REVIEW ARTICLE

What dentists should know about oral cancer screening?

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ABSTRACT

Although the advances in the diagnosis and treatment of oral cancer, it remains one of the most devastating malignancies. Early detection and prevention is a major key in combating policy of cancer. Screening offers an important opportunity for early detection. Several screening methods, visual examination, toluidine blue, fluorescence imaging, and brush biopsy, were used in oral cancer screening programs. General dental practitioner plays an important role in such programs. Therefore, this review aimed to outline the required information, knowledge, and evidence-based practice on oral cancer screening for dentists in order to incorporate this service into their daily routine.

Key words
Cancer, diagnostic aids, general dentists, oral, screening

INTRODUCTION

Head and neck cancer is a global health burden with high mortality and morbidity. It has been ranked as the sixth most common cancer worldwide with over 650,000 new cases with 50% associated deaths each year.[1,2] Five-year survival rates exceed 50% in only the best treatment centers. Causes are predominantly lifestyle-related: Tobacco, areca nut, alcohol, poor diet, viral infections, and pollution are all important etiological factors.[3] Early detection of cancer permits a more conservative therapeutic approach with a shorter recovery and a more favorable prognosis.[4] There is potential for the early detection of cancer through screening.[5] General dentists play a critical role in managing head and neck cancer patients. The first and most important role is to offer preventive services, particularly to smokers and to patients who drink alcohol to excess. In addition, practitioners in primary dental settings are key elements in implementing any screening program, thus, their knowledge on the science of oral cancer screening should be up to date. We aimed in this review to provide dentists with the latest knowledge on the current practice and evidence on oral cancer screening.

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Principles of cancer screening

Screening for cancer is based on the premise that earlier diagnosis of the disease, either in a precancerous condition or at an earlier stage, leads to a reduction in risk of mortality or development of invasive disease.[6] Screening has been defined as the examination (or testing) of people for early stages in the development of cancer even though they have no symptoms. The patterns of cancer in the population were studied to learn which people are more likely to get certain types of cancer. Fortunately, screening program for cervical cancer has resulted in a reduction of morbidity and mortality of invasive cervical lesions,[7] and breast cancer screening has also resulted in reduced mortality.[8] Moreover, screening studies have provided much interesting information regarding the natural history of the screened cancer.[9]

Considering the evaluation of a potential screening test for a given disease, there are basic principles should be fulfilled initially to start any screening programs.[10]

These are:

- The condition should be an important health problem or should be the cause of substantial mortality and morbidity
- The natural history of this disease should be understood

- The screening test should be safe and acceptable to patient with high sensitivity and specificity
- There should be an evidence of effectiveness in improving the mortality and morbidity associated with the disease
- The cost of screening should be balanced in relation to other health care expenditure.

A screening test or procedure should be cheap, easily performed, and acceptable to both screener and the person screened, and has high sensitivity and specificity to be considered as a measure for the outcome of screening.[11]

The randomized controlled trial, more than other any other methodology, provides for high-level, evidence-based practice for patient care.[12] Therefore, the best-chosen methodology to assess the effectiveness of screening should be a randomized controlled trial.[11]

Psychological effects associated with screening have an impact on the success of screening programs. Psychological morbidity such as distress can arise in relation to the different phases of a screening approach.[5] Distress has been reported as resulting simply from receiving an invitation for screening. However, these psychological side-effects at this stage are usually simple. Likewise, major distress can be observed when patients are recalled for a positive screening test. These psychological burdens can be easily induced in patients with cancer.[5] Thus, there is a need to reduce distress associated with screening not only to get rid of this problem but also because also it leads to better future attendance at screening. More importantly, patient's delay in diagnosis of oral cancer could be due to the psychological factors that are poorly understood and under-researched.

Screening for oral cancer

Given the fact that oral cancer occurs in a region of the body that is generally accessible to physical examination by the patient, the dentist, and the physician,[13] and also that advanced treatments have not resulted in decreasing the death rate, attention needs to be given to examining the effectiveness of oral cancer screening in decreasing the mortality associated with oral cancer.

Screening could be used to detect precancerous lesions and early invasive cancers with intervention offered to these groups being varied according to their status. Surgical excision could be done for early invasive cancers, if these cancers are small and without lymphatic spread, with minimal disfigurement and without the necessity to radiotherapy. For precancerous lesions, the intervention would depend on assessment of the progression risk, ideally by histological assessment of dysplasia in a biopsy specimen. Surveillance at regular intervals, surgical removal, cryosurgery, laser, topical chemotherapy, and retinoid treatment are currently the treatment options for this group of lesions.[14] Similar to other cancers, screening for oral cancer and pre-cancer has potential advantages and disadvantages [Table 1]. Careful consideration for these points should be taken before implementing any screening programs, and the benefits should outweigh the harms.

To date, there is debate on whether to employ screening methods for oral cancer in the daily routine work of health providers.

Interestingly, the National Cancer Institute (2012) reported that there is insufficient evidence to establish that screening would result in a decrease in mortality from oral cancer.[15] In the United Kingdom, a working group on oral cancer screening in 2010 concluded that there was insufficient evidence to implement oral cancer screening programs on a national basis. However, opportunistic screening in primary care settings for high-risk group was recommended.[16] The Canadian Task Force on Preventive Health Care (1999) on oral cancer mortality concluded that there is a fair amount of evidence to exclude screening the general population for oral cancer by clinical examination. Moreover, they reported that for opportunistic screening, there is insufficient evidence to recommend inclusion or exclusion of screening for oral cancer by clinical examination of asymptomatic patients. Only for high-risk patients, an annual examination by physician or dentist should be considered.[17] With the many criticisms of national-based screening programs for oral cancer and the lack of rigorous evidence to support them, attention on opportunistic screening for oral cancer has now become more noticeable recently as a substitute approach. The most encouraging outcome of such studies, published so far, comes from Oral

Table 1: Advantages and disadvantages of screening for oral cancer and pre-cancer

Advantages
Reduced mortality
Reduced incidence of invasive cancers
Improved prognosis for individual patients
Reduced morbidity for cases treated at earlier stages
Identification of high-risk groups and opportunities for intervention
Reassurance for those screened negative
Cost savings
Disadvantages
Detection of cases already incurable may increase morbidity for some patients
Unnecessary treatment of those potentially malignant lesions, which may not have progressed
Psychological trauma for those with a false-positive screen
False reassurance for those negative screen
Reinforcement of bad habits among individuals screened negative
Costs

Cancer Case Finding Program in Cuba.[18] The British Dental Association encouraged their members to screen opportunistically for oral cancer when patients attend for routine examination.[19] Lim *et al.* studied the feasibility of opportunistic oral cancer and pre-cancer screening in general dental practice.[20] Their results suggested that opportunistic screening in a general dental practice setting might be a realistic alternative to population screening. Compliance with referral as a result to positive screening test is a threat for any screening program. Many studies have shown that compliance is low.[21]

Current oral cancer screening methods

Visual examination

Visual screening is defined as positive if a white patch or red patch is present, which cannot be scraped off, or if an ulcer of longer than two weeks duration is detected. The UK Working Group on screening for oral cancer and pre-cancer concluded that the most suitable screening for oral cancer and pre-cancer is a thorough and a methodological examination of the mucosal surfaces of the mouth, in good and adequate lighting, by using dental and laryngeal mirrors. A detailed examination protocol, including palpation of both the lymph nodes and the posterior third of the tongue, has also been recommended.[22] The feasibility of carrying out this visual examination in the primary dental care was studied by Field *et al.*, confirming that a systematic and thorough examination of oral mucosa, as a method for screening, could be carried out as an integral part of the routine dental care.[23] The sensitivity and specificity of a visual examination to detect oral lesions is high [Table 2]. It was over 80% in a randomized control trial, evaluating the effectiveness of oral cancer screening program in India.[27,32,33] Simplicity, low cost, and a lack of harm in terms of anxiety in its application are terms used to describe visual screening. However, the value of a visual examination becomes lower when it is used to detect lesions either emerged from sites are difficult to be recognized visually such as pharyngeal sites because these lesions are not visually visible. So, it is valid to say that the need for adjunct tools for oral cancer screening is desirable.

Toluidine blue

The topical application of tolonium chloride *in vivo* was initially used in gynecological practice for the detection of malignant change of the cervix during colposcopy.[34] However, since 1960, many studies have focused on the suggested role of toluidine blue dye as an adjunct to the detection of oral cancer.[35] Most of the published studies have investigated toluidine blue as a diagnostic method rather than a screening test. Toluidine blue is a metachromatic dye of the thiazine group that has been used effectively *in vitro* as a nuclear stain because of its affinity for the perinuclear cisternae of DNA and RNA.[36] *In vivo* malignant lesions stain a brilliant deep blue. The suggested mechanism for the selective malignant and dysplastic cells staining might be the result of either these cells contain quantitatively more nucleic acids than normal tissue or a result of direct binding by sulfated mucopolysaccharides, which are found in higher quantities in active growing tissues such as tumors.[35] The staining technique involves rinsing the mucosal surfaces with 1% acetic acid as a preoperative phase, then applying a 1% aqueous toluidine blue dye to the suspicious lesion for approximately 30 seconds, followed by a tap water rinse. The lesion is then lightly blotted with 1% acetic acid to reduce the background level of staining. Only positive areas will retain stain after this de-colorization process.[37] The sensitivity and specificity of toluidine blue have been extensively studied. The technique is highly effective in detecting malignant disease with high sensitivity of over 90%.[38,39] However, this technique is significantly less useful in detecting premalignant lesions due to a high percentage of false-negative staining rates for carcinoma *in situ* and also due to false-positive results in ulcerated inflammatory or traumatic lesions.[38,39] Epstein *et al.* raised an issue that the use of toluidine blue by well-trained and experienced clinicians would minimize false-positive and false-negative results, thus giving this technique the credibility to be a valuable visual aid for the clinical examination of the oral mucosa.[40] The data, however, indicates that there is limited value in using toluidine blue stain as an adjunctive method for the detection oral cancer and pre-cancer. Although using toluidine

Table 2: Accuracy (sensitivity and specificity) of oral visual examination during interventions for screening and early detection of oral cancer

Author, publication year, country	First examiner (Setting)	Gold standard examiner	Sens (95% CI)	Spec (95% CI)	Sample size (Campaign type)
Mehta 1986,[24] India (1982-1983)	CH worker (Home)	Dentist	59	98	1921 (Community-wide)
Warnakulasuriya 1990,[25] Sri Lanka (1981-1982)	CH worker (Home)	Dentist	95	81	1872 (Community-wide)
Mathew 1997,[26] India (1995-1996)	CH worker (Home)	Physician	90	98	2069 (Community-wide)
Ramadas 2003,[27] India (1995-2002)	CH worker (Home)	Dentist or physician	81.5	84.8	78,969 (Community-wide)
Ikeda 1991,[28] Japan (1986-1988)	Dentist (Clinic)	Oral pathologist	NA	NA	3131 (Workplace)
Downer 1995,[29] UK (1992-1993)	Dentist (Clinic)	OC specialist	71	99	309 (Workplace)
Ikeda 1995,[30] Japan (1986-1993)	Dentist (Clinic)	OC specialist	81	69	42 (Community-wide)
Jullien 1995,[31] UK (1990-1993)	Dentist (Clinic)	OC specialist	74	99	2027 (Health system)

OC – Oral cancer; Spec specificity; CI – Confidence limit; CH – Care health worker; Sens sensitivity

blue staining may be helpful for clinicians in choosing incisional biopsy sites within suspicious lesions, this technique has limitations in terms of its accuracy and precision, particularly, positive and negative predictive values. This controversy suggests the need for a well-designed randomized control trial to assess the effectiveness of toluidine blue in detecting oral cancer and pre-cancer in both primary and secondary dental care. However, toluidine blue should always be considered as an adjunctive tool to the gold standard (clinical examination and biopsy).

Brush biopsy

OralCDX (OralScan Laboratories, Suffern, New York) is a computer-assisted method of analysis of the oral brush biopsy for the detection of precancerous and cancerous lesions of the oral mucosa, first described in 1999.[41] The kit consists of a glass slide, fixative, and an oral brush biopsy instrument to obtain a trans-epithelial specimen. The collected sample is spread onto the glass slide and bathed with the liquid ethanol-based fixative. The slide is sent to OralScan Laboratories where it is firstly stained in accordance with a modified Papanicolau method, then it is scanned by the OralCDX neural net computer system specifically designed to detect potentially abnormal cells. The OralCDX computer searches the brush biopsy specimen for a combination of abnormal cellular morphology and abnormal keratinization characteristic of dysplasia and carcinoma of oral epithelium. The computer software will be analyzed by specially designed and trained processor. Images of abnormal cells identified by computer system are individually displayed and reviewed by specially trained pathologists. The computer does not provide a diagnosis of the brush biopsy; its role is to help the pathologist to review the obtained images.[41] The results of biopsy assessment will be classified into one of the following categories:

- " Negative": No epithelial abnormality;
- "Atypical": Abnormal epithelial changes of uncertain diagnostic significance;
- "Positive": Definitive cellular evidence of epithelial dysplasia or carcinoma;
- "Inadequate": Incomplete trans-epithelial biopsy specimen.

According to the ADA Council on Scientific Affairs (2001) and by the manufacturer, all OralCDX "atypical" and "positive" results must be confirmed by incisional tissue biopsy followed by histologic examination to make a definitive diagnosis, whereas the "negative" specimen must receive follow-up evaluation.[42] Oral brush biopsy was described as having a high sensitivity and specificity over 95% for detecting oral malignant and dysplastic lesions.[41,42] However, a research group in the United Kingdom studied the effectiveness of brush biopsy in the diagnosis of oral epithelial dysplasia or neoplasia in patients with oral mucosal lesions suggestive of potential malignancy and their results suggest that brush biopsy does not always detect cellular atypia of subsequently histopathologically confirmed oral epithelial dysplasia, or neoplasia.[43] More recently, Adjunctive techniques like DNA image cytometry (DNA-ICM) have been attributed to enhance the diagnostic performance of oral brush biopsies. A latest study has concluded that DNA-ICM has the potential to substantially improve the sensitivity of a pure morphological interpretation of oral brush biopsies.[44] Given the controversial opinions and the lack of detailed data with regard to the role of brush biopsy in screening programs, further researches required evaluating its effectiveness as a reliable method for screening.

Fluorescence imaging

Since the early 1970s, researchers' attention has also been drawn to a selective intracellular deposition of fluorescent markers like hematoporphyrin derivatives and tetracycline's. Recently, diagnostic methods using the characteristics of autofluorescence emitted by cancer tissue upon irradiation with laser or xenon light have been developed for various malignancies such as lung[45] and oral cancers.[46] This method is based on the phenomenon that ulcerated squamous cell carcinoma (SCC) in human and experimental animals shows red fluorescence under ultraviolet light. There are different methods for using fluorescence imaging in detecting the malignant lesions. Betz *et al.* compared tumor discrimination and delineation properties of ordinary white light inspection, autofluorescence, and 5-ALA (5-aminolevulinic acid)-induced PPIX (protoporphyrin) fluorescence diagnosis as well as a combination of the latter 2 via fluorescence imaging, histopathologic evaluation, and spectral analysis. Their results showed that combined fluorescence diagnosis (CFD) was clearly better than the other 3 methods for identification of both tumor and borders.[47]

Chemiluminescence is a clinical inspection of oral mucosa with the aid of chemiluminescent blue/white light (Vizilite®). Several studies have shown improvement in the identification of mucosal abnormalities with respect to the use of normal incandescent light.[48] A combination with toluidine blue was proposed to improve the very low positive predictive value of Vizilite® and is called ViziLite Plus®.[49] Another new chemiluminescence device (MicroLux DL™) has been introduced as an adjunct tool for oral lesion identification, but few studies have been published to assess its effectiveness in detecting potentially malignant oral lesions.[50]

Similarly, the VELscope™ system was Federation Dentaire Association for direct visualization of autofluorescence in the oral cavity. Although this technique has reported high sensitivity and specificity values,[50] recent studies showed that the device was unable to discriminate high-risk from low-risk lesions.[51,52] Furthermore, the autofluorescence spectroscopy system was recently

tested.[53,54] Identafi™ 3000 technology consists of a small optical fiber that produces various excitation wavelengths and a spectrograph that receives and records on a computer and analyzes, via a dedicated software, the spectra of reflected fluorescence from the tissue. The findings of a more recent study support the ability of non-invasive multimodal optical imaging to accurately identify neoplastic tissue and premalignant lesions.[55] This promising technology has an impact on detection and treatment of patients with oral cancer and other epithelial malignancies, but further clinical studies are needed, as chemiluminescent light has produced reflections that made visualization more difficult and thus its usefulness could be compromised.

Summary

Oral cancer fulfills a considerable number of the required criteria for starting screening program as a method for prevention. However, the natural history of oral cancer is not yet to be fully understood. There are different methods for screening of oral cancer. It was clear that visual examination is the current appropriate method to detect visible lesions. On the other hand, for invisible lesions, there is need for an adjunctive method to visual examination to detect the premalignant lesion earlier. The current adjunctive methods are toluidine blue, brush biopsy, and fluorescence imaging.

It is very important to make clear that the benefits of screening for oral cancer should outweigh the disadvantages. Practitioners in primary dental settings are key elements in implementing any screening program and should have the knowledge on the science of oral cancer screening.

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