Early Diagnosis of Oral Cancer: A Review
M. Priya1* and Diksha Singh2

ABSTRACT
Oral cancer (OC) is a global burden. India has become the epicentre of OC globally. As clinicians we are responsible for recognizing and detecting early or incipient changes of the oral mucosa, because, inspite of numerous advances in the treatment of OC, 5-year survival rate remains only 50%. This poor prognosis is due to several factors. However, single most effective route to improving the long-term outcome of OC is early diagnosis. Dentists must be keenly aware of oral mucosal alterations; any observed suspicious mucosal abnormality must be sampled using biopsy. A variety of commercial diagnostic aids and adjunctive techniques are available to potentially assist in the screening of healthy patients, for evidence of otherwise occult cancerous change or to assess the biologic potential of clinically abnormal mucosal lesions. This article is aimed at helping the clinicians, about the various aids or adjuncts that can be used in OC detection; a systematic review of the literature by way of descriptive design was used.

KEYWORDS: Early diagnosis, Precancer, Cancer, Morbidity, Mortality

INTRODUCTION
Oral cancer (OC) is the fifth most common malignancy in the world, with an annual incidence of about 2,74,000 patients. This accounts for about 2.5% of all malignancies in both the sexes. An increase in OC prevalence among young adults is a cause of special concern. 5-year survival rate for patients with localized disease approximates 80% compared to 20% for those with distant metastasis. The high mortality rate from OC is due to several factors but undoubtedly, the most significant is delayed diagnosis[1,2]. Given the significant morbidity and mortality associated with advanced OC, the onus is on the clinicians, is sharing the responsibility of detecting and diagnosing OC by utilizing accurate diagnostic technique that will increase the detection at early stage. In this article, descriptive design has been used to review the various diagnostic procedures available for the detection of OC clinically and emphasizes about the importance of its early detection by the clinical practitioners.

History Taking
There are varieties of devices that assist in detecting OC, but it is needless to emphasize the importance of history recording, risk factor identification and clinical examination. Risk factors must always be considered, as this alerts the clinician to increased susceptibility. Thorough oropharyngeal and regional lymphnode examination should be performed under incandescent light or using activated light systems. If any suspicious lesions are observed, then adjunctive tests or devices can be utilized appropriately.

Chairside Diagnostic Procedure
Vital staining is a method of studying oral mucosal tissues, by applying staining material. Vital stains such
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as toluidine blue/tolonium chloride and lugol’s iodine[3]. Literature shows numerous studies on the utility of toluidine blue in screening though they are limited on lugol’s iodine. Toluidine blue is an acidophilic metachromatic dye that has strong affinity for areas of malignancy and other mucosal abnormality, than normal oral mucosa thus helping in differentiating normal from abnormal mucosa. This test is indicated in screening high risk patients for OC, selection of biopsy sites, especially when several surface abnormalities are present[4], follow-up of OC treated patients. This is a highly sensitive test but lacks specificity. It is commercially available as a ready to use kit-orascan, orascreen and oratest.

Light Based Detection Systems

Tissue reflectance systems are used as complementary visual aids in the examination of oral mucosa. Mucosal tissues undergoing abnormal metabolic and structural changes have different absorbance and reflectance properties when exposed to various forms of light. This property is used to delineate normal from abnormal mucosa. Commercially available as Vizilite plus and Microlux DL.

Vizilite plus is a chemiluminescent light detection system, whereas Microlux DL offers a reusable battery powered light source. Vizilite plus is also provided with tolonium chloride solution (T Blue) which helps in marking the lesion for subsequent biopsy once the target source is removed. On examination of the oral mucosa with this non toxic chemiluminescent light source, normal epithelium absorbs light and appears dark, abnormal epithelium reflects it and appears white, thus helps in differentiating normal from abnormal mucosa[5]. Examination with vizilite should be done within 10 minutes. Literature supporting Microlux DL is minimal.

Narrow Emission Tissue Fluorescence

Tissues naturally exhibit fluorescence (auto fluorescence) due to endogenous fluorophores thus normal mucosa excited to light of about 400 nm, they exhibit broad band of green autofluorescence but neoplastic tissue appears dark due to reduction in fluorescent cross links[6]. Thus this can be utilized in differentiating from normal mucosa. It can be enhanced by using Aminolaevulanic acid that helps accumulation of photosensitiser Protoporphyrin IX in cancerous tissue. Based on this principle, Fluorescence spectroscopy and fluorescence imaging were developed. Fluorescence spectroscopy involves exposure of tissues to various excitation wavelengths so that subtle differences between normal and abnormal tissues can be identified. Fluorescence imaging involves the exposure of tissue to a rather specific wavelength of light which results in the autofluorescence of cellular fluorophores after excitation. Literature shows imaging and spectroscopy are excellent in distinguishing between normal and malignant tissue.

Velscope is a portable hand held device that allows direct visualization of oral cavity. This device emits safe blue light (400–460 nm) under this light normal oral mucosa emits pale green auto fluorescence whereas abnormal or suspicious tissue exhibits decreased levels of normal autofluorescence and appears dark. Studies have shown that use of this narrow band light imaging have improved the quality of examination process[7].

LABORATORY METHODS

Exfoliative Cytology

Is a method of microscopic examination of epithelial cells obtained from the suspicious mucosal region. Conventional exfoliative cytology has proven to be of little value in diagnosis of OC because of its high false negative results which may provide a false sense of comfort and delay diagnosis[8,9]. Spectral cytopathology (SCP) is a novel approach for diagnostic differentiation of disease in individual exfoliated cells. SCP is carried out by collecting information on each cell’s biochemical composition via an infrared micro spectral measurement, followed by multivariate data analysis. Deviations from a cell’s natural composition produce specific spectral patterns that are exclusive to the cause of the deviation or disease. These unique
spectral patterns are reproducible and can be identified and used via multivariate statistical methods to detect cells compromised at the molecular level by dysplasia, neoplasia, or viral infection. In a recent study, benchmark for the sensitivity of SCP was established by classifying healthy oral squamous cells according to their anatomical origin in the oral cavity[10].

**Oral CDx test** is a computer-assisted method for the analysis of cellular samples collected by using a patented brush the improvement over conventional cytology is due to the brush, which collects a complete transepithelial sample, and the analysis of that sample with computer. The computer analyzes the scanned digital microscopic image of the collected cells using a specialized neural network-based image processing system. The analytical results and representative examples are presented to a cytopathologist who makes the final diagnosis and suggests follow-up to the clinical practitioner such as clinical close observation, repeat brush biopsy, surgical biopsy, etc. Oral CDx has been shown to have a sensitivity and specificity well over 90%[11,12].

**Biopsy**

Oral biopsy is an invasive procedure. They are of various types, incisional, excisional and punch biopsy. When lesions are extensive, the most representative areas must be selected to avoid diagnostic errors. If necessary vital stains are utilized. Based on the degree of dysplasia it is graded into mild, moderate and severe. Though it involves both psychological implications for the patient and technical difficulties for the health practitioner, this procedure is considered to be the gold standard for diagnosis of OC.

**Assessment of Molecular Changes**

In a highly complex oral carcinogenesis, molecular changes are far preceded by the structural changes. The use of molecular biology techniques to diagnose oral precancerous and cancerous lesions may markedly improve the detection of alterations even before they become visible under microscope.

**Tumour Markers**

Are biochemical analyses that are elaborated by the tumour or by the host in response? Qualitative and quantitative analysis of these help determine the degree of cell alteration and enable a better understanding of the degree of malignant degeneration of these cells[13–16]. Tumour markers are grouped into – tumour growth markers, markers of tumour suppression, angiogenesis markers, markers of tumour invasion, cell surface markers, intracellular markers, markers derived from arachidonic acid, enzymatic markers.

**Flow Cytometry**

Molecular alteration such as DNA Aneuploidy and non-diploidy are early changes seen in carcinogenesis. Flow cytometry is used to assess these to aid in early diagnosis.

**Genetic Alterations**

Advancements in array technology have documented that chromosome, gene, mRNA, and proteins undergo alterations that are characteristically seen in OC, thus genomic, proteomic and epigenetic studies provide an insight into the process of OC[17]. Study of chromosomal instability is a widely used molecular approach in diagnosis[18,19].

**Epigenetic Alterations**

Epigenetic alterations inactivate gene function by methylation of promoter region without changing the structure or sequence of gene. Sanchez Cespedes et al. were the first to use methylation state as a clinical marker. Gene methylation panels are useful in OC screening, done by PCR technique, this has shown to be a more sensitive test[20]. Literature shows that the use of molecular markers in diagnosis may lead to better survival and treatment associated morbidity through early recognition and intervention for lesions which are at risk, special concern is occurrence of OC in young adults[21]. However at present molecular and genetic analysis is not a routine procedure for OC detection.
CONCLUSION

There are several tests and devices available for early diagnosis of OC, but it still represents an important challenge for clinicians and patients. Simply holding knowledge about a factor does no good unless utilized to make intelligent decisions. Ideally, a diagnostic procedure should be relatively inexpensive, simple, non-invasive, risk-free technique, proven highly accurate and well accepted by patients. In addition to high sensitivity, should have the potential for automation. High specificity also avoids false-positives and, therefore, reduces patient anxiety, given the lack of data on the effectiveness of adjunctive cancer detection techniques the future is promising for further development and evaluation of OC diagnostic methods to enhance patient care provided by all clinicians. However, molecular markers are the focus for early recognition of precancer and cancerous tissue, but their availability is questionable for incorporation into practice. In general dental practice settings in a country like ours clinicians must rely on a thorough mucosal examination supported by specialty referral and/or tissue biopsy, assisted by staining methods or chemiluminscent procedures. By diagnosing OC at the early stages, dentists can contribute abundantly in reducing this global burden.

REFERENCES


