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A Review Of Innovations And Advances In The Management Of Oral Squamous Cell Carcinoma In Improving Quality Of Life

Raparthy Bhuvana chandra[1]*, Kathiravan Selvarasu[2], Murugesan K[3], Manoj Kumar V[4], Santhosh Kumar[5]

[1]Postgraduate, Department of Oral and Maxillofacial Surgery Saveetha Dental College and Hospital, Chennai, Tamil Nadu, Saveetha Institute of Medical and Technical Sciences, Saveetha University,162, PH Road, Chennai 600077, Tamil Nadu, India.

[2]Reader, Department of Oral and Maxillofacial Surgery, Saveetha Dental College and Hospital, Chennai, Tamil Nadu.

[3]Professor and head of the department Department of oral and maxillofacial surgery, Saveetha Dental College and Hospital, Chennai, Tamil Nadu.

[4]Fellow in microvascular reconstruction, Department of oral and maxillofacial surgery, Saveetha Dental College and Hospital, Chennai, Tamil Nadu.

[5]Professor, Department of Oral and Maxillofacial Surgery, Saveetha Dental College and Hospitals,

***Corresponding author:** Raparthy Bhuvana chandra, Postgraduate, Department of Oral and Maxillofacial Surgery Saveetha Dental College and Hospital, Chennai, Tamil Nadu, Saveetha Institute of Medical and Technical Sciences, Saveetha University,162, PH Road, Chennai 600077, Tamil Nadu, India, Email : raparthybhuvan@gmail.com

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ABSTRACT

Squamous cell carcinoma of the oral cavity is the sixth most common malignancy worldwide. A skilled multidisciplinary team is required for effective management and the best results. The contemporary practice of managing oral squamous cell carcinoma often requires a multimodal approach of surgery and chemoradiation. But despite this aggressive multimodal treatment, 40% to 60% of the patients will have a relapse. This paper briefly outlines the recent advances and innovations in diagnosis, management strategy, and prognostic aspects of head and neck squamous cell carcinoma. The most crucial objective of a biomarker in cancer is the accurate detection of the tiniest amount of tumor cells prior to growth, when the patient's clinical prognosis and outcome are still favorable.

Keywords: *head and neck cancers, multimodal treatment, biomarkers, robotic surgeries*

INTRODUCTION

Oral cavity cancers include an estimated 263000 new cases and 128000 deaths per year among the 10 most worsening human malignancies. (1) Identification of significant biomarkers for use in early health prediction, patient stratification for more effective and focused treatments, and identification of patients most likely to relapse or experience treatment failure.

In this review article, we will briefly discuss the contemporary practice of oral squamous cell carcinoma, its advancements and innovations from a diagnostic, imaging, molecular, and surgical perspective.

From a diagnostic perspective, we have biomarkers, which include DNA methylation biomarkers, mRNA biomarkers, and protein biomarkers. In the future, artificial intelligence based detection and biomarkers will be available, which will make cancer detection even easier. In imaging advances, PET-CT, PET-MRI and USG guided FNAC are emerging. (2) In diagnostic advances in oral cancer detection, we have sentinel node biopsy, telomerase activity,and optical molecular imaging using exogenous molecular probes.

Several diagnostic techniques are often employed in clinical settings. These include vital staining, oral cytology, and optical imaging technologies. In vital staining, cells that exhibit dysplastic alterations are stained using toluidine blue and a monochromatic dye. It has been proven that toluidine blue has high sensitivity but low specificity. (3) The effectiveness of toluidine blue staining, which was used as an additional tool to the standard clinical examination to help with the early diagnosis of malignant lesions in the oral cavity and oropharynx, was assessed in recent hospital-based diagnostic accuracy research. Lugol's iodine is another test that may be performed chairside and is used to distinguish between normal and pathological mucosa. In contrast, when a dysplastic or malignant tumor is present, relative to the nearby healthy tissue, Lugol's iodine causes little staining and a pale look.

Collecting the mucosal cells by scraping , brushing, or rinsing is called exfoliative cytology, which is a conventional technique. These collected cells are then fixed and stained, and an oral a pathologist examines them under a microscope. These methods are non aggressive and relatively painless, derived from the cervical pap smear. (4)

In 1963, oral cytological examination was used to evaluate and screen oral mucosal lesions. But this has not achieved the same success as the screening of cervical cancer. For patients who have difficulty opening their mouths, where scalpel biopsies cannot be done, brush cytology is advised, which will confirm the lesion site. There are some technologies like the OralCDx® Brush Test (CDx Diagnostics, New York, NY, USA), which is a minimally invasive brush biopsy technique that uses artificial intelligence and computer assisted tissue analysis. (5)

For several years, optical light based technologies have been used for detecting oral cancer in clinical practice. To pinpoint the oral mucosal lesions, chemiluminescence or fluorescent light are used as intraoral detectors. Based on the color reflected, the condition of the oral epithelium is assessed.

Autofluorescence is the process by which light of a specific wavelength interacts with cells to excite them and cause the re-emission of light at various wavelengths. Fluorophores that are present in human tissues naturally cause autofluorescence to be emitted from those tissues. Natural fluorophores include things like collagen, tryptophan, elastin, keratin, hemoglobin, and NADH. In potentially malignant oral diseases, the concentration of these fluorophores will be altered.

VELScope®Vx (LED Dental, British Columbia, Canada) is a CE-approved medical device that noninvasively screens for alterations in oral mucosal autofluorescence. (6) It is a handheld camera device that emits blue light. (400 nm and 460 nm wavelengths) are used in order to visualize oral abnormalities that are combined with proprietary optical filtering. The normal oral mucosa produces green autofluorescent light. The anomalous oral mucosal lesions absorb the autofluorescent light and appear as dark areas in contrast with the adjacent tissue. (7)

When electrons stimulated by a chemical exergonic process return to their ground state through chemiluminescence, visible light radiation is emitted. Upon the change in the molecules' electronic potential energy, light photons are emitted.

An FDA-approved medical device is the ViziLite® Blue oral examination kit (Zila Pharmaceuticals, Arizona, AZ, USA). It is mostly used to visually inspect lesions of the oral mucosa. (8) It is a portable, disposable gadget that illuminates the oral cavity with light at wavelengths of 430 nm, 540 nm, and 580 nm. Prior to beginning the light emission, a 1% acetic acid wash is utilized to clear away surface material and enhance the visibility of epithelial cell nuclei. When it comes to appearance, normal oral mucosa is somewhat bluish, while diseased oral mucosa is distinctly white (acetowhite). (9)

Fluorescence- and Reflectance-Based Multispectral Imaging A probe-like medical

device called Identafi® (DentalEZ, Pennsylvania, PA, USA) is FDA and CE approved and intended for multispectral screening of OPMDs. During an oral mucosal examination, Identafi® uses three light sources: white light, violet light (405 nm), and green-amber light (545 nm). These can be applied in any sequence. (10) The violet light excites endogenous fluorophores, enhancing the fluorescence of normal tissues, while the white light provides an optimal view for a VOE of the oral mucosa. This will result in a dark appearance when a suspicious oral lesion is present. (11, 12) Through reflectance spectroscopy, the green light stimulates hemoglobin molecules in the blood, enabling the visualization of diffuse or dilated vasculature. Due to the fact that malignant tumors are more likely to have aberrant vascular architecture than benign ones, the third wavelength is primarily used to discriminate between them.

Cancer Biomarkers

Biomarkers are described by the National Institutes of Health (NIH) as molecules that can be consistently and correctly quantified, are indications of healthy or ill biological processes, and react to therapeutic interventions.(13)

Biomarker concentrations are typically low in the body. When cancer first starts, it barely varies within a constrained range. Understanding the mechanism of a marker's manifestation is necessary to determine its specificity for cancer detection, even though its existence may not be causal to the underlying disease. (14,15) In order to maintain intracellular proteostasis, heat-shock proteins (HSP), a key chaperone protein, are expressed on the surface of solid and hematological malignant tumors. (16) There are several studies that have reported evidence for the association between heat shock protein expression and oral squamous cell carcinoma. (17)

Apart from the advantages of the biomarkers in oral squamous cell carcinoma, there are some challenges and practical considerations to be considered. Improper collection, transportation, and storage of specimens are the manual measurement errors to be considered. (18,19) Confounding variables that could skew the detection of biomarkers should be identified in advance. Age, gender, weight, and other metabolic variables are only a few of the internal elements that have an impact. While batches of detection kits can be used for external elements. Cost effectiveness is crucial. There are currently very few biomarker tests that have been FDA, CE, or CLIA approved and have clinical validation. These include indicators for mRNA and protein-based expression as well as DNA methylation. (20–22)

DNA Methylation Biomarker

ZNF582 and PAX1 ZNF582 belong to a large family of transcriptional regulators that encode Krüppelassociated box zinc finger proteins (KRABZFPs) (23) According to a recent study, ZNF582 controls Nectin-3 and NRXN3 expression and transcription, acting as tumor suppressor genes in nasopharyngeal carcinoma (NPC). Through the control of these adhesion molecules, hypermethylation of ZNF582 encourages NPC metastasis. In addition to playing a crucial developmental role in embryogenesis and functioning as a tumor suppressor gene, PAX1 is well known for its paired-box domain. Tumor development is induced by high PAX1 methylation levels, and this includes cervical and oral cancer. Both DNA methylation biomarkers were created as in vitro diagnostics (IVD) and have received CE approval under the names EpiGene ZNF582 DNA Detection Kit and EpiGene PAX1 DNA Detection Kit, respectively (iStat Biomedical, New Taipei City, Taiwan). By evaluating the methylation levels of ZNF582 and PAX1, this diagnostic procedure will identify the degree of oral cancer and precancerous lesions risk (24. The clinician will collect the oral exfoliated cells from the suspected site in the oral mucosa, and then these cells are subjected to genomic DNA extraction and DNA bisulfate conversion, where unmethylated cytosine will be converted into uracil but the methylated cytosine will remain unchanged. (25) A methylation-specific PCR is then carried out to determine the methylation level (methylated cytosines) of both genes following the conclusion of DNA bisulfite conversion.Similar to this, PAX1 methylation has a sensitivity and specificity of 72% and 86%, respectively, for detecting mild dysplasia or oral lesions. Positive results for both genes in samples with high levels of methylation are inversely correlated with greater disease severity. (26)

mRNA Biomarker

Ornithine decarboxylase antizyme, also known as OAZ1, is activated by a polyamine-dependent mechanism and has been proven to be significant in DNA repair. The OAZ1 multipanel mRNA also includes SAT and DUSP1. It is linked to the metastatic potential of human oral squamous cell carcinoma cell lines. (26)(27) The rate limiting acetyl transferase in the polyamine metabolism catabolic pathway is SAT. (28) This gene, SAT, is expressed more strongly in prostate and oral cancers. The type I cysteine-based protein tyrosine phosphatase subtype DUSP1 participates in a number of signaling pathways. (29) Salivary DUSP1 mRNA is significantly increased in OSCC patients compared with normal controls. (30)

Surgical advances in head and neck cancers include robotic neck dissection, navigation surgery, virtual surgical planning, the use of cutting guides, and microvascular surgical anastomosis techniques.

Robotic surgery in head and neck cancers

The key to preserving the function of the oropharynx during cancer treatment is to minimize damage to the surrounding musculature and motor and sensory nerves of the pharynx. Then robotic surgery holds an intriguing possibility. Robotic surgery has improved functional results in other anatomical regions and decreased the length of hospital stays. Malley et al. reported on transoral robotic surgery (TORS) in a canine model and three TORS procedures for BOT SCC to show the feasibility of this approach. (31) Weinstein et al. demonstrated preservation of oropharyngeal function and adequacy of tumor removal with TORS for tonsillar SCC, followed by staged neck dissections. (32)

Transoral robotic surgery provides new benchmarks of functional outcomes and complication rates, with which treatments for oropharyngeal squamous cell carcinoma can be compared. (26,33) The ideal patients for this transoral robotic surgery would be patients with exophytic oropharyngeal tumors that do not extend into the lateral neck structures or into the skull base. In future, we hope to add local control, locoregional control, and disease-specific survival rates for TORS to these benchmarks. Ultimately, this treatment can serve as a treatment arm for comparisons in prospective randomized trials to establish a more uniform consensus of treatments for this controversial disease.

Nanoformulated drugs

Significant challenges and advances have been identified in various nanotechnology techniques for oral cancer treatment. (34) These carriers can be loaded with anti-cancer drugs, effectively attacking malignant cells and reducing damage to healthy cells. They exhibit site-specific delivery behavior and are based on these targeted drug delivery systems with customized architectures and different physicochemical properties. (35) By using their subtle framework connections, the majority of the carriers showed great promise as prospective substitutes that may be utilized to get beyond the limitations imposed by oral medications and traditional formulations. (36) As of now, the targeted drug release and its controllability are extremely difficult. (37)

CONCLUSION

Oral SCC continues to be a life-threatening disease worldwide. The key to reducing cancer associated mortality remains early detection and diagnosis. One should have thorough knowledge and a comprehensive understanding of the clinicopathological risk factors, which will help prevent cancer in its preclinical stage. The emerging evidence has indicated that beyond the cancer itself, there is an intricate network of cellular and noncellular components that, in turn, will determine the growth and metastasis of the tumor cells. The multidisciplinary approach and advanced technologies for detecting early cancer will put future budding head and neck surgeons on the path to saving numerous lives.

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