Early Detection of Oral Cancer : A Perspective View

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Introduction

Oral cancer is a disease in which malignant cells form in the lips, oral cavity &oropharynx. traditionally known as squamous cell carcinoma of the lips,oral cavity & oropharynx. Head&neck cancer account for 5% of all tumours & about 50%of head &neck cancer occur in the oral cavity. In the year 2000, about 300,000 out of the 615000 new cases of oral cavity reported world wide were primary oral cavity squamous cell carcinoma.[1]Recent data from surveillance, epidemiology end result program suggested that 28,900 new cases of oral cancer will be identified&7400 death attributed to oral cancer each year in the U S.[2] The sixth leading cause of cancer related morbidity, oral cancer account for 1 death every hour in U S. Despite numerous advances in treatment the 5 year survival has remained approximately 50% for the last 50 years. [3]This poor prognosis is likely due to several factors. First, oral cancer is frequently associated with the development of multiple primary tumors. The rate of second primary tumors in these patients, 37% per year, is higher than for any other malignancy.[4]This characteristic led Slaughter to propose a theory known as "field cancerization". To underscore the significance of this complication, the most common cause of treatment failure and death in oral cancer patients is their second primary tumor.[5] Second, poor survival among oral cancer patients can also be attributed to the advanced extent of the disease at the time of diagnosis, with over 60% of patients presenting in stages III and IV. Such dismal statistics seem perverse since the disease primarily arises in the surface oral epithelium that is readily accessible to direct visual and tactile examination. The conclusion that at least some lesions are ignored or missed by patients,health care professionals or both, is inescapable. In part, this may be due to an incomplete understanding or awareness that even, small asymptomatic lesions can have significant malignant potential. One approach to this problem wold be to improve the ability of oral health care professionals to detect relevent potentially malignant lesions or cancerous lesions at their earliest or most incipient stage. Such a goal could be achieved by increasing public awareness about the importance of regular oral screening or case finding examinations to identify small, otherwise asymptomatic cancers and precancers (secondary prevention). Another strategy would be the development and use of diagnostic aids that could help the general dentist or dental specialist more readily identify or assess persistent oral lesions of uncertain biologic significance. This paper will examine the role of screening examinations in oral cancer and evaluate the literature regarding currently available diagnostic tests or techniques that are purported to aid in the detection and diagnosis of cancerous and precancerous lesions.

Screening or early detection

Screening is checking for cancer before a person has any symptoms.This can help find cancer at an early stage.When abnormal tisue or cancer is found early, it may be easier to treat.By the time symptoms appear ,cancer may have begun to spread. There are a numbers of characteristics that should be considered in the development of an ideal screening test(Table 1)

Table 1: Characteristics of a good screening test

A screening test should

1. Be simple, safe and acceptable to the public
2. Detect disease early in its natural history
3. Preferentially detect those lesions which are likelyto progress
4. Detect lesions which are treatable or where an intervention will prevent progression
5. Have a high positive predictive value and low false negatives (high sensitivity)

Current oral Cancer Screening Test

Among the screening tests or diagnostic aids now available for oral cancer, some have been used and studied for many years while others have recently become commercially available (Table 2). Screening or case-finding tests should always be evaluated with respect to their sensitivity, specificity and predictive values (Fig. 1). Such analysis requires that the test outcome from a sample of subjects be compared to the results of an appropriate gold standard on the same population. The gold standard is used to classify subjects as to their true state of disease (present or absent). The sensitivity measures the proportion of subjects with the disease who test positive, while the specificity determines the proportion without the disease who test negative. The predictive values determine the proportion of subjects with positive or negative test results that either do or do not have the disease. There are no defined values for the ideal screening test, but in general it is desirable to have both high specificity (few false positives) and high sensitivity (few false negatives).

The acceptable trade off between sensitivity and specificity will depend upon the consequences of failing to detect the disease versus the costs, anxieties and other added burdens associated with false positive tests. Another relevant issue is the overall prevalence of the disease in question. If the disease is rare, even tests with very high sensitivity and specificity will yield many false positive results

Table 2: Screening and case-finding aids to diagnosis of oral cancer and precancer

Standard screening test

- Conventional oral examination (COE)

Established diagnostic adjuncts

- Oral cytology
- Toluidine Blue (tolonium chloride)

Light-based detection systems

- ViziLite Plus
- MicroLux DL
- VELscope

	Disease Present	Disease Absent
+ Test Result	a True positive	b False positive
	c False negative	d True negative

$$\text{Sensitivity} = \frac{a}{a+c} \qquad \text{Specificity} = \frac{d}{b+d}$$

$$\text{PPV} = \frac{a}{a+b} \qquad \text{NPV} = \frac{d}{c+d}$$

Fig.1 A standard 2x2 table for the calculation of sensitivity and specificity.

Oral examination

A conventional oral examination (COE), using normal (incandescent) light, has long been the standard method for oral cancer screening. Conventional visual cancer screenings for some anatomic locations can be highly successful. For example, visual inspection of skin lesions can be an effective screening method for melanoma, with sensitivity and specificity rates as high as 98%.[15,16] However, while COE has traditionally been the mainstay of oral cancer screenings for decades, its utility remains controversial. A number of publications have suggested that COE may have limited value as a method for detecting pre-cancerous or early cancerous lesions.[6-8] Conversely, other studies have reported a relatively high degree of sensitivity, specificity and positive predictive value of COE. Although COE may be effective as a screening test, there are still many problems with this approach. First, approximately 515% of the general population have oral mucosal abnormalities.[9-11] Without question, the vast majority of these lesions are clinically/biologically benign. Second, the classic clinical presentation of an oral malignancy or premalignant lesion: a red patch, white patch or persistent ulcer that cannot be diagnosed as any other condition, is well recognized. In reality, most lesions are white patches or plaques, also known as true leukoplakias. The problem, however, is that only a small percentage of leukoplakias are progressive or become malignant and a COE cannot discriminate between these lesions and their nonprogressive counterparts. Furthermore, while COE may detect a number of clinical lesions and a small percentage of those may exhibit histological features of premalignancy, recent data suggests that some precancerous lesions may be lurking within mucosa that appears clinically normal by COE alone. This concept is supported by the work of Thomson, who found that 9/26 consecutive patients (36%) with a newly diagnosed head&neck SCC had histologic evidence of dysplasia or microinvasive cancer in a biopsy from clinically normal mucosa from the corresponding, contralateral anatomic site. Therefore, while COE may be useful in the discovery of some oral lesions, it does not identify all potentially premalignant lesions, nor does it accurately detect the small proportion of biologically relevant lesions that are likely to progress to cancer.

Brush Cytology

The Brush Biopsy (CDx Laboratories, Suffren, NY) was introduced as a potential oral cancer case-finding device in 1999. The most definitive, accurate, and reliable method for diagnosing oral mucosal lesions is the scalpel biopsy. The oral brush biopsy coupled with computer-assisted analysis (Oral CDx, OralScan Laboratories, Inc., Suffern, NY) has been developed as a technique for evaluating unexplained clinically detectable alterations of the surface epithelium of the oral mucosa whether cancer or pre-cancer is suspected (Sciubba, et al., 2003).[43] The goal of the oral brush biopsy is to provide a highly sensitive and specific technique that is less painful and simpler to perform than a scalpel or punch biopsy.

The oral brush biopsy, using a specially designed circular bristled brush, has been designed to access and sample all epithelial layers, including the basal cell layer and the most superficial aspects of the lamina propria (Sciubba, et al., 2003). Thus, the cellular material obtained should include all epithelial layers in a disaggregated form spread over the surface of a glass slide.

The argument for oral brush biopsy raises two questions. One question is whether indications for oral mucosal biopsy should be expanded to include certain "benign-appearing" lesions, either in high-risk patients (e.g., current or former smokers, heavy drinkers), or in all persons regardless of risk. A second question is what is the most effective and efficient method of biopsy of oral mucosal lesions.

It was designed for the interrogation of clinical lesions that would not be suspected to biopsy because the level of suspicion for carcinoma,based upon clinical feature,was low.[12-14] When abnormal result is reported (a typical or positive) ,the clinician must follow-up with a scalpel biopsy of the lesion, as the use of brush cytology does not provide a definitive diagnosis

Toluidine blue staining

Toluidine blue (also known as tolonium chloride) is a vital dye that may stain nucleic acids and abnormal tissues. It has been used for decades as an aid to the identification of mucosal abnormalities of the cervix as well as in the oral cavity. It has been valued by surgeons as a useful way of demarcating the extent of a lesion prior to excision. While not currently approved by the FDA for us as an oral cancer screening technique in the United States, toluidine blue has been championed in other parts of the world for several decades as a means of identifying clinically occult lesions in patients whose oral mucosa may otherwise be normal that is, as a screening test or adjunct.[15] Overall, there appears to be some evidence that toluidine blue can stain oral lesions and that it is useful as an adjunct to a clinical examination for the identification of potentially premalignant lesions. To date, however, it has only been evaluated in a secondary care environment in the hands of specialists. The literature on toluidine blue is large and a recent systematic review50 identified 77 publications.However, only 14 of these evaluated the ability of the dye to identify oral cancers that would not otherwise have been diagnosed by unaided clinical examination. Unfortunately, these studies are of limited relevance to the use of the dye as a screening test, because none were randomized controlled trials, none were conducted in a primary care setting, and most studies were case series conducted by specialists on high-risk populations, often with known lesions. Overall, the sensitivity of toluidine blue staining for the detection of oral cancers has ranged from 0.78 to 1.00 and the specificity from 0.31 to 1.0

Light-based detection systems

Tissue reflectance (ViziLite Plus, MicroLux DL)

Tissue reflectance has been used for many years as an adjunct in the examination of the cervical mucosa for "acetowhite" premalignant and malignant lesions. Recently, this form of tissue reflectance-based examination has been adapted for use in the oral cavity and is currently marketed under the names ViziLite Plus and MicroLux DL. These products are intended to enhance the identification of oral mucosal abnormalities. With both systems, the patient must first rinse with a 1% acetic acid solution followed by direct visual examination of the oral cavity using a blue-white light source. ViziLite Plus uses a disposable light packet, while the MicroLux unit offers a reusable, battery-powered light source. The 1% acetic acid wash is used to help remove surface debris and may increase the visibility of epithelial cell nuclei, possibly as a result of mild cellular

dehydration Underblue-white illumination, normal epithelium appears lightly bluish while abnormal epithelium appears distinctly white (acetowhite). ViziLite Plus also provides a tolonium chloride solution (TBlue), which is intended to aid in the marking of an acetowhite lesion for subsequent biopsy once the light source is removed. In summary, evidence that supports the use of reflective tissue fluorescence systems to aid in the detection of oral premalignant lesions is currently quite sparse. The published studies to date suffer from numerous experimental design issues, especially the critical comparison to the diagnostic gold standard (scalpel biopsy) in all cases. Furthermore, based upon the current suggested usage for these devices, it is unclear what added benefit they would provide to the practicing clinician. If a clinician is able to clinically identify a lesion, they are obligated to obtain a definitive diagnosis in order to direct the treatment of the patient's lesion. Thus, subjective improvement of one's ability to see a lesion would provide minimal diagnostic advantage to the practicing dentist or the patient, unless the test can also discriminate indolent lesions from those that are more biologically worrisome. On the other hand, some reports hint that this technique may help identify lesions that cannot be seen with incandescent light.[17,19] Well-controlled clinical trials are needed that specifically investigate the ability of these devices to detect precancerous lesions that are invisible by COE alone. If such discrimination can be confirmed, it would support the use of this technology as a true screening device.

Narrow-emission tissue fluorescence (VELscope)

Approximately 30 years ago, it was observed that the autofluorescence of tissues (tissue fluorescence) could potentially be used for cancer detection. As such, there has been considerable interest in the technologies of both fluorescence imaging and spectroscopy in cancer screening for a number of anatomic sites including the oral cavity.[2039] Fluorescence spectroscopy involves the exposure of tissues to various excitation wavelengths so that subtle differences between normal and abnormal tissues can be identified. Conversely, fluorescence imaging involves the exposure of tissue to a rather specific wavelength of light, which results in the autofluorescence of cellular fluorophores after excitation. The presence of cellular alterations will change the concentrations of fluorophores, which will affect the scattering and absorption of light in the tissue, thus resulting in changes in color that can be observed visually.

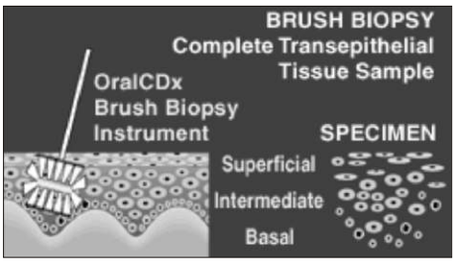

Fig.1-Oral Cdx Brush Biopsy.

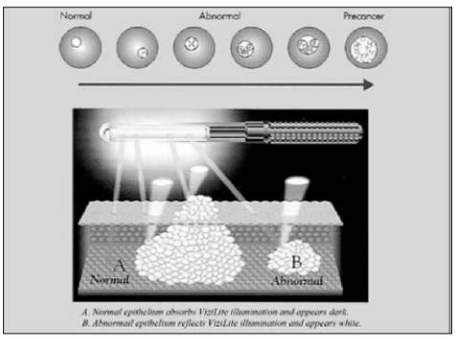

Fig .2-Vizilte showing normal and abnormal epithelial tissue.

Fig.3-Velscope

Summary

Screening and early detection in populations at risk have been proposed to decrease both the morbidity and mortality associated with oral cancer.[6-7] However, the visual detection of premalignant oral lesions has remained problematic throughout the world. This is in stark contrast to skin lesions such as melanoma, where visual screening has been shown to have sensitivity and specificity rates of 93 and 98%.[40-41] One explanation for this discrepancy is that early lesions of oral cancer and precancer are often subtle and rarely demonstrate the clinical characteristics observed in advanced cases: ulceration, induration, pain, or associated cervical lymphadenopathy.[32] Besides their clinical subtlety, premalignant lesions are highly heterogeneous in their presentation and may mimic a variety of common benign or reactive conditions. Furthermore, there is a growing realization that some premalignant and early cancerous lesions are not readily detectable to the naked eye.[42] As such, additional screening aids for oral cancer are desperately needed. Fortunately, there has been dramatic increase in the development of potential oral cancer screening or casefinding tools in the last decade. Each of them may hold promise in selected clinical settings. Unfortunately, no technique or technology to date has provided definitive evidence to suggest that it improves the sensitivity or specificity of oral cancer screening beyond COE alone. As discussed above, many of the studies have design flaws. Many studies that have been performed using these diagnostic devices also suffer from the fact that they are being employed in a "case-finding" fashion, rather than as true screening tools. That is to say, they are being used to aid in the diagnosis of a lesion that has already been identified by the naked eye. Several of the technologies (ViziLite Plus, Micro- Lux DL, toluidine blue and VELscope) may be useful in a true screening fashion. Yet, there is currently no hard data to support the contention that these technologies can help the clinician to identify premalignant lesions before they are detectable by COE alone. Nevertheless, studies to determine their utility in this setting are anticipated in the near future. Regardless of the outcome of these studies, new technology and even its attendant marketing has clearly made a positive impact on the field of dentistry by encouraging clinicians to more routinely perform thorough oral cancer exams. Untill recently, surveys had consistently demonstrated a limited understanding of proper oral cancer screening and diagn osis among the dental community.[3438] Preliminary results from a recent oral cancer awareness campaign in the United States, however, suggest that intensive, well-designed and prolonged attempts to educate the dental community as well as their patients may increase overall awareness about the disease.[39] To capitalize on this increasing awareness, well-designed

clinical studies are needed to help dental scientists and clinicians assess the various new and evolving diagnostic aids for oral cancer and precancerous lesions. Scientific journals and their readers must look to ensure that issues of validity, comparison to the gold standard of histopathologic analysis, appropriateness of patient population, use of proper study clinicians, specificity and potential for replication are satisfied. Improving oral cancer detection and diagnosis have long been major challenges facing both dental and medical providers around the globe. Combined with an increased public awareness of oral cancer in general, robust diagnostic aids that allow clinicians to detect lesions unseen by conventional examination techniques should help more affected patients become long term survivors of this challenging disease.

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