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A Brief Review of Current Status of Diagnostic Techniques in Oral Carcinoma

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1. ABSTRACT

Squamous Cell Carcinoma (SCC) accounts for about 90% of Head and Neck Cancers (HNC), which are the seventh most common malignancy globally. The mucosal linings of the sinuses, pharynx, larynx, and mouth cavity are the primary site of these malignancies. Tobacco usage, excessive alcohol use, and infections like Epstein-Barr Virus (EBV) and Human Papillomavirus (HPV) are major risk factors. The five-year survival rate for HNC is still between 40 and 50 percent, despite improvements in diagnostic and therapeutic approaches. This demonstrates the pressing need for innovative approaches for earlier detection and more successful treatment of this pathology. Imaging methods like 18F-FDG PET/CT are essential for lymph node assessment and tumour staging. Oral Squamous Cell Carcinoma (OSCC), the most common subtype of HNC, is often diagnosed at advanced stages, leading to high morbidity and mortality rates. Nuclear medicine techniques play a crucial role in improving diagnostics for OSCC.

Keywords: Oral squamous cell carcinoma (OSCC); Diagnostic techniques; Nuclear receptors; PET-CT; Sentinel lymph node biopsy (SLNB); Artificial intelligence (AI); Optical coherence tomography (OCT); Photoacoustic imaging (PAI); Machine learning (ML)

2. INTRODUCTION

Head and Neck Cancers (HNC) are the seventh most common malignancies globally, with Squamous Cell Carcinoma (SCC) accounting for about 90% of cases [1-3]. These malignancies primarily develop on mucosal surfaces, including the oral cavity, sinuses, pharynx, and larynx. The significant risk factors for HNC include tobacco use, alcohol consumption, and viral infections such as HPV and EBV [4-6].

Although there have been substantial advancements in imaging and therapeutic techniques, the survival rate for HNC patients remains suboptimal at 40% to 50%. The most probable cause for this is delayed diagnosis especially in developing countries where accessibility and availability of diagnostic technology remains a challenge. It is the time for advanced imaging modalities, such as 18F-fluorodeoxyglucose PET/CT, facilitate the evaluation of tumor staging and lymph node involvement, aiding in the precise diagnosis and management of these cancers. OSCC, being the most prevalent HNC subtype, contributes substantially to the global cancer burden, with late-stage diagnoses exacerbating the challenges associated with treatment.

3. MATERIALS AND METHODS

This descriptive review incorporates findings from studies focusing on recent advancements in imaging techniques for diagnosing oral carcinoma.

3.1. World View Status

Oral Squamous Cell Carcinoma (OSCC) is a significant global health challenge, accounting for 350,000 new cases and 177,000 deaths annually [1-3]. Ranking as the eleventh most prevalent cancer worldwide, its incidence is notably higher in low- and middle-income countries, particularly in South Asia. In countries like India, the burden is high due to the widespread use of tobacco, betel quid, and alcohol, coupled with limited access to healthcare resources. Early detection plays a pivotal role in improving outcomes, with studies indicating that timely intervention can elevate 5-year survival rates from 15% to 50% to nearly 80% [4,5].

Risk Factors and Pathogenesis

Key risk factors for OSCC include lifestyle habits such as smoking, alcohol consumption, and betel quid chewing. Other contributors include advanced age, male gender, UV exposure, poor oral hygiene, and infections like Human Papillomavirus (HPV) and Epstein-Barr Virus (EBV). OSCC often progresses from Oral Potentially Malignant Disorders (OPMDs), including leukoplakia, erythroplakia, oral submucous fibrosis, and Proliferative Verrucous Leukoplakia (PVL) [6-8]. These disorders signify a heightened risk for malignant transformation, necessitating regular monitoring. Oral epithelial dysplasia, characterized by histopathological changes, often serves as a precursor to OSCC, further emphasizing the need for early and accurate diagnostic measures [9].

3.2. Challenges in Early Diagnosis

The early diagnosis of OSCC and OPMDs remains challenging due to variability in clinical presentation and the absence of overt symptoms in the initial stages [10]. Although considered the gold standard, histopathology may not always be practical for large-scale screening due to resource constraints and its invasive nature. Moreover, interpreting histopathological results requires specialized expertise, and results may vary based on lesion size, depth, and location. Alternative diagnostic methods, including non-invasive tools and molecular techniques, are being explored to address these limitations [10].

3.3. Advancements in Diagnostic Techniques

Diagnostic methods have advanced significantly in recent years, emphasizing increasing sensitivity and specificity. Toluidine blue and Lugol's iodine are *vital* staining methods frequently employed to detect cancer and dysplastic cells. Combining toluidine blue with additional staining techniques improves diagnostic accuracy despite its poor specificity. Chemiluminescence and fluorescence-based methods, such as autofluorescence, provide non-invasive substitutes that depend on how light interacts with tissue constituents. Although they have shown value in clinical settings, tools such as the VELScope® Vx and ViziLite® Blue still need to be improved regarding their ability to distinguish benign from malignant lesions [13-15].

Imaging modalities such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and ultrasound are indispensable in diagnosing and staging OSCC. CT scans provide detailed information on tissue invasion and bone involvement, while MRI excels in soft tissue imaging, albeit at a higher cost [17-19]. High-frequency and intraoral ultrasound are accessible, non-invasive tools for assessing tumor size and vascularization. Positron Emission Tomography (PET), especially FDG PET/CT, has emerged as a cornerstone in OSCC diagnostics, offering insights into metabolic activity and lymph node metastasis [20]. High Standardized Uptake Values (SUV) indicate malignant activity, aiding in accurate staging [20]. Emerging PET tracers, such as 68Ga-FAPI-PET, have enhanced tumor localization and characterization accuracy [21]. Similarly, novel tracers like [64Cu]Cu-DOTA-AE105, targeting urokinase-type Plasminogen Activator Receptors (uPAR), offer promise in precise OSCC diagnosis [22,23].

3.4. Nuclear Receptors and Their Role in OSCC

The involvement of Nuclear Receptors (NRs) in OSCC pathogenesis has garnered significant attention in recent research [24-26]. The human NR family, comprising 48 receptors responsive to ligands like steroid hormones, retinoic acid, and vitamin D, plays a critical role in cellular processes such as differentiation, proliferation, and apoptosis. Several NRs, including Androgen Receptors (AR) [27], Estrogen Receptors (ER) [28], and peroxisome Proliferator-Activated Receptors (PPAR-γ) [29], have been implicated in OSCC progression. For instance, AR expression has been linked to increased cancer cell motility and invasion in nearly 67% of OSCC cases [27]. Similarly, ERs, particularly ERα and ERβ, are overexpressed in OSCC, and therapeutic strategies targeting these receptors are being investigated [28]. PPAR-γ activation with synthetic ligands has demonstrated the potential to suppress OSCC growth [29]. Retinoid Receptors (RAR and RXR) [30,31], often downregulated in OSCC, present opportunities for risk reduction through retinoid therapies. Additionally, Vitamin D Receptors (VDRs), frequently overexpressed in oral cancer, have shown promise in inhibiting OSCC cell proliferation when activated by vitamin D analogs [32].

3.5. Sentinel lymph nodal dissection in oral carcinomas

Sentinel lymph node dissection, a well-known nuclear medicine imaging method used in cancer treatment, is another crucial area in identifying oral malignancies. Sentinel Lymph Node Biopsy (SLNB) is not inferior to Elective Neck Dissection (END) in terms of overall survival and recurrence-free survival, according to recent randomized controlled trials comparing the two procedures for head and neck squamous cell carcinoma (HNSCC). Sentinel Lymph Node Biopsy (SLNB) offers similar survival rates to Elective Neck Dissection (END), with SLNB perhaps linked to decreased morbidity, according to the Senti-MERORL trial (Garrel et al.) and research by Hasegawa et al. The ongoing NRG-HN006 trial aims to investigate SLNB's effectiveness further, focusing on functional outcomes and oncologic non-inferiority. Important factors in SLNB include the difficulty of correctly identifying sentinel lymph nodes, the use of Depth Of Invasion (DOI) to predict nodal metastasis, and problems like false negatives brought on by skip metastases and "shine through" effects. The implementation of SLNB is also influenced by the controversy surrounding pathological evaluation methods, such as step-sectioning versus frozen sections, and the variation in surgical results depending on the operator's experience. Sentinel Lymph Node Biopsy (SLNB) accuracy is being improved by developments in intraoperative and preoperative imaging techniques, including freehand SPECT/CT and near-infrared fluorescence imaging. As a result of these advancements, SLNB is becoming a *viable* substitute for Elective Neck Dissection (END), which can minimize postoperative morbidity while preserving oncologic efficacy. More research is necessary to improve these procedures and patient outcomes [33-35].

A diagnostic technique called Photoacoustic Imaging (PAI) allows for deep tissue penetration and high resolution, which makes it possible to distinguish between proteins like melanin and haemoglobin. Preclinical studies and the examination of different types of cancer have both made use of PAI. Increased PAI signal strength in precancerous and cancerous lesions has been found in studies evaluating its *viability* for oral cancer screening. More investigation is necessary to assess the clinical use of PAI in screening and diagnosis [36,37].

3.6. Emerging Imaging Techniques and AI Applications

Innovative imaging technologies, such as Optical Coherence Tomography (OCT), provide high-resolution, non-invasive imaging of oral tissues. Variants like time-domain OCT (TD-OCT) and spectral-domain OCT (SD-OCT) have shown potential in distinguishing between cancerous and non-cancerous tissues, enhancing diagnostic precision [38].

Artificial Intelligence (AI) and Machine Learning (ML) are revolutionizing the field of OSCC diagnostics. Deep learning algorithms trained on histopathological and radiological images have accurately identified malignancies [39]. AI tools can analyze large datasets, detect subtle patterns, and predict patient outcomes, enabling earlier detection and personalized treatment planning. AI-assisted platforms are also integrated with imaging modalities to provide real-time diagnostic support, reducing dependency on specialist interpretation [40-44].

3.7. Therapeutic Implications

Simultaneous improvements match the advancements in diagnostics for Oral Squamous Cell Carcinoma (OSCC) in treatment strategies. Multimodal treatment approaches remain the standard, including surgery, radiation therapy, and chemotherapy. However, personalized therapies targeting specific molecular pathways, including those involving nuclear receptors, are gaining traction. Integrating precision medicine with AI and advanced imaging promises to enhance treatment efficacy while minimizing adverse effects.

3.8. Future Directions

To further improve OSCC outcomes, future research should focus on refining diagnostic technologies, exploring novel biomarkers, and expanding the therapeutic applications of nuclear receptors. Integrating AI with molecular imaging and histopathology can bridge the gaps in early detection and personalized care. Additionally, efforts to make these advanced technologies accessible in resource-limited settings will be crucial in addressing the global burden of OSCC.

4. CONCLUSION

OSCC continues to pose a significant health burden worldwide, but recent advancements in imaging techniques, nuclear medicine, and AI-driven diagnostics are improving outcomes. The role of nuclear receptors in OSCC offers promising therapeutic avenues, while innovations in imaging and AI-based tools are transforming diagnostic approaches. Continued research is essential to harness these advancements and optimize patient care for improved survival and quality of life.

5. ETHICAL CONSIDERATIONS

Not Applicable

6. CONFLICT OF INTEREST

None

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