Review

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Review

Real-Time Assessment of Surgical Margins During Radical Prostatectomy: A Comprehensive Review

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Simple Summary: This review highlights advancements in real-time surgical margin assessment during radical prostatectomy (RP) for prostate cancer. Achieving negative margins is crucial to reduce the risk of biochemical recurrence and the need for additional treatments. Traditional methods like frozen section (FS) remain common but are time-consuming and dependent on skilled teams. Emerging technologies such as Confocal Laser Endomicroscopy (CLE), Optical Spectroscopy, Fluorescence Confocal Microscopy (FCM), and Augmented Reality (AR) offer real-time, high-resolution imaging to guide surgeons during surgery. These techniques aim to reduce positive surgical margins (PSMs) and preserve critical structures. However, challenges such as high costs, limited availability, and the need for further validation remain. The integration of AI and robotics with these technologies holds potential to improve surgical precision and outcomes. Overall, real-time margin assessment technologies are poised to enhance prostate cancer surgery, improving both oncological and functional outcomes for patients.

Abstract: Background/Objectives: Radical prostatectomy (RP) is a widely used treatment for localized prostate cancer, where achieving negative surgical margins is essential to reduce the risk of biochemical recurrence (BCR) and avoid additional treatments like radiation therapy. Positive surgical margins (PSMs) are associated with increased recurrence rates, higher costs, and patient anxiety. This review aims to evaluate real-time technologies for surgical margin assessment during RP, focusing on their clinical utility, advancements, and potential to improve intraoperative decision-making. Methods: A non systematic review was conducted by searching PubMed/MEDLINE and Google Scholar for studies on real-time intraoperative margin assessment technologies in RP, including traditional and emerging methods. The review assessed technologies such as frozen section analysis, Confocal Laser Endomicroscopy (CLE), Fluorescence Confocal Microscopy (FCM), Optical Spectroscopy, and Augmented Reality (AR). Data from clinical trials and studies were analyzed based on their sensitivity, specificity, operational feasibility, and potential to reduce PSMs. Results: Emerging technologies like CLE and FCM have shown significant potential for intraoperative tissue imaging, offering high-resolution, real-time feedback that can help identify cancerous tissue and guide surgical margins. Frozen section analysis remains the gold standard for intraoperative assessment due to its high sensitivity and specificity, but it is time-consuming and dependent on specialized pathology teams. AR, CLE, and optical spectroscopy technologies are gaining attention for their ability to provide real-time data and improve surgical precision. However, challenges such as high costs, technical complexity, and limited availability in resource-limited settings hinder broader adoption. Further clinical validation is needed to confirm their effectiveness and feasibility.

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Conclusions: Real-time assessment technologies offer promising advancements in reducing PSMs during RP, potentially improving both oncological and functional outcomes. While frozen section analysis remains the most widely used method, emerging technologies like CLE, FCM, AR, and optical spectroscopy show promise in enhancing surgical precision and patient outcomes. Continued innovation and large-scale clinical trials are crucial for integrating these tools into standard clinical practice and making them more accessible to a broader patient population.

Keywords: surgical margins; radical prostatectomy; Real- Time Imaging Technologies;

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1. Introduction

Prostate cancer (PCa) remains one of the most commonly diagnosed malignancies in men worldwide [1] . Radical prostatectomy (RP) is a curative option for localized and locally advanced cases. However, achieving negative surgical margins—defined as the absence of cancer cells at the resection edge—is crucial to reducing the risk of biochemical recurrence (BCR) [2,3]. Positive surgical margins (PSMs) are associated with increased likelihood of secondary therapies, higher costs, and patient anxiety [2,3].

Achieving oncological precision while preserving neurovascular bundles (NVBs) for functional outcomes poses a significant surgical challenge [4,5]. Real-time assessment of surgical margins during RP has emerged as an innovative solution, enabling surgeons to optimize resection while minimizing collateral damage. This review examines traditional methods, advances in real-time technologies, and future prospects in intraoperative margin assessment.

Prostate cancer surgery has evolved significantly over the decades. With increasing focus on precision medicine, the need to balance oncological outcomes with functional preservation has become a central theme. Innovations in imaging, pathology, and technology now allow surgeons to approach this balance with greater confidence. The real-time assessment of surgical margins represents a critical advancement in this regard, enabling more informed intraoperative decisions and reducing the reliance on adjuvant therapies. By implementing such advancements, the field of urology continues to push boundaries in improving patient survival and quality of life.

2. Materials and Methods

2.1. Search Strategy and Study Selection

A comprehensive literature search was conducted using PubMed/MEDLINE and Google Scholar databases to identify studies related to real-time intraoperative margin assessment technologies in radical prostatectomy (RP) for prostate cancer. The search included articles published from 2000 until December 2024. Keywords used in the search included “real-time margin assessment,” “frozen section analysis,” “Confocal Laser Endomicroscopy,” “Fluorescence Confocal Microscopy,” “Optical Spectroscopy,” “Augmented Reality,” and “radical prostatectomy.” The inclusion criteria were original research studies involving human participants that evaluated the clinical application of real-time margin assessment technologies during RP. Excluded from this review were studies involving animal models, conference abstracts, and review articles.

2.2. Study Eligibility

Studies were included if they met the following criteria: 1. Focused on real-time intraoperative margin assessment technologies (e.g., frozen section analysis, CLE, FCM, optical spectroscopy, AR). 2. Conducted in a clinical setting (i.e., human trials). 3. Published in English. 4. Reported clinical outcomes such as sensitivity, specificity, operational feasibility, and impact on surgical margins or patient outcomes. Studies were excluded if they: 1. Involved non-human subjects or animal models. 2. Were conference abstracts or systematic reviews. 3. Did not report clinical data or outcomes. Other reviews that are referred to in the text are different in the way that they do not include the first large trial on frozen section analysis.

2.3. Data Extraction

Data were independently extracted from each study by two authors. Discrepancies in data extraction were resolved through discussion, and if needed, a third author was consulted. Extracted data included study design, sample size, patient demographics, technology used, clinical outcomes (e.g., sensitivity, specificity, time required for the technique), and any reported limitations or challenges.

2.4. Technologies Evaluated

The following real-time intraoperative technologies were evaluated in this review: 1. Frozen Section Analysis (FS):The gold standard for real-time margin evaluation, which involves freezing tissue samples to facilitate histological examination. The analysis focused on its sensitivity, specificity, and limitations, especially regarding processing time and resource requirements. 2. Confocal Laser Endomicroscopy (CLE): A technique that provides high-resolution, in vivo cellular imaging using laser excitation and fluorescein dye to distinguish cancerous from benign tissues. Studies examining CLE's feasibility and efficacy in RP surgeries were included. 3. Fluorescence Confocal Microscopy (FCM): A method utilizing dual lasers to generate high-resolution images similar to H&E staining for rapid tissue evaluation. Clinical applications and trials related to prostate cancer surgeries were reviewed. 4. Optical Spectroscopy:Methods such as Raman and fluorescence spectroscopy, which rely on tissue-light interactions to differentiate between malignant and benign tissues. Studies focusing on the application of optical spectroscopy during RP were included. 5. Augmented Reality (AR):This technology overlays 3D models derived from imaging data (e.g., mpMRI) onto the surgical field in real-time, enhancing the surgeon's ability to navigate complex anatomy. Clinical trials assessing AR's accuracy and real-time utility during RP were evaluated.

2.5. Data Synthesis and Statistical Analysis

Due to the heterogeneity of the included studies (e.g., study design, technology evaluated, outcome measures), a meta-analysis was not conducted. Instead, a qualitative synthesis of the findings was performed. Descriptive statistics were used to summarize the sensitivity, specificity, and time requirements for each technology. The outcomes were compared based on clinical relevance, technological feasibility, and impact on surgical margin assessment.

2.6. Availability of Data and Materials

All data, materials, and protocols associated with this review are available upon request. No significant restrictions on data availability were encountered. Data from studies included in this review can be accessed through the respective journals or databases from which they were sourced.

3. Results

3.1. Conventional and Established Techniques

3.1.1. Frozen Section Analysis

Frozen section (FS) remains the gold standard for intraoperative pathological evaluation of surgical margins. Introduced in the late 1800s, this method involves freezing tissue specimens to facilitate rapid histological examination [6]. FS is particularly useful for high-risk areas such as the apex, posterolateral margins, and bladder neck [7-11]. The NeuroSAFE (neurovascular structure-adjacent frozen section examination) protocol, pioneered in 2012, has further optimized this technique for preserving NVBs while achieving oncological safety [12].

Advantages:

- High sensitivity and specificity (up to 97.3%) [12].
- Enables intraoperative decision-making for additional resection or NVB sparing [12].

Limitations:

- Time-intensive (37-57 minutes) [13,14].
- Requires dedicated pathology teams and infrastructure [13,14].

Frozen sections are especially valuable in high-risk settings, such as for patients with advanced PCa or those undergoing nerve-sparing procedures. Several studies have demonstrated a significant reduction in PSM rates with the use of FS, with some reporting reductions of over 20% in select cases [15,16]. It also has a reported higher incidence of nerve sparing during surgery [17]. A recent randomized phase 3 trial, which is the first on this subject, evaluated the impact of the NeuroSAFE technique on postoperative erectile function and urinary continence in men undergoing robot-assisted radical prostatectomy (RARP). Conducted across five UK hospitals, the study found that patients who received NeuroSAFE-guided RARP experienced significantly better erectile function at 12 months (as measured by IIEF-5 and IIEF-6 scores) and improved urinary continence at 3 months compared to those who underwent standard RARP, without an increase in serious adverse events. These findings suggest that integrating NeuroSAFE into surgical practice can enhance functional outcomes, especially in cases where bilateral nerve-sparing would not typically be pursued [18].However, the utility of FS is constrained by its dependence on a skilled pathology team, making it less feasible for widespread adoption in smaller or resource-limited centers.

The FS technique involves several critical steps, including the rapid freezing of tissue specimens, sectioning with a cryostat, staining with hematoxylin and eosin, and microscopic evaluation by a pathologist [6]. These steps require precise execution and coordination among surgical and pathology teams, underscoring the importance of expertise and infrastructure. Furthermore, the quality of frozen sections can vary depending on factors such as tissue type and freezing speed, highlighting the need for standardized protocols [13,14].

Efforts to optimize FS have focused on improving processing times and enhancing diagnostic accuracy. For instance, automated cryostat systems and digital pathology platforms are being integrated into FS workflows, reducing turnaround times and enabling remote consultations. Additionally, research into the use of molecular markers to complement FS findings holds promise for improving its predictive value in identifying high-risk tumor features.

3.2. Multiparametric MRI (mpMRI)

While primarily a preoperative staging tool, mpMRI has shown potential in guiding surgical dissection. Imaging features indicative of extracapsular extension (ECE) can influence margin-negative resection strategies. However, its moderate sensitivity (57%) limits its intraoperative utility [19]. Advances in imaging protocols, including the development of the Prostate Imaging-Reporting and Data System (PI-RADS), have improved the predictive value of mpMRI, but challenges remain in translating these findings into real-time intraoperative guidance [20,21].

mpMRI has become a cornerstone of preoperative planning in prostate cancer surgery. By providing detailed anatomical and functional information, mpMRI enables surgeons to identify high-risk areas and tailor their approach accordingly. Innovations, such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging, have further enhanced the utility of mpMRI. However, the integration of mpMRI data into intraoperative workflows remains a work in progress, with ongoing efforts to develop real-time imaging solutions and improve the accuracy of ECE detection [22].

One area of active research involves the use of artificial intelligence (AI) algorithms to enhance the interpretation of mpMRI data. AI-driven tools have demonstrated promise in automating the detection of ECE and other high-risk features, potentially reducing inter-observer variability and improving diagnostic confidence [23,24]. Furthermore, efforts to integrate mpMRI with other imaging modalities, such as PSMA-PET, are opening new avenues for more comprehensive preoperative assessments [25].

4. Emerging Real-Time Technologies

4.1. Confocal Laser Endomicroscopy (CLE)

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CLE provides high-resolution cellular imaging in vivo using blue laser excitation and fluorescein [26]. This technique allows visualization of cancerous and benign tissues without extensive tissue preparation.

Clinical Trials:

- Demonstrated feasibility during robotic-assisted RP [27].
- Emerging atlases of prostate pathology enhance its diagnostic utility [28].

CLE represents a paradigm shift in intraoperative pathology. Its ability to provide near-histological resolution images in real-time has positioned it as a strong candidate for widespread adoption. Moreover, recent studies have demonstrated its applicability in distinguishing cancerous from non-cancerous tissues, with sensitivity and specificity exceeding 85% in many trials [29]. However, the technique's reliance on fluorescein and the need for operator training present barriers to broader clinical implementation.

The use of CLE in prostate cancer surgery has been particularly promising in the context of robotic-assisted procedures, where real-time visualization of tissue characteristics can guide surgical decisions. By integrating CLE into the robotic platform, surgeons can obtain high-resolution images of the surgical field without interrupting the workflow. This capability has the potential to enhance precision and reduce the risk of PSMs, especially in challenging cases involving high-grade or multifocal tumors [27].

In addition to its applications in RP, CLE has been explored for other urological procedures, such as bladder and kidney cancer surgeries [28]. These studies have highlighted the versatility of CLE in identifying tumor margins and guiding resections, further underscoring its potential as a universal tool for intraoperative imaging.

4.2. Optical Spectroscopy

Optical spectroscopic methods, such as Raman and fluorescence spectroscopy, rely on tissue-light interactions to differentiate malignant and benign tissues [29-31]. Raman spectroscopy has demonstrated sensitivity and specificity exceeding 85% in experimental settings, making it a promising real-time diagnostic tool [29].

The principle of optical spectroscopy lies in its ability to detect molecular differences between normal and cancerous tissues. For example, Raman spectroscopy identifies vibrational energy changes in tissues, while fluorescence spectroscopy relies on the emission of light from specific molecules within the tissue [32]. These techniques have shown promise not only for identifying PSMs but also for characterizing tissue at a molecular level, potentially offering insights into tumor aggressiveness and heterogeneity.

Recent advances in spectroscopic technologies have focused on miniaturization and integration with surgical instruments, enabling real-time tissue analysis during RP. These developments have opened new avenues for intraoperative guidance, with the potential to complement existing techniques such as FS and CLE [29-31] . Furthermore, the use of multimodal spectroscopy, combining multiple spectroscopic methods, has shown promise in improving diagnostic accuracy and expanding the scope of applications [33].

The potential of spectroscopy to identify subtle molecular changes associated with tumor biology has also spurred interest in its use for risk stratification and treatment planning. For instance, studies are exploring the use of Raman spectroscopy to predict the likelihood of tumor recurrence based on molecular signatures, paving the way for more personalized approaches to prostate cancer management.

4.3. Fluorescence Confocal Microscopy (FCM)

FCM utilizes dual lasers to generate high-resolution, H&E-like images of freshly excised tissues. Studies have shown sensitivity and specificity exceeding 90% for detecting malignant tissues, with processing times under 30 minutes [34].

Clinical Applications:

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- Used in initial trials to assess prostate biopsies with high accuracy [35].
- Capable of providing digitalized images for remote pathology consultation [36].

While still in its early stages of clinical adoption, FCM has demonstrated immense potential. By offering rapid, accurate, and digitally transferable imaging, FCM aligns well with modern surgical workflows that emphasize efficiency and precision.

The adoption of FCM in prostate cancer surgery has been driven by its ability to provide near-instantaneous feedback on tissue status. This capability is particularly valuable in high-stakes scenarios, such as when attempting to preserve NVBs while ensuring complete tumor excision. Moreover, the digital nature of FCM images facilitates remote consultation and collaboration, enabling access to expert opinions even in resource-limited settings [37].

Advancements in FCM technology have also focused on improving its usability and accessibility. Portable FCM devices and user-friendly interfaces are being developed to facilitate wider adoption, while ongoing research into novel fluorescent dyes aims to enhance image contrast and diagnostic accuracy. These efforts are expected to expand the applications of FCM across a broader range of surgical procedures and clinical settings.

5. Innovative Intraoperative Techniques

5.1. Augmented Reality (AR)

AR combines three-dimensional reconstruction from mpMRI data with real-time visualization during surgery [38, 39 ,40]. This technique enhances the surgeon's ability to localize and avoid critical structures while ensuring complete tumor excision.

Clinical Applications:

- Pilot studies report concordance rates exceeding 85% between AR models and final histopathology [23].
- Elastic AR models adapt to tissue manipulation, improving precision [24].

AR represents a significant advancement in surgical planning and execution. By overlaying virtual models onto the surgical field, AR provides real-time feedback that enables surgeons to navigate complex anatomical structures with unprecedented accuracy. Current limitations include the high costs of AR systems and the need for integration with existing surgical platforms [26].

Recent innovations in AR technology have focused on improving the accuracy and usability of 3D models. For example, the use of elastic AR models, which adapt to changes in tissue geometry during surgery, has shown promise in enhancing the precision of surgical navigation. Additionally, efforts to integrate AR with robotic platforms and other advanced surgical tools are underway, with the goal of creating a seamless and intuitive user experience.

Beyond prostate cancer surgery, AR has been explored for various surgical applications, including neurosurgery and orthopedics. These studies have demonstrated the versatility of AR in improving surgical outcomes, highlighting its potential as a transformative tool across multiple specialties. As AR technology continues to evolve, its integration with machine learning algorithms and real-time imaging modalities is expected to further enhance its capabilities and broaden its clinical impact.

6. Comparative Evaluation\

Table 1. Comparison of the different techniques for real time assessment of surgical margins during radical prostatectomy.

Technology	Sensitivity (%)	Specificity (%)	Time Required	Clinical Availability
Frozen Section	90-97	90-98	37-57 min	Widely available
Confocal Laser Endomicroscopy	85-90	85-92	<15 min	Experimental

Technology	Sensitivity (%)	Specificity (%)	Time Required	Clinical Availability
Fluorescence Confocal Microscopy	83-95	93-96	10-30 min	Limited availability
Augmented Reality	79-85	80-90	Real-time	Experimental

7. Future Directions

The rapid advancement of molecular imaging and AI-driven diagnostic tools holds promise for further enhancing the accuracy and feasibility of real-time margin assessment. Techniques such as PSMA-PET-MRI integration, AI-enhanced histopathology, and non-invasive optical probes are likely to revolutionize intraoperative practices.

Key Challenges:

- High cost and logistical demands of advanced technologies.
- Limited availability in resource-constrained settings.
- Need for robust clinical validation through large-scale trials.

Emerging areas of interest include the use of machine learning algorithms to improve the interpretation of real-time imaging data. By analyzing large datasets, AI tools could provide surgeons with actionable insights, further reducing the likelihood of PSMs.

The integration of advanced imaging modalities with robotics represents another exciting frontier. Robotic systems, equipped with real-time imaging capabilities, could autonomously detect and alert surgeons to PSMs during dissection, streamlining decision-making and potentially improving outcomes.

Furthermore, the development of cost-effective, portable imaging technologies could address the disparities in access to advanced surgical tools. Such innovations would be particularly impactful in low-resource settings, where the burden of PCa is often significant.

The role of multidisciplinary collaboration cannot be overstated in advancing the field of real-time margin assessment. By bringing together experts in imaging, pathology, surgery, and data science, new solutions can be developed and validated more effectively. Additionally, patient-centered approaches that prioritize quality of life alongside oncological outcomes will be essential in guiding future innovations.

8. Conclusions

Real-time assessment of surgical margins during RP represents a paradigm shift in prostate cancer surgery, enabling oncological precision without compromising functional outcomes. While frozen section analysis remains the gold standard, emerging technologies such as CLE, FCM, and AR are poised to complement or replace traditional methods. Continued innovation and validation are imperative to integrate these tools into routine clinical practice, ultimately improving patient outcomes.

As we look toward the future, the synergy between technological advancements, multidisciplinary collaboration, and patient-centered care will be crucial. By leveraging the strengths of novel imaging modalities, surgical expertise, and data-driven insights, we can redefine the standards of prostate cancer management, ensuring that each patient receives the highest quality of care.

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