Oral Cancer Screening

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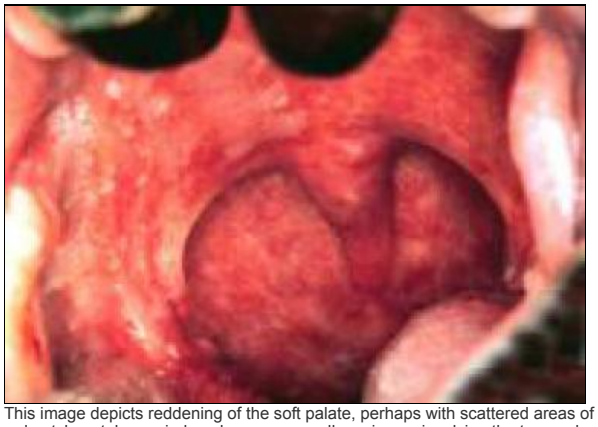
Overview

The American Cancer Society estimates that in 2016 about 48,330 people will get oral cavity or oropharyngeal cancer, and an estimated 9,570 people will die of these cancers. These cancers are more than twice as common in men as in women. They are about equally common in blacks and in whites.[1] The death rate for these cancers has been decreasing over the last 30 years.

These statistics suggest that oral cancer death rates are higher than those from Hodgkin lymphoma, laryngeal cancer, cancer of the testes, and endocrine system cancers such as thyroid and skin cancer (eg, malignant melanoma). The incidence or oral cancer also appears to be significantly different based on race and other confounders such as smoking, and alcohol consumption.

Given the prevalence of these behaviors in the World, the WHO and the 58th World Health Assembly Resolution on Cancer Prevention and Control has urged Member States to develop and reinforce cancer control programs to prioritize tumors and risk factors. Age is another confounder of oral cancer risk.

The most common oral cancer is squamous cell carcinoma (see image below). Other less common cancers occurring intraorally include adenocarcinoma, Kaposi sarcoma, and melanoma.



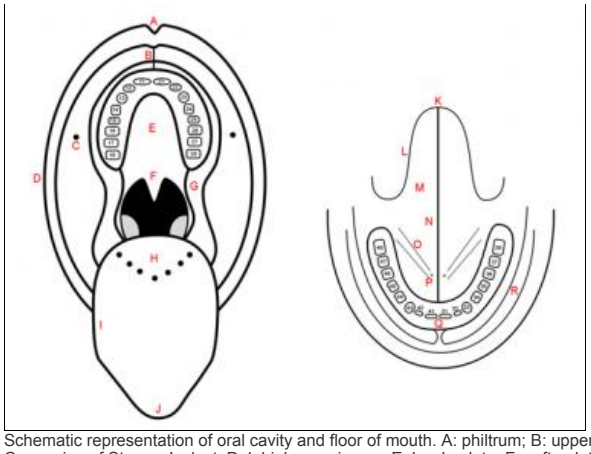
This image depicts reddening of the soft palate, perhaps with scattered areas of white and velvet red patches; tobacco-induced squamous cell carcinoma involving the tongue base and/or supraglottis; and a firm, mobile mass that is palpable at the left carotid bifurcation.

One explanation for the high death rate is that oral cancer may not be readily identified until it has metastasized because of its location. This may, in part, be because oral cancer is often painless initially (until it invades the deeper tissues) and thus goes unnoticed by the patient.[2] Of course, prognosis is much worse when undetected disease has spread to the neck lymph nodes. Not only is the primary tumor detection an issue, but in the patient with primary oral cancer, a higher risk exists for the development of undetected secondary lesions.

Thus, early detection of oral cancer is extremely important in terms of morbidity and mortality. Note that the 5-year survival rate for oral cancer depends not only on the site of the malignancy but the length of time that the lesion has been present, particularly since chronic lesions are more likely to be associated with metastasis and lymph node involvement.[3]

Relevant Anatomy

The oral cavity (see image below) is oval shaped and is separated into the oral vestibule and the oral cavity proper. It is bound by the lips anteriorly, the cheeks laterally, the floor of the mouth inferiorly, the oropharynx posteriorly, and the palate superiorly. The oropharynx begins superiorly at the junction between the hard palate and the soft palate, and inferiorly behind the circumvallate papillae of the tongue. The bony base of the oral cavity is represented by the maxillary and mandibular bones. The oral cavity includes the lips, gingivae, retromolar trigone, teeth, hard palate, cheek mucosa, mobile tongue, and floor of the mouth.



Schematic representation of oral cavity and floor of mouth. A: philtrum; B: upper labial frenulum; C: opening of Stensen's duct; D: labial commissure; E: hard palate; F: soft palate; G: intermaxillary commissure; H: base of tongue; I: lateral border of tongue, dorsal view; J: tip of tongue, dorsal view; K: tip of tongue, ventral view; L: lateral border of tongue, ventral view; M: ventral surface of tongue; N: lingual frenulum; O: floor of mouth; P: opening of Wharton's duct; Q: vestibular gingiva; R: vestibule. Teeth are numbered according to international classification.

The tongue is basically a mass of muscle that is almost completely covered by a mucous membrane. From anterior to posterior, the tongue has 3 surfaces: tip, body, and base. The tip is the highly mobile, pointed anterior portion of the tongue. Posterior to the tip lies the body of the tongue, which has dorsal (superior) and ventral (inferior) surfaces.

For more information about the relevant anatomy, see Mouth Anatomy and Tongue Anatomy.

Screening for Risk Factors in the History

The etiology of oral cancer, and particularly squamous cell carcinoma, is multifactorial, with the published research suggesting that exposure to tobacco and alcohol coupled with genetic predisposition are major contributors to the disease. The combination of smoking and alcohol seems to present the greatest risk for patients. Other factors that are considered potentially causative or at least confounding in some cases include virus, diet, radiation exposure, immunocompetence, and even mouthwash. The Oral Cancer Foundation provides a good overview of the state of the science with respect to oral cancer risk factors.

Oral cancer screening should include assessment of these factors by way of the verbal or self reported written history.

Smoking

Specific questions to consider asking the patient who smokes or has smoked include the following:

- The duration of the smoking habit
- The type of smoking pursued (eg, cigar/pipe, cigarette)
- The duration of smoking abstinence (if a prior history exists)
- Use of smokeless tobacco

The risk of the development of oral cancer is significantly greater for smokers than those individuals identifying themselves as having never smoked. The ration is 5-6:1, but some studies have suggested a 10:1 ratio. One important consideration is the duration of the habit, as the risk of death has been found to be directly related to the number of cigarettes consumed daily. With former smokers, at least one study suggests that at least a 50% reduction in risk occurs in the first 3-5 years of smoking abstinence.[4]

In terms of the type of smoking habit pursued, some evidence exists that cancer risk may be higher for individuals using cigars or pipes. Data does not seem to be available regarding commercial versus "handmade" cigarettes, whether filtered or unfiltered. All smoking habits should be considered equivalent in terms of cancer risk screening additional research assesses these variables.

Alcohol consumption

An important history questions for the patient using alcohol include is the amount of intake. The degree of consumption appears important, whereas the type of alcohol consumed does not appear to make any difference in terms of risk. Asakage et al found that, in their Asian population, moderate to heavy drinkers were significantly more likely to develop cancer in the oral cavity.[5] Interestingly, this and some other studies by Asakage and A Hiraki suggest that genotype, alcohol consumption, and oral cancer may interact.[6]

As the DHHS article (above) points out, the greatest odds for the development of oral cancer is when patients are heavy smokers and heavy drinkers. Use of these products appear to act synergistically to substantially increase the risk of cancer.

Virus

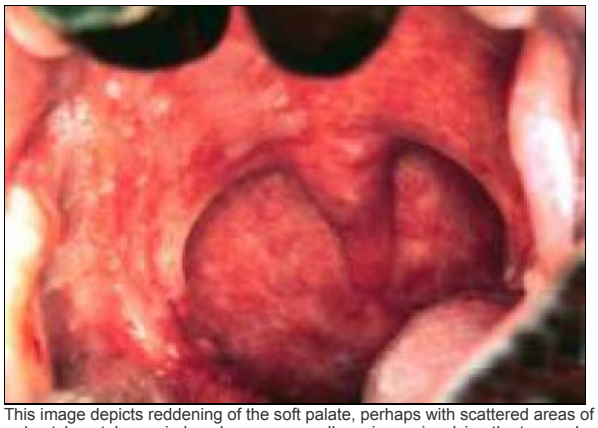
Two viruses, suspected of interacting with oncogenes and tumor suppressors, have been implicated in the etiology of oral cancer: human papillomavirus and herpes simplex virus. The isolate HPV-16 and HPV-18 have been indentified in squamous oral carcinoma.[7] Cancer in which the virus has been isolated appears to have a better prognosis than that associated with tobacco or alcohol use.[8, 9] Herpes simplex viral nucleic acids have been isolated from lip cancer cells, and when HSV antibodies are elevated together with smoking, an increased cancer risk may exist.[10] The Epstein-Barr herpes virus has also been linked to oral cancer.

Other factors

Other factors in the history that should be included in cancer screening include immunocompetence, diet, and the use of mouthwash. Suppression of the immune system resulting from HIV or non-Hodgkin lymphoma has been reported in relation to oral cancer. A number of dietary factors have been suggested as important in the etiology of oral cancer. Betel quid chewing has clearly been shown to increase cancer risk. Several studies suggest that a low intake of fruits and vegetables may increase the risk of oral cancer.[11] Low levels of vitamin C may increase the risk of cancer in the oral cavity.

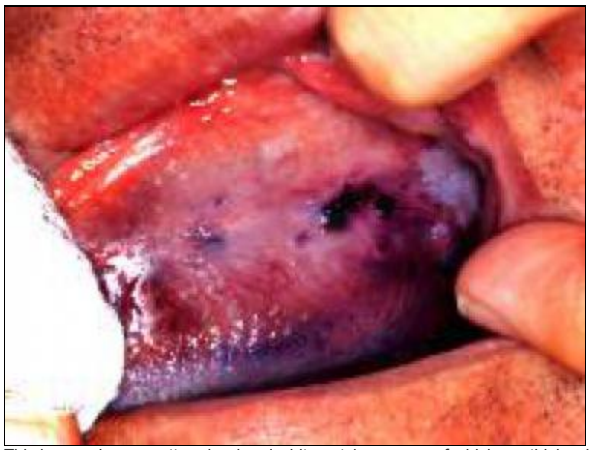
Physical Examination

Oral cancer can occur on any mucosal surface. Squamous cell carcinoma (see image below), the most common intra-oral cancer, is most commonly observed on the lateral border of the tongue. However, the floor of the mouth, attached gingival, mucosa in the retromolar and buccal region, and mucosa of the soft and hard palate may also be involved. One of the more difficult places to observe is the posterior-inferior tongue, but no mucosal surface should be overlooked with general inspection.[12, 13]

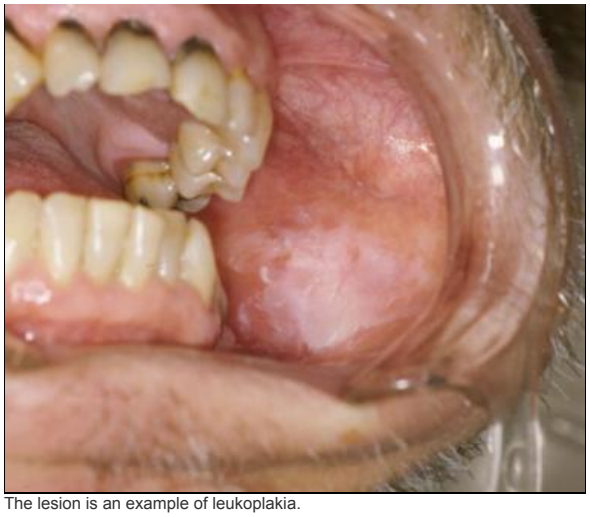


This image depicts reddening of the soft palate, perhaps with scattered areas of white and velvet red patches; tobacco-induced squamous cell carcinoma involving the tongue base and/or supraglottis; and a firm, mobile mass that is palpable at the left carotid bifurcation.

Squamous cell carcinoma manifests in various red/white color configurations and surface textures. Tissue may appear red (erythroplakia or erythroplasia), red and white (patchy erythema), or white (leukoplakia). The surface mucosa may be flat, slightly raised as a plaque, stippled or corrugated, or eroded and ulcerated. A cardinal feature of neoplasm is failure to heal with conservative management. See images below.



This image shows scattered red and white patches, some of which are thick, with inflammation of the underlying mucosa.



The lesion is an example of leukoplakia.

In cases in which the tumor is poorly differentiated, regional cervical lymph node involvement occurs. Thus the submaxillary, superficial, and deep cervical nodes should be palpated. Involved nodes are firm, nonmobile, and fixed to the adjacent structures; and they will be painless. In advanced cases with metastases, distant tumor sites can include the lungs, bone, and liver.

A number of oral conditions are considered to be precancerous. Bouquot et al provide a good overview of the potential for conversion of these lesions.[14] Those considered the most likely to convert to squamous carcinoma include erythroleukoplakia, granular leukoplakia, laryngeal keratosis, actinic cheilosis, and syphilitic glossitis with dorsal leukoplakia. Smooth and thick leukoplakia, smokeless tobacco keratosis and the erosive form of lichen planus have also been linked to neoplastic conversion. The problem that presents itself with evaluation of these various conditions is that when they are large, one part may be normal while another section involved and biopsy may be negative if it is not taken in the abnormal area.

Radiology

Imaging can be useful for lesions involving the attached alveolar gingival as the underlying bone may be involved. Plain film imaging is not considered particularly accurate for assessing bone involvement but CT scanning and, more recently, cone beam CT (CBCT) has been recommended for assessing cancer involving the bone.[15] MRI should be pursued for lesions involving the tongue and other intra-oral soft tissues.

Diagnostics

A number of new methods and technologies that aid oral cancer screening have been developed. These strategies are particularly useful for assessing large lesions, where the area of involvement is unclear and where secondary sites might be involvement.[16, 17] Limitations are described below.

Visualization adjuncts

Toluidine blue

Numerous articles and web sites describe toluidine blue (TB) as an adjunctive screening technique for oral cancer. Patton, Epstein, and Kerr provide a thorough review of the literature and meta analysis of the research assessing the PPV, sensitivity and specificity of the technique.[18] For their review, 15 studies met the inclusion criteria. Several studies assessed the technique in low-risk populations, one in patients with prior treatment for cancer, and 8 studies looked at its use in subjects with suspicious lesions or histologically proven dysplasia or cancer. Most were prospective case series, and one study was a prospective longitudinal study. Taken together, 2,400 lesions had been stained using TB.

The standard technique for applying 1% TB includes a prerinse with a 1% acetic acid solution, application of TB by mouthrinse or topical swab, and a postapplication rinse with 1% acetic acid. The chemical stains nucleic acids and produces a variable blue color, marking abnormal tissues. In the Patton review, when studies with low-quality ratings were excluded, the sensitivities of TB as a diagnostic adjunct varied from 38-98% and specificity from 9-93%. The positive predictive values (PPV) ranged from 33-93%.

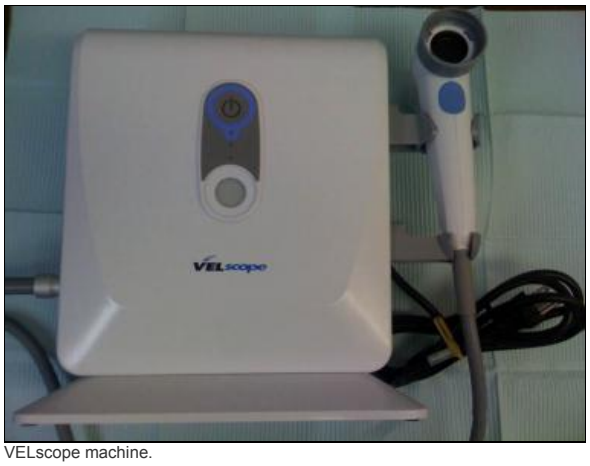
The authors conclude, given these highly variable results, that TB should be used as a surveillance adjunct in high-risk populations. In addition, most authors recommend that the technique should only be used by skilled clinicians. The FDI commission issued such a statement regarding the use of TB, noting that while the sensitivity and specificity of this screening test is adequate, less than 50% of precancerous dysplasias demonstrate stain uptake. The West Midlands Regional

Evaluation Panel in England produced a similar recommendation.[19]

Fluorescence visualization

Several products on the market use the above tissue reflective based systems for cancer screening in the oral cavity. These include the ViziLite System (see first image below), MicroLux DL system, the Orascoptic DK system, and the VELscope system (see second image below). The patient first rinses with 1% acetic acid, which is followed by direct visual inspection using a blue-white light source. This illumination of the tissues causes abnormal tissue to be disclosed as white, while normal tissue will be bluish white. Toluidine blue can also be used to augment the technique. Lingen et al provides a critical assessment of these diagnostic systems.[20] The authors conclude that supportive evidence is sparse and diagnostic advantage over standard inspection may be limited. Whether these techniques help to define precancerous lesions that cannot be seen with incandescent light remains unclear, but, should this be the case, the technique may prove beneficial.

ViziLite kit.



VELscope machine.

A more recent 2008 review of the ViziLite system by Patton et al revealed inconsistent accuracy values with 0-14% specificity and PPVs of 18-80%.[18] When one of the studies was eliminated because of a low quality rating, the analysis from the remaining 2 studies was consistent but disappointing: 0% specificity, 20% PPV, and 0% NPV. ViziLite is now available as a kit with TB swabs. Two studies assessing this strategy suggest that the addition of the toluidine blue improved the specificity and PPV and increased the NPV to 100%. Visual examination was significantly enhanced.

Note that, to date, the MicroLux DL or Orascoptic DK systems have not been studied. It has also been suggested that the ViziLite Plus system, MicroLux/DLTM, and Orascoptic DK systems are contraindicated for use in lactating or pregnant women, individuals hypersensitive to TBlue630 ingredients, children, and in people with renal or liver impairment.[21]

The VELscope is another light-based technology using fluorescence provided via a halide lamp for visualization. Lighted tissue emits a green fluorescence and it is the difference in the degree of green that is reported to reveal abnormality. Dark green to rust is thought to demonstrate abnormal tissue while normal tissue appears a pale lime green. There is no pre-rinse with this system and TB is not utilized.

In 2006 the FDA approved the VELscope as an adjunct to standard visual inspection of the mucosa to aid in the detection of cancer and for surgeons to help in the assessment of diseased margins of biopsies and surgical resections. The latter was based on a small study of 20 patients undergoing surgical excision of cancer. It is reported that 19 of the 20 tumors in this study had loss of autofluorescence extending 25mm beyond the apparent tumor and that 89% of the tissue subsequently excised in these regions demonstrated either dysplasia or carcinoma.[22]

Two other studies of the VELscope from researchers at the same center report

sensitivities of 98-100%, specificity of 78 and 100%, PPV of 100 and 66%, NPVs of 86 and 100%.[23, 24] .

Another variation on a theme is the combination of photofrin (Auadra Logic Technologics, Inc. Vancouver BC, Canada) with fluorescence illumination. A 2.5 mg/mL solution is applied topically; after 3 hours the mucosa is then illuminated. In a study of 20 patients with oral cancer, suspicious lesions were biopsied by visible fluorescence and evaluated by a pathologist.[25] The red, green, blue, and gray scale mode was used to determine contrast between the healthy and diseased tissue and compared with the biopsy results. Sensitivity was found to be 92.45% in the macroscopic study and 93.75 % in the microscopic and for specificity 95.65% and 97.50% in the macroscopic and microscopic studies, respectively. The difference between normal tissue and the tissue with lesions was statistically significant. This system is undergoing further study.[25] Other labeling studies (eg, 5-aminolevulinic acid) also show promise for detecting neoplastic lesions in the oralcavity.[26]

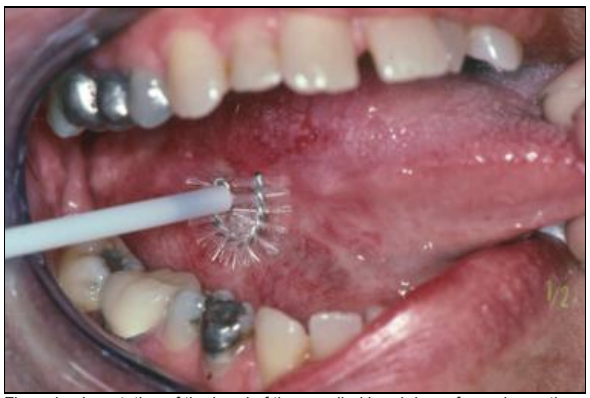
Oral Cytology

Cytomorphometry (oral CDx brush test)

The role of brush biopsy and DNA cytometry for screening oral cancer is reviewed by A Bocking, et al in their article published in the Journal of Oncology, 2011.[27] The authors point out that while biopsy is considered the criterion standard, exfoliative cytology may be useful in the screening of preneoplastic lesions such as leuko-/erythroplakias and lichen ruber (eg, lichen planus, verrucous leukoplakia, erythroplakia). The limited studies assessing this diagnostic screening technique are with sensitivities from 71-100%, specificities from 27-94%, PPVs from 38-88%, and NPVs from 50-100%.

The data from these and other studies suggest that false-positive findings may limit the utility of this screening technique. Accuracy of the test may be related to lesions that have already been assumed to be suspicious based on visual inspection. However the manufacturer of the test suggests that it is not intended to be used to assess suspicious lesions (as well as fibromas, mucoceles, or pigmented lesions –class 1 lesions). The benefit of the system is that it is relative non-invasive.

The technique itself involves scraping the mucosa (a rotation with firm pressure 5-15 times) with a provided brush with the collected tissue then placed on a slide, fixed, and sent to the OralScan Lab for evaluation by a pathologist. See images below.



Firm, circular rotation of the head of the supplied brush is performed over the surface of an alteration on the ventral part of the tongue.

Contents of the diagnostic kit include the sterile circular brush, a barcode-labeled slide, a fixative pouch, and a plastic transport container. Also included is a history form with a barcode corresponding to that on the slide and a prepaid Express Mail container.

Tissue molecular markers

Brush biopsy has been combined with a technique that assesses biomarkers and peptide profile patterns from the provided sample by means of ‘matrix-assisted-

laser-desorption/ionization-time-of-flight-mass-spectrometry (MALDI-TOF-MS).[28] . Brush biopsies from 27 patients with proven squamous cell carcinomas were compared with 40 biopsies from 10 healthy controls. Analysis suggested that the technique could distinguish between health patient tissue and that with cancer with a sensitivity of 100% and specificity of 93%. Additional validation trials are planned to assess its screening potential for pre-symptomatic head and neck cancerous lesions.

Other molecular markers such as podoplanin expression, serine protease inhibitor, clade B, P1N1, a prolyl isomerase which regulates phosphorylation, HIF-1a (hypoxia-inducible factor-1a, and other cellular markers may, when combined with brush biopsy, prove helpful in screening for oral cancer.

DNA image cytometry

DNA cytometry, a technique that has been used to differentiate keratoacanthomas from squamous cell carcinoma of the dermous[29] has also been combined with brush biopsy in assessment of oral leukoplakia for prediction of oral dysplasia.[30] Sensitivity and specificity has been estimated to be 100% when combined with oral brush biopsy.

Stereo-optical microscopy

Another technology that shows promise in detecting oral cancer is microscopy or stereo-optical microscopy. This system takes advantage of capillary changes that precede tumor growth and the patterns that these vessels make in the growth process. However at present the costs of using such instrumentation place its use at a disadvantage.

Laser scanning confocal endomicroscope

Laser scanning confocal endomicroscope (LSCEM) is a new imaging modality reportedly used to perform noninvasive, in vivo, scanning of the mucosa at a microscopic scale extending beneath the surface epithelium. It is said to be useful for capturing volumetric datasets via assessment of progressive depth level slices. The technology does not appear to have been evaluated in terms of reliability, sensitivity, specificity, or predictive value for diagnosing oral cancer.[31]

Biopsy

Tissue biopsy remains the criterion standard for oral cancer screening. The one disadvantage of this assessment strategy is that its accuracy may be limited for large lesions, dysplastic or pre-malignant lesion, or when there has been field cancerization.

Summary

Oral cancer is an international problem with cases increasing yearly, but with the death rate remaining relatively constant. The etiology of oral cancer is likely complex and multi-factorial. However, numerous confounding and/or causative factors are well known and need to be considered in the screening for disease. Some evidence exists that early diagnosis of precancerous lesions might reduce the morbidity associated with the disease. But, to date, little evidence exists that mortality has been altered by the available diagnostic instruments,[32] and conflicting evidence exists with respect to diagnostic reliability for some systems. Nonetheless, the adjunctive visualization strategies outlined in this article should, if used prudently, aid the clinician in screening for oral cancer.[33]

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