REVIEW ARTICLE

Diagnosis of Oral Precancerous and Cancerous Lesions

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ABSTRACT

Oral cancer is the sixth most common malignancy with almost 500,000 new cases reported worldwide annually. The diagnosis of oral cancer at an early stage has a good prognosis as the survival rate is high (around 80%). However, the majority of oral cancer cases are diagnosed at a later stage with a considerably poor 5-year survival rate of 50% according to the World Health Organization statistics. Thus, an effective management strategy for oral cancer will depend on its early identification and intervention which would pave the way for superior prognosis. Despite the obvious advantage of earlier diagnosis of oral cancer, no approach has yet proven to be a reliably successful in diagnosis of oral cancer at an early stage. At present, the primary line of screening of oral cancer is performed by visual inspection, which is a subjective examination. Among the screening tests or diagnostic aids now available for oral cancer, few (toluidine blue, brush biopsy, salivary, and serum biomarkers) have been utilized and studied for many years while others have recently become commercially available. This review provides a summary of all the diagnostic modalities that were used earlier and the newer more advanced techniques with merits and demerits of each technique described briefly.

Keywords: Biomarkers, Early diagnosis, Malignancy, Oral cancerous lesions, Oral precancerous lesions.

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INTRODUCTION

The incidence of oral cancer worldwide is around 500,000 new cases every year, accounting for approximately 3% of all malignancies, thus creating a significant worldwide health problem.[1] Tobacco use and alcohol consumption are regarded as the main risk factors for oral squamous cell carcinoma (OSCC), while human papillomavirus infection is emerging as the leading risk factor in cancers of the oropharynx. The most common form of oral cancer is squamous cell carcinoma, which accounts for 96% of all cancers of the oral cavity.[2] Delayed diagnosis can also be due to incomplete understanding or awareness that a small lesion can also have a high malignant potential. Over the years, a number of diagnostic aids have been developed to aid in early diagnosis of oral precancerous and cancerous lesions which would be discussed in this article.

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VITAL STAINING

Toluidine blue, an acidophilic metachromatic dye has been used as a vital stain, for the identification of dysplasia cases and early OSCC. Dysplastic and anaplastic cells contain more nucleic acids quantitatively than normal tissues, hence used *in vivo*. In addition, intracellular canals of the malignant epithelium are wider than normal epithelium; this is a factor that would enhance penetration of the dye. The test is sensitive, simple, non-invasive, and highly cost-effective. It assists in identifying the preferred area of biopsy and marking the borders of the lesion. This may lead to early detection, diagnosis, and in directing surgical management.[3]

ORAL BRUSH BIOPSY

Oral brush biopsy provides cytological evaluation of cellular dysplastic changes, which uses the concept of exfoliative cytology. The procedure is rapidly conducted chair side that is cost-effective and perhaps the best approach for the initial evaluation and diagnosis of oral diseases. It permits better selection of cases for biopsy and to help localize the optimal site for brushing an abnormality, conventional oral brush biopsy combined with the application of toluidine blue is used to localize suspected mucosal areas. Brush cytology is an advantageous diagnostic procedure because it is non-invasive, relatively painless with minimum bleeding, and requires a minimum of technical skills. Despite the advantages of brush cytology, it has certain disadvantages such as inadequate sampling and false-negative results.[4]

LIQUID-BASED CYTOLOGY (LBC)

LBC is a method of preparing and processing smears. LBC has recently become an alternative to conventional papanicolaou smear in the detection of intraepithelial lesions. The smear takes a sample of cells from the lesion and places them into a liquid solution (polymer solution containing agarose, polyethylene glycol, poly-l-lysine, and alcohol). The material collected in the liquid fixative preserves the cells. The centrifugation machine removes excess blood, mucous, and inflammatory cells and produces a thin layer of cells on a glass slide. The cells are stained and examined under the microscope in the same way as the conventional smear test.[5]

HISTOPATHOLOGY

The gold standard for diagnosis and staging of many diseases is histopathology, evolved from an era of diagnosis based on hematoxylin and eosin-stained slides. Grading systems have been developed to predict tumor aggressiveness, and the pathologist's report often guides clinical treatment decisions. Although it is a fairly reliable and inexpensive method for detection of pre-cancer and cancer, there are several limitations. In this method, the quantitative measurement lacks objectivity and reproducibility, it is less sensitive and prone to a lot of errors, time-consuming, and there is an increase in interobserver variability.[6]

IMMUNOHISTOCHEMISTRY (IHC)

IHC is a technique for identifying cellular or tissue constituents (antigens) using antigen-antibody interactions, the site of antibody binding being identified either by direct labeling of the antibody or by use of a secondary labeling method. It has an apparent advantage over traditionally used special and enzyme staining techniques that identify only a limited number of proteins, enzymes, and tissue structures. The advantages of IHC are that it is compatible with standard fixation and embedding procedures, it can be performed retrospectively in archival material, and it is sensitive and specific and is applicable to almost any immunogenic molecule.

PHOTODIAGNOSIS

It is a non-invasive procedure which provides tissue diagnosis in real-time through optical spectroscopy. It can be used in performing guided biopsies, hemoglobin estimation and monitoring, tissue perforation in free flap surgeries and monitoring drug levels during chemotherapy, detection of dysplasia, assessment of surgical margins, and in sentinel node biopsy.[7]

VELSCOPE SYSTEM

The VELscope uses a blue light with peak intensity at approximately 436 nm; this wavelength especially stimulates a green fluorescence. The principle of tissue autofluorescence was used in screening and diagnosis of precancerous lesions in the lung, uterine cervix, and skin in the past. This concept of diagnosing dysplastic lesions in the oral cavity is based on the structural and metabolic changes of the epithelium as well as the connective tissue when interacting with the light.[8]

IDENTAFI 3000

The Identafi 3000 technology combines anatomical imaging with fluorescence, fiber optics, and confocal microscopy to map and delineates precisely the lesion in the area being screened. The advantage of this device over the VELscope is its small size and easy accessibility to all tissues in the oral cavity.[7] Besides detection of autofluorescence similar to the VELscope system, this device also examines tissue reflectance which is based on the premise of detecting changes in angiogenesis with green-amber light (540–575-nm wavelength) illumination. The amber light is thought to enhance the reflective properties of the oral mucosa, allowing a distinction between normal and abnormal tissue vasculature. Increased angiogenesis is a known process during oral carcinogenesis and oral cancer progression. It is important to develop imaging technology for evaluating the status of tumor angiogenesis.[9]

SALIVA AS A DIAGNOSTIC TOOL

Saliva from patients has been used in a novel way to provide molecular biomarkers for oral cancer detection. Saliva is a mirror of the body, reflecting virtually the entire spectrum of normal and disease states and its use as a diagnostic fluid meets the demands for an inexpensive, non-invasive, and accessible diagnostic tool. Discovery of analytes in saliva of normal and diseased subjects suggests a very promising function of saliva as a local and systematic diagnostic tool. The ability to analyze saliva to monitor health and disease is a highly desirable goal for oral health promotion and research. So far, saliva has been used to detect caries risk, periodontitis, oral cancer, breast cancer, salivary gland diseases, and systemic disorders such as human immunodeficiency virus and hepatitis C virus.[7,8] However, due to lack of knowledge of disease markers and an overall low concentration of these markers in saliva when compared to serum, the diagnostic value of saliva has not been fully realized. However, nowadays, highly sensitive and high-throughput assays such as DNA microarray, mass spectrometry, and nanoscale sensors

can measure protein and RNA markers at low concentrations in saliva, thus expanding the utility of saliva as a diagnostic tool.[10-13]

CONCLUSIONS

Dentists' knowledge and education in detecting oral cancer at its pre-cancerous phase is the key to prevent its progression to later stages. To improve early detection, it is imperative to increase the health-care providers' depth of knowledge about oral cancer, their risk factors, and the most common oral precancerous conditions. Future research can also be directed toward establishing appropriate clinical practice standards for early detection exams.

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