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Oral Cancer Diagnostics: A Review

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Introduction

Oral cancer includes cancer of the lip, oral cavity, nasopharynx and pharynx. Squamous cell carcinoma (SCC) is the most common type of oral cancer contributing to around 84% to 97% of the cases. Oral cancer results from preclinical stage of oral potentially malignant disorders (OPMD) such as leucoplakia, lichen planus, erythroplakia, oral submucous fibrosis, etc. India has the greatest number of oral cancer cases than any other nation worldwide and recently came to be known as "The Oral Cancer Capital of the World". It ranks among the top three cancers in the country. [1]

Other malignant diseases that can occur in the oral cavity include tumors of the salivary glands, lymph nodes, bone, and soft tissue. Individuals who have had a previous cancer are at high risk of developing a second primary oral cancer. [2]

Sex ratio indicates 2:1 male predominance. In males, oral cancer and lung cancer contributes greater than 25% cancer deaths in India and in females, breast cancer and oral cancer contributes 25% cancers in India.

The cure for cancer is like the Holy Grail since most of the existing treatments are not effective enough to provide full protection from this disease.

Reasons for difficulties in cancer treatment are:

- Targeting cancer stem cells (CSCs) is difficult
- Drug resistance properties of cancer stem cells make them immune to anticancer drugs

- Lack of cancer epigenetic profiling and specificity of existing epi-drugs
- Problems associated with cancer diagnosis make it difficult to treat
- Metastasis poses a huge problem in cancer treatment

There are two approaches in the early detection of oral dysplasia and cancer:

- Oral cancer screening programs that identify asymptomatic patients with suspicious lesions
- Employing specific diagnostic tools to identify dysplasia and early oral cancers in asymptomatic patients with an oral abnormality. [3]

Early detection is very important to reduce the mortality rate of patients suffering from oral cancer. Thus, there is a huge demand for oral cancer diagnostic techniques that are non-invasive, rapid, and easy-to-use

Chemoprevention

Chemoprevention refers to the administration of an agent to prevent a cancer from occurring. The agent can be a drug or a natural product. The agent must be easy to administer, cause little or no toxicity, cause no long-term adverse sequelae, be affordable, and ideally, should have the need to be administered only for a short time.

Promising agents for chemoprevention of oral cancer:

Retinoids: Retinoids can act through induction of differentiation and can inhibit proliferation, as well as cause programmed cell death.

β Carotene: It is one of several carotenoids in the body and is a precursor of vitamin A. It is found in leafy green vegetables and yellow and orange fruits and vegetables. As a chemo preventive agent, it may involve antioxidant mechanisms as well as inhibition of free radical reactions.

***N*-acetylcysteine**: It is an antioxidant and free-radical scavenger that has shown chemo preventive activity in lung and tracheal tumours in animals.

Nonsteroidal anti-inflammatory agents (NSAIDs): It have shown activity in tumour inhibition in preclinical head and neck cancer models. Because these compounds may be inhibitors of proliferation, they may be useful as chemo preventive agents.

Vitamin E: Epidemiologic studies have noted an inverse relationship between serum vitamin E levels and oral cancer. Its mechanism of action postulated to be as an antioxidant agent.

Interferons: It have shown additive or synergistic antitumor effects in combination with retinoids.

Curcumin: It has inhibited carcinogen-induced tumorigenesis in an oral cancer model and is nontoxic. This is under consideration as a cancer preventive agent. [4]

Techniques used for diagnosis of oral cancer:

- Physical examination
- Vital staining
- Detailed brush cytology and Biopsy
- Biomarker detection
- Spectroscopy
- Histopathological examination
- Imaging techniques
- Salivary biomarkers
- Lab – on – a – chip
- Microscopy

Physical examination

The physical examination consists of systematic inspection and palpation. The extraoral soft tissues are examined first, followed by the intraoral soft tissues.

Inspection of various tissues:

Lip: The closed lips are inspected for texture and colour. The vermilion border should be observed and palpated for ulceration, blistering, induration and swelling.

Parotid gland: It is palpated intraorally and extra orally, either bimanually (placing one hand on the cheek and two fingertips of the other hand on the buccal mucosa) or bi-digitally (placing the gland between the fingertips of one hand).

Submandibular and Sublingual gland: It is palpated by either pressing four fingertips bilaterally on the soft tissue under the chin or resting the thumbs of each hand near the inferior mandibular border while pressing the fingertips inferior and medial to the mandibular border. The finger-tips are moved inferiorly to the hyoid bone and then medially and superiorly until the inferior part of the submandibular gland is felt.

Anterior deep cervical Lymph nodes: It is palpated with the patient's head hyperextended and turned to distend the sternocleidomastoid muscle. Using two hands, the fingertips of one gently retracts the sternocleidomastoid backward while the fingertips of the other hand, hooked around the front of the neck, palpate the region of the carotid sheath.

Preauricular and postauricular Lymph nodes: The auricular lymph nodes are palpated by the bilateral placement of both hands on the skin surface with the fingertips arranged to cover a large surface area.

Labial mucosa: It is inspected and then palpated using the fingertips of two hands to invert the upper and lower lips.

Buccal mucosa: It is retracted for inspection and palpated using a bimanual or bi-digital technique.

Tongue: The lateral borders of the tongue are common areas for oral malignancies to develop. The borders should be inspected for ulceration, inflammation, swelling or white patches. The tongue is inspected by grasping the tip with a gauze square and pulling out and moving it to the sides and upward to permit complete visualization of the dorsal lateral borders and ventral surfaces.

Floor of the mouth: The submandibular glands located in the anterolateral floor of the mouth are palpated by placing the fingertips of one hand in the floor of the mouth while the fingertips of the other hand are placed under the chin to support the mandible. The sublingual glands are more difficult to palpate than the submandibular glands because they are more compressible and less distinct.

Hard palate: With the mouth wide open and the patient's head tilted back, the hard and soft palates should be carefully inspected and palpated. [5]

Staining techniques

A large majority of oral neoplasms are squamous cell or epidermoid carcinomas. Since these tumors continually exfoliate malignant cells, it was felt that examination of saliva specimens taken from the entire oral cavity following irrigation with some form of mouthwash might be an effective screening test for oral cancer. [6]

Mouthwash technique: In this Gey's balanced salt solution is used. Irrigation of mouth for 60 seconds with one ounce of Gey's Solution has to be done. A specimen with a cell population typical of the entire oral cavity is obtained and smear and stain the specimen in the usual Papanicolaou method. Malignant cells will usually appear singly not in clumps and present little problem in identification. [6]

Toluidine blue staining: Toluidine blue (TB) chemically is referred to as tolonium chloride. In this technique, application of 1% TB solution for 20 s either with cotton swab has to be done when a mucosal lesion

is seen or given as a rinse when no obvious lesion is detected. A dark blue (royal or navy) stain of either the entire lesion or a portion of it is considered as positive stain, lack of colour absorption by the lesion as negative stain, and light or pale blue staining as doubtful. [7]

Methylene blue staining: Methylene blue (MB) dye system includes two bottles of solution. Bottle A, the dye rinse solution containing Methylene blue and bottle B containing pre- and post-rinse solution. Rinsing with 1% MB dye for 20 s has to be done. Local, stippled, patchy, and deep blue stains are marked as positive reaction. Wide, shallow, or faint blue stains are marked as negative reaction. If the blue stain is washed out, negative reaction is recorded. [7]

Lugol's iodine staining: Lugol's solution consists of iodine and potassium iodide. It has been used in varying concentrations: 1, 1.25, 1.5, 2, 3, and 10%. Staining with 3% Lugol's solution, followed by 5% has been found to be more effective. It is found to be useful in determining the adequacy of surgical margins for local resection and hence thereby useful in reducing the locoregional recurrence. Further studies are essential to assess the effectiveness of Lugol's iodine. [7]

Acetic acid staining: A piece of gauze soaked with 5% of acetic acid is applied on to a cleaned and dried lesion for 60 s. Positive finding is designated as a lesion that changes colour to opaque white and negative finding is a lesion that shows no change or changes to transparent white. It acts by causing dehydration of the cells, thereby producing a white appearance. The higher nuclear content in premalignant and malignant lesions reacts with the acetic acid producing an acetowhite appearance. [7]

Double staining: Studies have been done wherein few authors have used combination of two dyes to aid in the assessment of oral malignant diseases. The basis of the mucosal double staining technique was that MB stains lesion blue and Lugol's iodine reversibly stains glycogen brown. Normal squamous epithelium appears unstained because it does not absorb MB, but in abnormal mucosa the superficial epithelium is often stained blue because it absorbs MB. Therefore, the areas-stained blue indicates the existence of carcinoma, the area-stained brown belongs to normal squamous mucosa and the area between both the colours clarifies the invasive lesion of carcinoma. [7]

Rose Bengal (RB) staining: Studies demonstrated that RB staining may be a valuable diagnostic technique in the detection of oral premalignant disorders and oral cancer. Zhang et al. (2013) combined fluorescence spectroscopic techniques with RB staining to detect oral premalignant disorders in an animal model in vivo and reported that the method showed excellent sensitivity. Studies have demonstrated that Rose - Bengal-conjugated Gold Nanorod (RB-GNR) platform has positive significance in detecting cancer cells, but it has not yet been used in a clinical setting. [8]

Detailed brush cytology

Brush cytology can be a non-invasive means of diagnosing dysplasia and early carcinoma in those patients who are either asymptomatic or in those with minor symptoms who do not warrant immediate biopsy. The dysplastic and cancerous cells tend to have weaker connections to each other and to their neighboring normal cells. Therefore, tend to "slough off" or exfoliate preferentially and can easily be collected from the surface of the lesion. Exfoliative cytology performed on oral cancers has high false negative rates, due to the fact that cytology instruments do not sample the deepest layers of the oral lesion that is basal cell layer, where

abnormal cells within an oral precancerous or cancerous lesion will be present. [9]

Biopsy: Biopsy is the removal of a tissue sample from a living body with the objective of providing the pathologist with a representative, viable specimen for histopathologic interpretation and diagnosis.

Incisional biopsy: It provides a representative sample of tissue for diagnostic purposes. It is the method of choice when the differential diagnosis includes malignancy. [10]

Excisional Biopsy: It is the complete removal of a lesion for functional and aesthetic purposes, as well as to confirm the clinical diagnosis. Small, pedunculated, exophytic lesions in accessible areas are excellent candidates for excisional biopsy.

Punch Biopsy: The punch is placed on the lesioned tissue, and a downward, twisting motion is applied. The tissue core is then severed at the base with curved scissors. The lateral tongue and buccal mucosa are appropriate sites.

Liquid biopsy: They are non -invasive blood tests that detect circulating tumor cells (CTC) and circulating nucleic acids such as mRNA, microRNA, and cell-free circulating tumor DNA, also known as ctDNA. The presence of ctDNA or CTCs in the plasma has prognostic impact. Since ctDNA is the DNA fragments released by tumor cells, it can provide a molecular profile of cancer. [11,12]

Endoscopic biopsy: "Turn -and-suction" endoscopic biopsy technique was developed that permits the acquisition of larger mucosal samples. The sample is obtained by endoscope tip by avulsing a superficial mucosal sample. Endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNA) has a major impact on the therapeutic management of patients by obtaining a definite tissue diagnosis from lesions outlined by endosonography. [13, 14]

Biomarker detection

Biomarkers are the molecular signatures and indicators of normal biological, pathological process, and pharmacological response to treatment hence may provide useful information for detection, diagnosis, and prognosis of the disease. Saliva's direct contact with oral cancer lesions makes it more specific and potentially sensitive screening tool, whereas more than 100 salivary biomarkers (DNA, RNA, mRNA, protein markers) have already been identified, including cytokine s (IL-8, IL-1b, TNF-α), defensin-1, P53, Cyfra 21-1, tissue polypeptide-specific antigen, dual specificity phosphatase, spermidine/spermineN1 -acetyltransferase, profilin, cofilin-1, transferrin, and many more. However, further research is still required for the reliability and validation of salivary biomarkers for clinical applications. [15]

Gene/DNA arrays: DNA microarrays (collections of DNA probes arranged on a shared base) are the commercially available laboratory-ready kits in molecular biology. They are used in search for various specific genes (e.g., connected with an infectious agent) or in gene polymorphism and expression analysis. They will be widely used to investigate expression of various genes connected with various diseases in order to find causes of these diseases and to enable their accurate. DNA microarrays allow simultaneous evaluation of the expression of hundreds of genes in a single assay. The parallel format of micro assay slides is designed to allow rapid comparison of gene expression between two samples, for example tumor cells and healthy cells. [16]

Enzyme assays: It is the method for determining cytotoxicity is based on measuring the activity of

cytoplasmic enzymes released by damaged cells. Example of cytoplasmic enzymes is Lactate dehydrogenase (LDH), which is rapidly released into the cell culture supernatant when the plasma membrane is damaged, a key feature of cells undergoing apoptosis, necrosis, and other forms of cellular damage. Histone modifying enzymes (HMEs)-catalyzed histone modifications are important epigenetic markers that play critical roles in the regulation of gene expression. The aberrant histone modifying enzyme activity and the abnormal histone modification level are closely associated with cancers. Consequently, the development of efficient assays for accurate and sensitive detection of histone modifications and HMEs are crucial for disease diagnosis. Alteration of glycosylation, a hallmark of cancer, results in the production of tumor-associated glycans or glycoproteins. The glycosylation markers, applicable for detection and monitoring of cancer, include CA19-9, CA125, CEA, PSA and AFP. various enzyme -linked lectin assays (ELLA) and chemokines in oral fluids can also be used as a marker of both the early detection of malignant disease and progression to malignancy. [17-20]

Liquid chromatography: Specifically, different types of cancer might exhibit differentiated metabolic profile where an ensemble of metabolites are secreted extracellularly into the blood. Profiling such secreted metabolites using liquid chromatography mass spectrometry (LC-MS) might provide clues to the type of cancer and its clinical stage. Example: An ultra-performance liquid chromatography-electrospray ionization-mass spectrometry (UPLC-ESI-MS) method for the determination of salivary L-phenylalanine and L-leucine for early diagnosis of oral squamous cell carcinoma (OSCC). [21, 22]

Immunohistochemistry (IHC): It is the utilization of monoclonal and polyclonal antibodies for the detection of specific antigens in tissue sections. Immunohistochemistry techniques have allowed labs to develop and validate multiplex assays that improve diagnostic utility-such as CD5/PAX5 and TCF4/CD123 dual-colour stains-and have the potential to enhance the specificity of biomarker detection and it can detect mutant proteins (e.g., BRAF V600E and IDH1 R132H), which provides a helpful replacement and/or adjunct for molecular testing. [23, 24]

Immunoprecipitation: It is a technique in which an antigen is isolated by binding to a specific antibody attached to a sedimentable matrix. Cell-free chromatin Immunoprecipitation (cfChIP), which for genes having high expression specifically in the tumor, can determine such gene - expression from blood plasma. immunoprecipitation analysis was used to determine the endogenous interaction between Osteopontin (OPN) and integrin αvβ3. OPN, a chemokine-like protein, plays a crucial role in the proliferation and metastasis of various cancers. More importantly, soluble OPN could promote immunohistochemistry progression via the integrin αvβ3-NF-kappa B pathway, and the combination of OPN and Interleukin-6 had a better prognostic and diagnostic performance in immunohistochemistry than either molecule alone. [25, 26]

Spectroscopy

Study of the absorption and emission of light and other radiation by matter, as related to the dependence of these processes on the wavelength of the radiation. [27]

Raman spectroscopy (RS): This technique probes molecular vibrations/rotations associated with chemical bonds in a sample to obtain information on molecular structure, composition, and intermolecular interactions.

Since each sample has a unique composition, the spectroscopic profile arising from Raman -active functional groups of nucleic acids, proteins, lipids, and carbohydrates allows for the evaluation, characterization, and discrimination of tissue type. This work studies the efficacy of RS in detecting oral cancer using sub -site-wise differentiation. [28]

Elastic scattering spectroscopy (ESS): It is a real time in vivo optical technique which detects changes in the physical properties of cells and has been shown to be accurate in the identification of abnormalities of soft tissue such as ischemia and inflammation, pre - cancer and cancer. The contact fibre optic probe will be used to obtain spectral signals and it is placed in direct contact with tissue. Four to ten spectral readings can be obtained from various sites including gross tumor and normal appearing mucosa in the surgical margin. Each reading should be correlated with the histopathologic findings of biopsies taken from the exact location of the spectral readings. [29, 30]

Fourier transform infrared (FTIR) spectroscopy: It probes the vibrational properties of amino acids and cofactors, which are sensitive to minute structural changes. In cancer research, it has the ability to elucidate qualitative and quantitative information of biochemical content and molecular-level structural changes in complex biological systems. The diagnosis of a disease is based on biochemical changes underlying the disease pathology rather than morphological changes of the tissue. It is a versatile method that can work with tissues, cells, or body fluids. It is a useful tool for analyzing in situ and at cellular level, very small areas of tissues and cells, with minimal sample preparation and without the use of stains or probes. [31-33]

Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS): It identifies the distributions of proteins, peptides, small molecules, lipids, and drugs and their metabolites in tissues, with high spatial resolution. This unique capacity to directly analyze tissue samples without the need for lengthy sample preparation reduces technical variability and renders MALDI-IMS ideal for the identification of potential diagnostic and prognostic biomarkers and disease gradation. [34]

Optical coherence tomography (OCT): It is a non-invasive diagnostic technique providing cross-sectional images of biologic structures based on the differences in tissue optical properties. It is used to clinically scan oral precancer and cancer patients for statistically analyzing the effective indicators of diagnosis. Three indicators are considered:

- Standard deviation (SD) of an A-mode scan signal profile
- Exponential decay constant (alpha) of an A-mode-scan spatial-frequency spectrum
- Epithelium thickness (T) when the boundary between epithelium and lamina propria can still be identified

Generally, in abnormal mucosa, the standard deviation becomes larger, the decay constant of the spatial-frequency spectrum becomes smaller, and epithelium becomes thicker. The sensitivity and specificity of the three indicators are discussed based on universal and individual relative criteria. It is found that SD and alpha are good diagnosis indicators for moderate dysplasia and squamous cell carcinoma. On the other hand, T is a good diagnosis indicator for epithelia hyperplasia and moderate dysplasia. [35, 36]

Laser-induced autofluorescence (LIAF): It is an emerging non-invasive technique in the biomedical field, especially for cancer detection. It will help to develop a spectral ratio reference standard (SRRS) to discriminate different grades of oral cancer. This imaging exploits the difference in tissue autofluorescence properties between normal and cancerous tissues. [37, 38]

Diffuse reflectance spectroscopy (DRS): In this technique, output of a tungsten halogen lamp is guided to the tissue through the central fibre of a reflection probe who's surrounding six fibres collects tissue reflectance. Reflectance spectral intensity is higher in malignant tissues and shows dips at 542 and 577 nm owing to absorption from oxygenated hemoglobin (HbO2). It is observed that reflectance intensity ratio of hemoglobin bands, R540/R575, from malignant sites are always lower than that from normal sites and vary according to the histological grade of malignancy. This diffuse reflectance intensity ratio R540/R575 appears to be a useful tool to discriminate between malignant lesions and normal mucosa of the oral cavity. [39]

Histopathological examination

It means the study of tissues related to disease. Samples of tissue can be obtained with procedures such as endoscopy, colonoscopy, and colposcopy, or with surgical procedures such as a breast biopsy. Many of the pathologist's findings are used to help determine prognosis, especially in cases of cancer. Prognosis is the prediction or estimate of survival or recovery from a disease. [40, 41]

Imaging techniques

Preoperative imaging has been shown to predict known prognostic determinants in oral cancer, such as bone involvement, nodal involvement, extra nodal extension, and perineural invasion. Although the sensitivity and specificity vary with the imaging modality and with several patient-related factors, reliable prognostic detail can be achieved for a proportion of patients.

optimal imaging methods for oral squamous cell carcinoma:

- Multi detector computed tomography (MDCT) with intravenous contrast along with puffed cheek technique as the sole imaging modality in resource-limited regions
- Optimized imaging choices depending on the clinical need in centres with state-of-the-art facilities:
    - MDCT for lesions of the oral cavity, including retromolar trigone region
    - Magnetic resonance imaging (MRI) for the oral tongue, hard and soft palate, for advanced disease with bone marrow or skull base involvement, or when there is an indication to exclude perineural spread
- Nodal assessment is optimally performed with computed tomography (CT) or MRI. In addition, ultrasound-guided fine-needle biopsy can be useful in defining involved cervical nodes
- Chest evaluation is best undertaken with MDCT performed in concert with primary site CT for pulmonary abnormalities such as tuberculosis
- Positron emission tomography computed tomography (PETCT) is the method of choice for evaluating distant metastases but is generally performed subsequent to initial staging cross-sectional imaging (MDCT and/or MRI). [42]

Ultra sound (US) is a useful tool for the pre- and intraoperative assessment of oral tongue squamous cell carcinomas and show potential as a predictor of lymph node metastasis. Further prospective research using

standardized imaging protocols and well-defined patient populations needs to be done to establish US as a robust adjunct to prognostic counselling and therapeutic decision making. [43]

Saliva as a diagnostic tool

Saliva testing, a non-invasive effective modality for diagnosis and for prognosis prediction of oral cancer, as well as for monitoring post therapy status, by measuring specific salivary macromolecules, examining proteomic or genomic targets such as enzymes, cytokines, growth factors, metalloproteinases, endothelin, telomerase, cytokeratins, mRNAs and DNA transcripts. [44]

Lab – on – a – chip

Broadly, microfluidics technology -also referred to as lab-on-a-chip or micro-total-analysis systems (TAS)-is the adaptation, miniaturization, integration, and automation of analytical laboratory procedures into a single device or "chip." Microfluidics is often regarded as the chemistry or biotechnology equivalent of the silicon integrated circuit chip that has revolutionized electronics, computers, and communications. The detection of oral dysplastic and cancer cells within the chip utilizes mem braneassociated cell proteins that are singularly expressed on the cell membranes of dysplastic and cancer cells as well as their unique gene transcription profiles. [45]

Microscopy

Spectral cytopathology (SCP) is a recently developed technique for diagnostic differentiation of disease in individual exfoliated cells. Multispectral digital microscope (MDM) has also been utilized as a tool to improve detection of oral neoplasia. MDM acquires in-vivo images in different modes i.e., fluorescence, narrow-band (NB) reflectance, and orthogonal polarized reflectance (OPR) to enable evaluation of lesions. The direct visualization of subclinical field changes around oral cancers, documenting alterations in fluorescence and direct FV can identify subclinical high-risk fields with cancerous and precancerous changes. [46-48]

Conclusion

Early diagnosis of oral cancer is a priority health objective, in which oral health professionals may play a pivotal role. There has been a dramatic increase in the development of many potential oral cancer screening techniques in last few years. So, it is highly important to have clear knowledge about the usage of various diagnostic aids that can be used during chair side diagnosis mentioned here. Which on proper usage can decrease the risk of morbidity and mortality associated with oral cancer.

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