Making *oral cancer screening* a routine part of your patient care

PART 2

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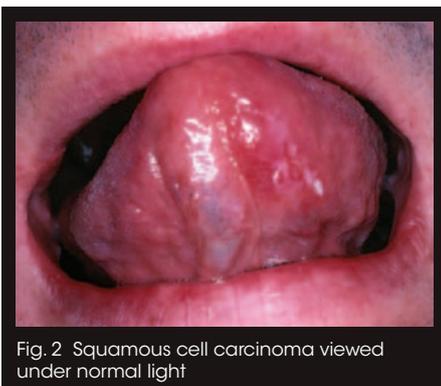Fig. 1 Vizilite pre-rinse solution and light stick/mirror

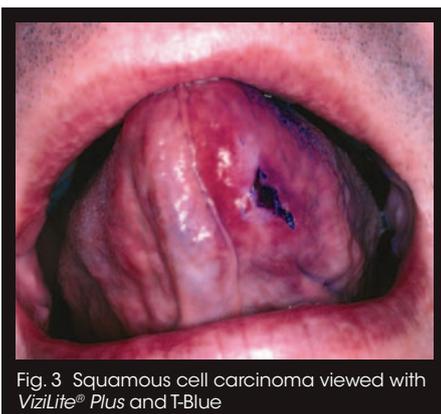Fig. 2 Squamous cell carcinoma viewed under normal light

Fig. 3 Squamous cell carcinoma viewed with *ViziLite® Plus* and T-Blue

On completion of this CPD paper, the participant will be able to:

- List examples of screening techniques which have improved survival rates for other cancers
- Define screening and discuss the criteria for evaluating screening techniques
- Describe adjunctive technologies for oral cancer screening
- Discuss some of the current research on oral cancer, including aetiology, prevention, diagnosis and treatment.

Introduction

Oral cancer is the world's sixth most common malignancy and has one of the lowest survival rates, often due to late diagnosis. Most oral cancers are preceded by precancerous lesions and early cancers that can be identified by visual inspection of the oral cavity. Oral cancer is therefore potentially amenable to primary and secondary prevention.[1] A cluster randomised controlled trial in India found that oral visual screening can reduce mortality in high-risk individuals.[2] However, while conventional oral examination is useful in the discovery of some oral lesions, it does not identify all potentially premalignant lesions, as some are not readily apparent to visual inspection alone.[3] Adjunctive techniques have emerged that may facilitate early detection of oral premalignant and malignant lesions.[4]

Screening techniques which have improved survival rates for other cancers[5]

Screening involves checking for the presence of disease in an asymptomatic individual.

Screening for breast, cervical, and colorectal cancers saves lives through early detection; it is often the first step in preventing colorectal and cervical cancers from developing. Routine screening can reduce deaths from colorectal
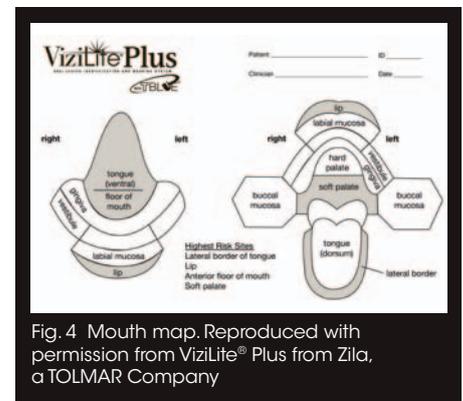

Fig. 4 Mouth map. Reproduced with permission from ViziLite® Plus from Zila, a TOLMAR Company

cancer by at least 60%. Mammograms performed every one or two years for women aged 40 years and over can reduce mortality by approximately 20% to 25% during a ten-year period. Rates of cervical cancer death dropped by 20% to 60% after screening programmes began.

Criteria for assessing the results of screening tests[6]

- Sensitivity refers to how accurately a test identifies people who have the disease
- Specificity refers to how accurately a test identifies people who do not have the disease
- The best tests demonstrate high sensitivity and high specificity
- The predictive value of a test reflects the probability that the test result is correct or incorrect.

Characteristics of a good screening test[3]

- Simple, safe and acceptable to the public
- Detects disease early
- Detects lesions which are likely to progress
- Detects lesions which are treatable, or where intervention will prevent progression
- High positive predictive value and low false positives.

*These structures should be felt by massaging with fingers

1. **Mandible*** chin and jaw bone

2. **Anterior auricular lymph nodes*** in front of ears

3. **Posterior auricular lymph nodes*** behind ears

4. **Occipital lymph nodes*** back of the neck

5. **Temporomandibular joint** (TMJ) jaw hinge

6. **Parotid gland*** salivary gland mid cheek

7. **Submental lymph gland*** under chin

8. **Submandibular lymph glands*** under chin

9. **Sternocleidomastoid muscle** (SMC) large muscle side of neck

10. **Thyroid gland –** butterfly shaped gland in neck

11. **Larynx –** voice box moves when swallowing

12. **Supraclavicular lymph nodes*** next to collar bone, related to breast tissues

13. **Lips** inside and outside

14. **Labial mucosa and frenum** soft tissue inside lips

15. **Alveolar ridges** gums & bone top and bottom

16. **Parotid gland** duct or small opening mid cheek

17. **Retromolar pads** on bottom gum tissue behind 2nd or 3rd molar

18. **Maxillary tuberosity** on top gum tissue behind 2nd or 3rd molar

19. **Floor of the mouth, underside of tongue** tissues, ducts and muscle under tongue

20. **Submandibular & submental glands*** under chin and tongue

21. **Lateral & base of tongue** sides and back of tongue

22. **Tongue**

23. **Hard & soft palate** roof of mouth

24. **Uvula anterior and posterior pillars** back of throat

25. **Palatine tonsils and posterior wall of the pharynx** back of throat

Fig. 5 Quick guide: 25 steps for head, neck & mouth exam. Reproduced with permission from Eileen McQuade RDH BS, and GoToDDS.com

Adjunctive techniques for oral cancer screening

These adjuncts may be used in conjunction with oral cancer screening, to aid in the detection of oral precancers and cancers (Figs 1-4).

Visualisation adjuncts

When using adjunctive visual screening technologies, the same sequence of assessment applies as for the conventional intra-oral examination, so that all areas of the mouth are methodically and thoroughly inspected (Fig. 5).

Chemiluminescent illumination

Chemiluminescent light is used to visualise the oral cavity after rinsing the mouth with 1% acetic acid. Acetic acid dessicates the cells slightly, to enhance visibility of abnormalities. Chemiluminescent light is reflected by leukoplakias, highlighting them as acetowhite regions; red lesions reportedly appear darker than normal tissue. Vizilite Plus utilises this technique together with Toluidine blue (T-Blue) staining, to enhance sensitivity and specificity.

Toluidine blue staining

This has been shown to identify lesions with molecular changes associated with increased risk of progression to oral cancer. Toluidine blue staining demarcates malignant/dysplastic areas, to identify sites for biopsy.

Autofluorescence

Autofluorescence of tissues is produced by fluorophores that naturally occur in living cells after excitation with a suitable light wavelength. Healthy tissue emits fluorescence, while abnormal tissue exhibits loss of fluorescence, and appears dark. Autofluorescence may be useful in detecting lesions that are not easily noticed by visual inspection, and to distinguish the margins of lesions for biopsy. Images of the fluorescence produced can be recorded using a camera. VELscope (Visually Enhanced Lesion Scope) and Identafi® (Fig. 6) utilise this technology.

Identafi® uses fluorescence and reflectance to enhance visualisation of mucosal abnormalities.
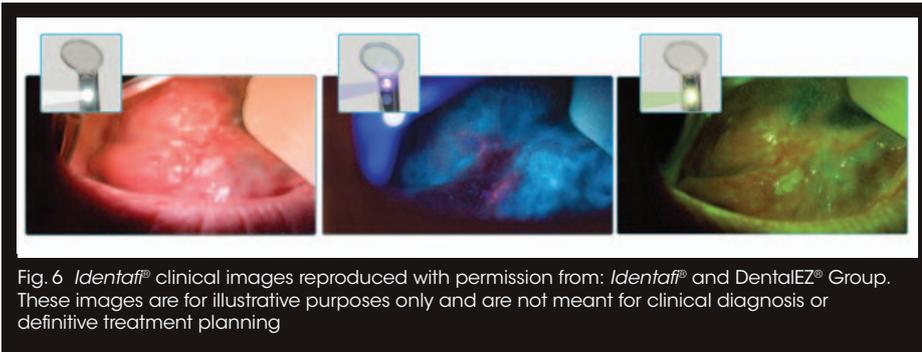
Fig. 6 *Identafi®* clinical images reproduced with permission from: *Identafi®* and DentalEZ® Group. These images are for illustrative purposes only and are not meant for clinical diagnosis or definitive treatment planning
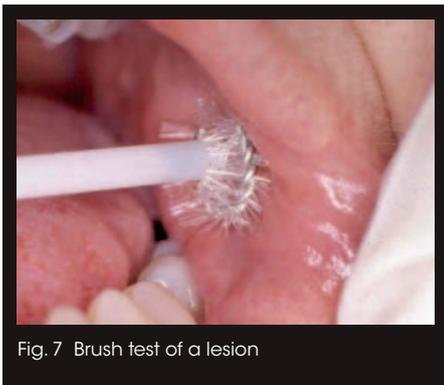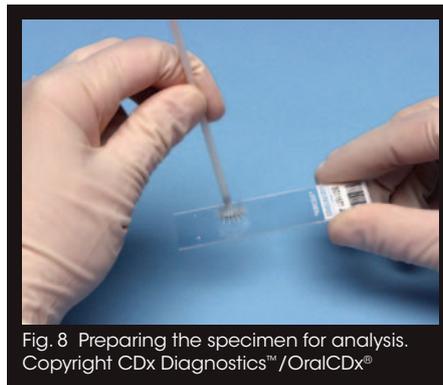

Fig. 7 Brush test of a lesion

Fig. 8 Preparing the specimen for analysis. Copyright CDx Diagnostics™/OralCDx®

Intra-oral visual examination is first done with a white light, then with a fluorescent violet light, followed by the amber reflectance light wavelength, which is absorbed by haemoglobin to highlight the vasculature around lesions. Abnormal tissue exhibits loss of fluorescence, and disorganised vasculature.

Adjunctive screening technologies which involve laboratory analysis
Oral exfoliative cytology
With this adjunct, the lesion must be visually identified before taking the specimen. A cytobrush is used to obtain a sample of the full thickness of stratified squamous epithelium for interpretation. The cells can be evaluated using the following methods: computer-assisted image analysis, DNA cytometry, immuno histochemistry, monolayer cytology and molecular biological analysis. OralCDx is one such brush test, recording 72.7% sensitivity and 92.3% specificity in diagnosing and monitoring oral leukoplakia[7] (Figs 7 and 8).

The OraRisk HPV salivary test
Oral Human Papilloma Virus (HPV) is primarily found in the oropharyngeal complex: it is an *oncovirus*, meaning that it could potentially lead to cancer. Incidence of HPV-related oropharyngeal cancers is increasing: particularly from HPV types 16 and 18; approximately 74% of HPV-positive cancers are found on the tonsils. The OraRisk® HPV test identifies the type(s) of oral HPV, and could facilitate risk assessment for oropharyngeal cancer. An example of a squamous cell

carcinoma of the posterior pharyngeal wall is shown in Figure 9 and a tonsillar carcinoma in Figure 10.

Current research on oral cancer
Aetiology and prevention
Recent research finds that the human cytomegalovirus (HCMV), a herpes virus found in the mouth, could have a role in the development of oral cancer.[8]

Researchers at Columbia University Medical Centre and Harvard School of Public Health found that women with high folic acid intake are at lower risk from oral cancer.[9] Recent research has also shown that an increase in foods with omega 3 and foods high in fibre can help decrease the risks.

'Wide variations are seen in the research findings for each adjunctive screening technology...'

Xylitol inhibits carcinogenic acetaldehyde production by Candida species[10]
Acetaldehyde is a highly toxic and mutagenic product of alcohol fermentation and metabolism, which has been classified as a Class I carcinogen for humans.[11] Many oral Candida species are capable of acetaldehyde production from ethanol.[12] Xylitol was found to reduce acetaldehyde production by Candida to below mutagenic levels.

Screening and diagnosis
Salivary analysis to enhance oral cancer screening
Researchers at UCLA have developed the Oral Fluidic Nanosensor Test: saliva from individuals with head and neck cancer was profiled and analysed. Salivary mRNA and proteomic biomarkers were able to predict if a sample was from someone with oral cancer, or from a healthy subject, with 82% accuracy.[13]

Salivary metabolomes can also aid in the detection of oral squamous cell carcinoma. Subjects with oral squamous cell carcinoma, oral leukoplakia, and those in healthy control groups demonstrated characteristic salivary metabolic signatures.[14]

Enhanced imaging
PET/CT (Positron Emission Tomography with Computed Axial Tomography)[15-17] involves intravenous injection of Fludeoxyglucose (FDG), a radioactive glucose analogue; several tumours show increased FDG uptake. FDG is taken up by high-glucose-using cells, and the CT scanner forms images of its distribution. The PET gives the metabolic information, while the CT is higher resolution and gives the anatomic location. These are overlaid to produce a CT scan with areas that 'light up' to coincide with the higher metabolic uptake.

Innovative therapy[18] – chemoprevention
Researchers have developed a mucoadhesive oral patch that releases Fenretinide, a chemoprevention drug, directly into oral precancerous lesions over an extended time.[19] Fenretinide is a synthetic derivative of vitamin A with anticancer properties. Scientists had previously failed to achieve a therapeutic systemic dose of Fenretinide because of drug toxicity and rapid release from the body.

Conclusion
Wide variations are seen in the research findings regarding sensitivity, specificity and predictive values for each adjunctive screening technology: this appears to be partially related to differences in study design. A 2005 Cochrane

systematic review by Kujan et al.[20] and 2007 research by Lingen et al.[3] found that 'the implication that adjunctive screening technologies may improve detection of oral cancers and precancers beyond conventional oral examination alone has yet to be rigorously confirmed'.
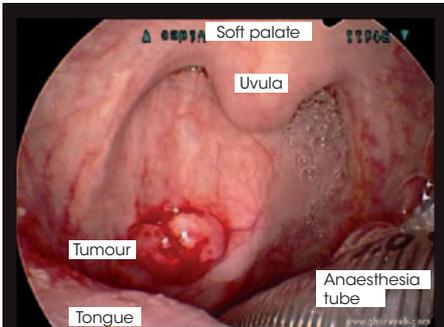

Fig. 9 Squamous cell carcinoma of the posterior pharyngeal wall. Reproduced with permission from Otolaryngology Houston www.houstonoto.com
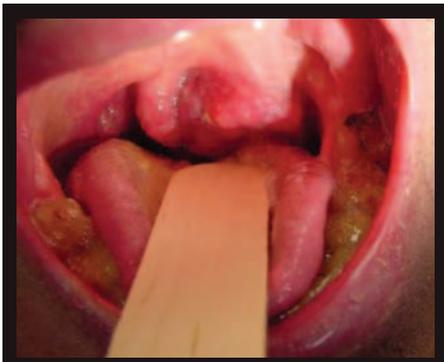

Fig. 10 Tonsillar carcinoma. Reproduced with permission from Otolaryngology Houston www.houstonoto.com

Patton, Epstein and Kerr's 2008 research[4] found evidence that Toluidine blue is effective as a diagnostic adjunct for use in high-risk populations and suspicious mucosal lesions, and OralCDx is useful in assessment of dysplastic changes in clinically suspicious lesions. However, they concluded that 'overall, there is insufficient evidence to support or refute the use of visually based examination adjuncts in general dental practice settings; therefore clinicians must rely on thorough oral mucosal examination, supported by specialty referral and/or tissue biopsy for diagnosis of oral premalignant and malignant lesions'.

Conversely, since there is no compelling evidence against utilisation of adjunctive technologies for oral cancer screening, their application is not precluded: they might potentially enhance early detection of oral cancers and precancers. Nevertheless, re-evaluation of lesions in 14 days to confirm persistence reduces potential errors in diagnosis,[21] and regardless of which screening technique is used, the most reliable method to confirm exact diagnosis is still scalpel biopsy and histopathological examination.

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Useful resources

Short tutorials on adjunctive screening technologies http://vivalearning.com/tutorials.asp?x_action=search&x_type=category&x_catID=95&1324672852869#results

A digital manual for early diagnosis of oral neoplasia (WHO International Agency for Research on Cancer)
http://screening.iarc.fr/atlasoral_detail.php?flag=0&lang=1&Id=A4000034&cat=A4

The British Dental Health Foundation website
http://www.dentalhealth.org/home

The Risk of Omission: Performance of Screening Exams
http://www.dentistrytoday.com/oral-cancer-screening/4814-the-risk-of-omission-performance-of-screening-exams

Oral cancer e-supplement
http://www.dentistryiq.com/etc/medialib/new-lib/dentstryiq2/online-articles/documents/2011/04.Par.73665.File

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http://services.aamc.org/30/mededportal/servlet/s/segment/mededportal/?subid=7768

Oral Cancer Screening Video
http://www.dentalce.umn.edu/OralCancerVideo/home.html