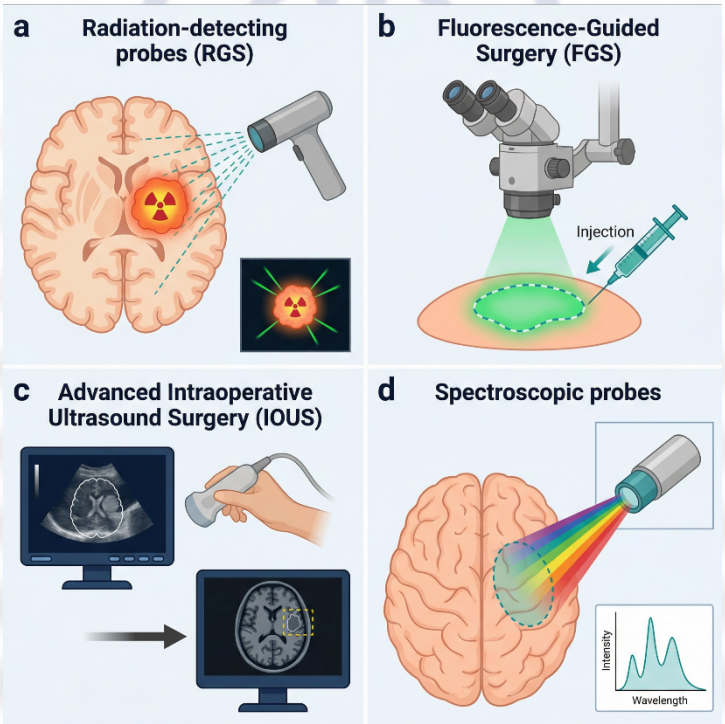

Figure 1. Principal Classes of Intraoperative Probe Technologies. (a) Radiation-detecting probes localize tissues using gamma-emitting radiotracers. (b) Fluorescence-guided surgery (FGS) uses fluorescent agents to make tumors visually distinct. (c) Intraoperative ultrasound (IOUS) provides real-time anatomical imaging, often integrated with navigation. (d) Spectroscopic probes perform in-situ molecular analysis ("optical biopsy") to differentiate tissue types. The figures are original illustrations created by the authors (Created with BioRender.com).

Table 1: Comparative Analysis of Modern Intraoperative Probe Technologies.

Technology	Physical Principle	Primary Oncologic Applications	Most Common Tumor Types	Reported Diagnostic Accuracy (Sensitivity/Specificity)	Regulatory Status / Clinical Stage	AI / Computational Dependency	Workflow Integration	Specific Examples (Agent/Device)	Key Advantages	Clinical Limitations & Challenges
Conventional Gamma Probe	Scintillation or semiconductor detection of gamma photons (^{99m}Tc)	Sentinel lymph node biopsy (SLNB), localization of radiolabeled tumors	Breast Cancer, Melanoma (11,19)	High sensitivity for SLNB (>95%) (11)	Established Standard of Care; FDA/CE marked devices widely available (12)	**Low:** Simple count rate and audio signal interpretation by the user.	Preoperative radiotracer injection; intraoperative scanning of surgical field to find "hot spot" (11)	Neoprobe, C-Trak, Europrobe (23,30)	Deep tissue penetration, established workflow, high maneuverability, relatively low cost	Uses ionizing radiation, requires preoperative radiotracer injection, provides non-spatial count rate only
Portable Gamma Camera (PGC)	Miniaturized gamma camera providing a 2D scintigraphic image	SLNB, intraoperative tumor imaging	Breast Cancer, Cutaneous Malignancies (25,26)	Superior node detection vs. conventional camera; higher sensitivity at close range (25)	Commercially available; FDA/CE marked devices in clinical use (26)	**Low:** Provides a direct 2D image for visual interpretation by the surgeon.	Pre-incision overview, intraoperative localization, and post-excision cavity check (27)	Sentinella, CrystalCam (25,26)	Provides spatial/visual information, high sensitivity	Uses ionizing radiation, limited maneuverability due to size/weight, higher cost than probes
PET RGS Probe	Detection of high-energy (511 keV) annihilation photons ([^{18}F] FDG, PSMA-tracers)	Resection of metabolically active tumors/metastases	Prostate Cancer, Neuroendocrine Tumors, Medullary Thyroid Cancer (28,29)	Varies, promising for complete resection and salvage surgery (28,29)	Largely investigational; used in Phase II/III clinical trials (29)	**Low:** Count-based detection similar to conventional probes.	Leverages preoperative PET/CT for planning; intraoperative probe finds PET-avid lesions ((30)	Drop-in probes, dedicated high-energy probes under development (28)	Targets tumor biology (metabolism, receptor expression), leverages preoperative PET imaging	High-energy photons are challenging to collimate, probes can be bulky, requires PET tracer access
FGS (Targeted/Activatable)	Detection of NIR fluorescence from biologically targeted agents	Real-time margin assessment, tumor bed visualization, nerve sparing	Ovarian, Lung, Gliomas, Head & Neck Cancers (36,39)	High sensitivity and specificity (e.g., 100% Sens / 85% Spec for residual breast cancer) (7)	Varies: some agents FDA-approved (5-ALA); many in Phase I-III trials (OTL38, VGT-309) (39)	**Low-Medium:** Primarily visual, but AI is emerging for quantitative fluorescence analysis ((35)	Preoperative agent administration; real-time visual guidance during resection and cavity assessment (7)	5-ALA (Gleolan), LUM015 (Lumicell System), OTL38, VGT-309 ((7,39)	High SBR, real-time visual feedback, no ionizing radiation, targets tumor biology	Limited tissue penetration depth (<1 cm), requires novel agent administration and regulatory approval
Navigated Ultrasound (nUS)	Real-time acoustic imaging integrated with surgical navigation	Tumor debulking (esp. neurosurgery), correcting for tissue shift	Brain Tumors (esp. Gliomas) (47,48)	Increases rates of gross total resection (e.g., 64% in HGG) (49)	Established clinical use; FDA/CE marked systems commercially available (47)	**Medium:** AI used for image fusion and segmentation; emerging for real-time tumor detection (55)	Real-time registration with preoperative MRI to correct for brain shift; continuous guidance (48)	Brainlab, BK Medical systems (48)	Real-time anatomical updates, no ionizing radiation, relatively low cost, widely available	Operator dependent, image quality can be limited, requires navigation system infrastructure
Raman/FTIR Spectroscopy	Inelastic light scattering or infrared absorption (molecular vibrations)	"Optical biopsy" for in-situ margin assessment	Brain Tumors (Glioma), Gynecological Cancers (ex-vivo) ((61,62)	High ex-vivo accuracy (e.g., 90% Sens / 95% Spec for glioma) (62)	Largely investigational; used in ex-vivo studies and early-phase clinical trials (56)	**High:** Clinical utility is completely dependent on sophisticated machine learning algorithms for spectral interpretation (59)	Point-based "optical biopsy" of margins; Stimulated Raman Histology (SRH) for rapid ex-vivo slide generation (56)	Handheld fiber-optic probes, SRH microscopes (56,62)	Label-free (no agent required), provides molecular/biochemical information, rapid	Very limited penetration depth (microns), data complexity requires advanced AI, largely investigational
RF Spectroscopy (MarginProbe)	Measurement of tissue dielectric properties across radiofrequencies	BCS margin assessment	Breast Cancer (BCS) (4,58)	Sensitivity: ~65%; Specificity: ~68% (meta-analysis data) (4)	FDA-approved; commercially available (58)	**Medium:** Relies on a proprietary, pre-trained algorithm to classify tissue based on RF signature.	Post-excision assessment of lumpectomy specimen margins by touching probe to specimen surface (58)	MarginProbe System ((58)	No agent required, provides immediate binary feedback	Modest impact on re-excision rates, significant false-negative rate (~25%) (58), limited to surface measurements

two distinct but complementary layers of information: the 5-ALA fluorescence provides high-sensitivity visualization of microscopic tumor infiltration on the surface, while CEUS offers real-time information about the tumor's deep vascularity and its relationship to underlying anatomical structures. A retrospective study of 230 glioblastoma patients found that fusing these data streams, either mentally or through integrated imaging platforms, allows surgeons to make more informed decisions, leading to demonstrably higher rates of complete resection than with either modality alone (63).

This paradigm suggests that the future of intraoperative guidance lies not in the victory of a single technology, but in the intelligent orchestration of "procedure-specific technology cocktails" tailored to the unique biological and anatomical challenges of each operation. For instance, a glioblastoma resection cocktail might involve navigated IOUS to correct for brain shift and provide deep anatomical context (47), combined with 5-ALA fluorescence for microscopic tumor visualization on the surface (39) and CEUS to identify foci of residual vascularized tumor (63). A nerve-sparing prostatectomy cocktail could fuse PSMA-targeted RGS for identifying positive lymph nodes (28) with IOUS/Elastography for real-time anatomical guidance near delicate neurovascular bundles (52). Similarly, a head and neck cancer cocktail might pair FGS for assessing superficial mucosal margins (40) with IOUS to determine the depth of invasion and proximity to critical structures like the carotid artery. As illustrated in Figure 2, the convergence of these disparate data streams, increasingly processed and integrated by artificial intelligence algorithms (35,59), is transforming surgical guidance from a process of simple detection into one of comprehensive, real-time, data-driven decision-making.

DISCUSSION

The last decade has marked a transformative period for oncologic surgery, driven by a clear evolutionary trajectory toward data-driven, biologically informed guidance, as summarized in **(Figure 2)**. This progress is characterized by a shift from non-spatial detection to high-resolution imaging in radioguidance (16,26), a paradigm shift from passive agents to "smart" targeted probes in fluorescence imaging (36,64), the revitalization of mature technologies like ultrasound through multimodal integration (47,63), and the emergence of spectroscopy for in-situ "optical biopsy" (56,57).

Despite this technological progress, the path from prototype to standard-of-care is fraught with formidable hurdles. The translation of these innovations is contingent on overcoming substantial regulatory and economic barriers that can stifle innovation (64). Furthermore, seamless workflow integration is critical, as any device that is cumbersome or slow will face resistance from surgical teams accustomed to the efficiency of established methods like intraoperative pathology, despite its known delays and limitations (9,13,65).

A critical insight from this review is that artificial intelligence (AI) is the central enabling technology for the next generation of intraoperative probes. Rather than merely automating tasks, AI is actively being deployed to interpret complex intraoperative data streams with concrete clinical applications. For instance, in neurooncology, AI models applied to stimulated Raman histology (SRH) and vibrational spectroscopy can accurately classify glioma infiltrations versus healthy brain tissue in near real-time, matching the diagnostic accuracy of traditional neuropathology (57,62). Similarly, machine learning algorithms are being utilized for the real-time segmentation of tumors during intraoperative ultrasound (IOUS), providing immediate boundary delineation for the surgeon (55). Beyond interpretation, AI fundamentally improves raw data quality; deep learning techniques can perform real-time image de-noising to enhance the signal-to-background ratio in modalities like fluorescence imaging (66,67). The future vision is an "Intelligent Surgical System" where an AI core fuses real-time molecular data with preoperative radiomics (68,69) to provide predictive, risk-adapted guidance. This will be built on continued hardware progress (31) and the clinical translation of concepts like theranostics (10), safer nanoparticle agents (70), and integration with robotic platforms (5).

CONCLUSİON

In conclusion, the sophisticated tools reviewed herein are steadily replacing the uncertainty of cancer surgery. With the continued adoption of activatable fluorescent agents and other "smart probes" targeting specific molecular markers, the application and precision of guided surgery will expand significantly (1). The trajectory of surgical oncology is evolving toward a paradigm where surgical resection is guided not only by anatomy and tactile feedback but also by real-time data on the tumor's molecular identity. This shift promises to significantly reduce the incidence of positive surgical margins, potentially rendering them an avoidable outcome in a new era of precision surgery.

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