Review Article

Exploring Paradigms in Intraoperative Assessment of Resection Margins (IOARM) in Oral Cancer: A Comprehensive Review

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ABSTRACT

Oral squamous cell carcinoma (OSCC) presents significant challenges in surgical management, particularly in achieving clear resection margins, which are crucial for reducing recurrence and improving patient outcomes. Traditional methods like visual inspection and palpation are often insufficient for accurate margin assessment. This review delves into advanced intraoperative imaging and assessment techniques, including intraoral ultrasound (ioUS), magnetic resonance imaging (MRI), fluorescence imaging, Raman spectroscopy, and confocal laser endomicroscopy (CLE). It aims to discuss the principles, applications, advantages, limitations, and clinical efficacy in enhancing surgical precision in OSCC treatment.

Key words: Oral, Carcinoma, Management, MRI

Human face is the most unique identity, not limited to real-life tasks but largely to emotionality and sociability traits[1, 2]. Preserving an individual's unique identity is the most arduous task for facial ablative and reconstructive surgeons[3]. The close proximity of the facial sub-units with relatively smaller boundaries often puts a challenging situation not favouring liberal or generous resection[4]. Oral cancer remains a significant public health concern in India, with its incidence steadily rising due to factors such as tobacco consumption, betel quid chewing, and poor oral hygiene. According to the latest data from the Indian Council of Medical Research (ICMR), India accounts for nearly 30% of global oral cancer cases, with Uttar Pradesh reporting the highest incidence among all states[5].

The prevalence is particularly alarming in rural areas, where delayed diagnosis and limited access to advanced healthcare facilities contribute to poor prognosis and high mortality rates[5]. Oral cavity cancer, particularly oral squamous cell carcinoma (OSCC), poses significant challenges in surgical treatment due to the necessity of achieving clear resection margins[6]. The primary goal of surgery is to excise the tumor along with a margin of healthy tissue, typically greater than 5 mm[7]. However, studies indicate that only 15% to 26% of resections achieve adequate margins, leading to increased rates of local recurrence and adverse outcomes for patients[8]. A major reason for this low number is the lack of information during surgery as the margin status is only available days after surgery after the final histopathologic examination[9]. Inadequate margins are associated with higher recurrence rates and diminished survival[10]. Consequently, there is a pressing need for reliable intraoperative assessment tools that provide real-time, accurate delineation of tumor boundaries.

Rationale for the Review: Given the significant impact of margin status on prognosis, this review aims to explore the latest intraoperative imaging and assessment techniques that enhance surgical precision in OSCC treatment. By analyzing emerging modalities such as ioUS, magnetic resonance imaging (MRI), fluorescence imaging, Raman spectroscopy, and confocal laser endomicroscopy (CLE), this review seeks to evaluate their efficacy in improving margin assessment and reducing recurrence rates. Addressing the current gaps in intraoperative assessment, this review emphasizes the importance of real-time, reliable margin evaluation techniques in optimizing oncologic outcomes and preserving the functional and aesthetic integrity of patients undergoing OSCC surgery.

Challenges in Intraoperative Assessment of Resection Margins (IOARM) In Head and Neck

Besides the known challenges in current IOARM techniques ie. subjectivity, limited assessment, failure to provide real time and accurate margin status, and time constraints; IOARM in the head and neck region presents significant challenges, particularly in cases involving composite resections where both soft tissue and bone must be excised[11]. While various reliable intraoperative techniques have been developed to

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evaluate margins in soft tissue—such as frozen section analysis and fluorescence-guided surgery—there remains a critical gap in effective methods for assessing margins in hard tissue, specifically bone. It has been observed that positive bone margins are more detrimental to survival outcomes compared to positive mucosal margins[12]. Tumors that spread further along the bone than the mucosa are associated with worse prognoses. In 10% of patients, microscopic bone invasion was observed, significantly affecting survival rates. A sufficient bone margin is generally attained when the resection is at least 15mm from the clinically detectable tumor[13]. The current lack of reliable intraoperative tools for bone margin assessment complicates surgical decision-making and may compromise the thoroughness of oncologic resection[14].

Traditional Methods of Margin Assessment

Conventional techniques for intraoperative margin assessment include visual inspection, palpation, and frozen section analysis (FSA). While these methods are widely used, they have notable limitations:

Visual Inspection and Palpation: Subjective and dependent on the surgeon's experience, these methods may miss microscopic tumor extensions, leading to positive margins[15]. Clinical examination (inspection and palpation) has shown a sensitivity of 75.39% and specificity of 94.43%, frozen section analysis is often criticized for its cost and resource demands, with a lower sensitivity of 66.5%[16].

- **Frozen Section Analysis (FSA)**: Involves rapid histopathological examination of excised tissue. Although useful, FSA is time-consuming, may delay surgery, and is limited by sampling errors, especially in large or complex specimens. Studies have shown that FSA from the tumor bed has low sensitivity (11%) but high specificity (99%) in assessing final margin status, indicating its limitations in accurately detecting residual tumor cells[17].

Advanced Intraoperative Imaging Techniques

To overcome the limitations of traditional methods, several advanced imaging modalities have been explored:

1. Intraoral Ultrasound (ioUS)

Intraoral ultrasound offers a non-invasive imaging modality that can be used intraoperatively to assess tumor margins. This technique utilizes high-frequency sound waves to create detailed images of soft tissues, allowing for real-time visualization of tumor boundaries relative to surrounding healthy tissues. The application of ioUS in oral cancer surgeries has shown promise in enhancing the accuracy of margin assessment[18].

Principle

Utilizes high-frequency sound waves to produce real-time images of soft tissues, allowing assessment of tumor dimensions and depth of invasion[18].

Advantages of IOUS

Real-Time Imaging: ioUS provides immediate feedback during surgery, enabling surgeons to make informed decisions about additional tissue resection if necessary[19].

Enhanced Visualization: The ability to visualize deep tissue structures improves the identification of tumor margins that may not be apparent through visual inspection alone[18].

Reduced Sampling Errors: By providing comprehensive imaging rather than relying on small tissue samples, ioUS minimizes the risk of missing tumor-positive margins.

Non-Invasiveness and Portability: ioUS is a non-invasive technique that can be performed at the bedside or in the operating room without the need for complex equipment setups. This accessibility makes it easier to integrate into routine surgical practice compared to MRI, which requires specialized facilities and longer preparation times[20].

Cost-Effectiveness: Compared to MRI and other imaging modalities, ioUS is generally less expensive, making it a more viable option for many healthcare settings

Limitations

Operator-dependent; limited penetration depth may restrict assessment in larger tumors.

Clinical Efficacy

Studies have demonstrated that ioUS can improve the accuracy of margin assessment, potentially reducing the rate of positive margins. However, its effectiveness is influenced by the operator's expertise and the tumor's anatomical location.

2. Magnetic Resonance Imaging (MRI)

MRI offers several advantages for intraoperative margin assessment due to its high-resolution imaging capabilities and ability to provide detailed anatomical information. Recent studies have demonstrated that MRI can accurately evaluate surgical margins in OSCC by distinguishing between tumorous and healthy tissue [21]. The sensitivity and specificity of MRI for detecting close and involved margins range significantly across studies, with some reporting sensitivities as high as 75% and specificities approaching 100%[22]. In a systematic review, it was highlighted that intraoperative MRI could improve the rate of free-margin resections by approximately 35% compared to traditional methods. This improvement is particularly notable in early-stage tumors (T1–T2), where accurate margin assessment is crucial for successful outcomes[22].

Limitations

High cost; limited availability; intraoperative use is challenging due to the need for specialized equipment and potential interference with surgical instruments.

Clinical Efficacy

MRI offers high sensitivity and specificity in detecting tumor margins, especially in complex anatomical regions. Intraoperative MRI can guide surgeons in achieving clear margins, though logistical challenges limit its widespread use.

3. Fluorescence Imaging

Principle

Fluorescence-based imaging, particularly autofluorescence, detects tissue alterations by measuring the emission of light from intrinsic fluorophores (e.g., NADH, FAD, collagen) within the tissue[23]. Malignant or precancerous tissues display altered fluorescence patterns due to changes in biochemical and morphological properties, often seen as a loss of fluorescence in neoplastic areas[24].

Application

Fluorescence imaging technologies are used during oral cancer surgeries to delineate tumor margins more accurately:

1. **Wide-Field Autofluorescence Imaging:** Devices like the VELscope highlight areas with reduced fluorescence, indicating potential malignancy.
2. **High-Resolution Fluorescence Imaging:** Confocal microscopy and microendoscopy provide detailed subcellular resolution to differentiate benign from malignant tissues.
3. **Combination Imaging:** Integrating wide-field and high-resolution imaging allows surgeons to scan large areas quickly and zoom into suspicious regions for detailed analysis.

Advantages

1. **Non-Invasive:** Fluorescence imaging avoids the need for excessive biopsies during surgery.
2. **Real-Time Feedback:** Provides immediate visualization of tumor margins.
3. **Enhanced Accuracy:** High sensitivity (~95-98%) in identifying dysplasia and carcinoma.
4. **Reduced Recurrence:** Studies show fluorescence-guided resections result in significantly lower recurrence rates compared to standard methods.
5. **Wide Applicability:** Effective for identifying subclinical lesions missed by white light examination.

Limitations

1. **Subjectivity:** Reliance on visual interpretation can lead to variability among practitioners.
2. **False Positives:** Benign conditions such as inflammation and pigmentation may mimic malignancy due to similar fluorescence loss.
3. **Technology Access:** Requires specialized equipment and trained personnel, limiting widespread use.
4. **Limited Efficacy in Low-Risk Populations:** Studies have shown reduced specificity in populations with a low prevalence of oral cancer.
5. **Cost:** High initial investment in fluorescence imaging systems can be a barrier.

Clinical Efficacy

1. **Improved Outcomes:** Studies with the VELscope reported a recurrence rate of 0% in fluorescence-guided surgeries compared to 32% in standard visual guidance[25].
2. **High Sensitivity and Specificity:** Achieved ~98% sensitivity and ~94% specificity in clinical trials for distinguishing neoplastic tissues[26].
3. **Adjunctive Tool:** Particularly effective as a supplementary method alongside conventional visual examination, aiding in comprehensive tumor margin assessment.

4. Raman Spectroscopy

Principle

Raman spectroscopy is a non-invasive, optical technique that uses light scattering to identify molecular compositions of tissues. It operates by analyzing the Raman spectrum, especially the high-wavenumber regions, to distinguish cancerous from healthy tissues[27].

Application

This device uses a fiber-optic needle probe to measure the distance between the tumor and resection surface, providing real-time guidance for surgeons to achieve adequate tumor removal[9].

Advantages

1. **Accuracy:** High sensitivity (85%) and specificity (92%) for detecting tumor tissues.
2. **Real-Time Use:** Allows immediate evaluation of surgical margins during operations.
3. **Minimally Invasive:** Reduces the need for extensive pathological handling during surgery.
4. **Enhanced Outcomes:** Potential to increase adequate tumor resections, improving patient survival rates.

Limitation

1. **Complex Decision Rules:** Relies on threshold-based tumor probability models, which might require further standardization.
2. **Moderate Sensitivity:** A 78% sensitivity in detecting inadequate margins, which may leave some undetected[27].
3. **Logistical Challenges:** Requires specialized equipment and trained personnel, potentially limiting widespread use initially.
4. **Validation Scope:** The model and device performance were validated on a relatively small dataset, indicating the need for broader clinical trials[9].

Clinical Efficacy

Early studies suggest that Raman spectroscopy can accurately differentiate between malignant and benign tissues, aiding in precise margin assessment. A mean margin length prediction error of <1 mm compared to histopathology has been seen, confirming its clinical reliability. It significantly enhances margin assessment accuracy, reducing the need for postoperative treatments and associated complications.[27] With further optimization, it holds promise for broader applications in other types of cancer surgeries.

5. Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) and confocal microscopy utilize focused laser beams and pinhole filtering to create high-resolution, optical sections of tissues. CLE offers real-time histological imaging, known as "optical biopsy," with fluorescence or reflectance modes, allowing visualization of cellular structures without tissue removal[28]. Ex vivo confocal microscopy (EVCM) performs similar imaging on excised tissues with minimal preparation, providing immediate evaluation of tumor margins[29].

Application

1. **Real-Time Margin Assessment:** CLE is used intraoperatively to assess tumor margins, guiding surgeons to achieve complete resections while minimizing unnecessary tissue removal.
2. **Diagnosis of Malignant Lesions:** CLE and EVCM detect cellular-level abnormalities, distinguishing malignant tissues from benign or healthy tissues[30].
3. **Integration with Fluorescent Dyes:** Various dyes (e.g., fluorescein, acriflavine) enhance image contrast, aiding in the delineation of tumor boundaries[29].
4. **Combination with Robotics:** CLE can be integrated into robotic systems to evaluate less accessible tumor sites during surgery.
5. **Alternative to Frozen Sections:** EVCM provides a faster and artifact-free alternative to frozen sections for margin evaluation.

Advantages

1. **Non-Invasive and Real-Time:** CLE enables live imaging without the need for extensive tissue excision[30].
2. **High-Resolution Imaging:** Both CLE and EVCM offer cellular-level visualization, aiding in precise diagnosis.
3. **Minimized Tissue Loss:** Reduces the need for multiple biopsies and conserves tissue for histopathological analysis.
4. **Reduced Procedure Time:** Faster than traditional histopathology methods like frozen sections.
5. **Versatility:** Applicable to various head and neck cancer sites, including oral, laryngeal, and oropharyngeal tumors.

Limitation

1. **Field of View and Depth:** CLE has a limited field of view (~240 µm diameter) and depth penetration (~100 µm), restricting the evaluation of deeper tissues[28].
2. **Image Artifacts:** Motion, saliva, blood, and rough tissue surfaces can degrade image quality, necessitating careful handling and preparation.
3. **Subjectivity in Interpretation:** Lack of standardization in image reading and the need for expert training reduce reproducibility.
4. **High Cost:** The equipment and associated dyes increase financial barriers for widespread adoption.
5. **Limited Validation:** Most studies involve small sample sizes, requiring larger trials to confirm clinical efficacy.

Clinical Efficacy

1. **Diagnostic Accuracy:** Studies report sensitivity and specificity ranging from 73% to 95% for detecting malignant tissues, with accuracy improving with training and standardization[28].
2. **Margin Detection:** Pilot studies demonstrate feasibility in identifying tumor margins with 80-86% accuracy during surgeries, reducing recurrence risks[30].
3. **Potential Replacement for Frozen Sections:** EVCM can provide quicker results with fewer artifacts, improving intraoperative decision-making.
4. **Technological Advancements:** Integration with artificial intelligence has enhanced diagnostic reliability by automating image analysis.
5. A brief summary of the various modalities has been summarised in table1

Table 1: Summary of various modalities

Method	Principle	Advantages	Limitations	Clinical Efficacy
Intraoral Ultrasound (ioUS)	Uses high-frequency sound waves to produce real-time images of soft tissues.	Real-time imaging, enhanced visualization, cost-effective.	Operator-dependent, limited penetration depth.	Improves accuracy of margin assessment but dependent on operator skill.
Magnetic Resonance Imaging (MRI)	Provides high-resolution imaging of anatomical structures.	High sensitivity and specificity, detailed anatomical imaging.	High cost, limited availability, interference with surgical instruments.	High accuracy in detecting tumor margins but logistical challenges exist.

Fluorescence Imaging	Detects altered fluorescence patterns in cancerous tissues.	Non-invasive, real-time feedback, high sensitivity.	Subjectivity, false positives, high initial investment.	Reported to lower recurrence rates and improve margin detection.
Raman Spectroscopy	Analyzes light scattering to differentiate between malignant and benign tissues.	High accuracy in tumor detection, real-time guidance.	Complex decision rules, moderate sensitivity, requires specialized equipment.	Enhances tumor margin accuracy but requires further standardization.
Confocal Laser Endomicroscopy (CLE)	Utilizes laser beams to create high-resolution optical sections of tissues.	Live imaging, high-resolution cellular visualization, fast assessment.	Limited field of view, image artifacts, high cost.	Effective in distinguishing malignant tissues, potential replacement for frozen sections.

CONCLUSION

Intraoperative assessment and imaging techniques play a pivotal role in the surgical management of OSCC, significantly influencing patient outcomes. Traditional methods, though widely used, often fall short in ensuring precise margin evaluation, highlighting the necessity for advanced techniques. Emerging technologies such as intraoral ultrasound, magnetic resonance imaging, fluorescence imaging, Raman spectroscopy, and confocal laser endomicroscopy have shown substantial promise in overcoming these limitations by offering real-time, accurate, and non-invasive tumor delineation.

While each modality has unique advantages and challenges, their integration into clinical practice has the potential to redefine surgical precision, reduce recurrence rates, and improve survival outcomes. However, widespread adoption requires addressing barriers such as cost, operator expertise, and accessibility to advanced equipment. Future research and technological advancements should focus on enhancing the accuracy, affordability, and applicability of these techniques to ensure equitable and effective treatment for all OSCC patients. By bridging these gaps, we move closer to a standard of care that prioritizes both oncological safety and the preservation of patient's quality of life.

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