Title: Detection of Oral Cancer: Guidelines and a Clinical Effectiveness Review

Date: 20 May 2008

Context and policy issues:

Oral cancer is defined as squamous cell carcinoma of the lip, oral cavity and oropharynx. It is the sixth most common malignancy in the world, with more than 400,000 cases diagnosed worldwide annually.1 Approximately 3,200 Canadians will be diagnosed with oral or pharyngeal cancer per year.2 If oral cancers are found early, survival rates are 80% to 90%. Unfortunately, many oral cancers are found at late stages and the death rate is 50% at five years from diagnosis.3 Efforts have been made to detect potential cancerous lesions at their earliest stage. Various tools have been developed for screening and case-finding for detection and diagnosis of oral cancer and precancer. Screening (detection) involves checking for the presence of disease in a person who does not have symptoms, while case-finding (diagnosis) is used to establish a diagnosis on patient who has abnormal signs or symptoms.

The following screening tests and diagnostic aids are available.4

1. Standard screening test
   - Conventional oral examination (COE)

2. Established diagnostic adjuncts
   - Brush cytology
   - Toluidine Blue (tolonium chloride)

3. Light-based detection systems
   - ViziLite Plus
   - MocroLux DL
   - VELscope

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In light of the diversity of screening and diagnostic tools for oral cancer, there is a need to review their clinical effectiveness and to identify guidelines for early detection of oral cancer.

Research questions:

1. What is the clinical effectiveness of tools for the early detection of oral cancer?
2. What are the guidelines for detection tools to be used for early detection of oral cancer?

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 2, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and April 2008, and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

The scope is limited to identify information contained within the highest levels of evidence, and therefore health technology assessments, systematic reviews, meta-analyses and guidelines within the past five years were included.

Summary of findings:

Three systematic reviews,⁵⁻⁷ one comprehensive and critical review,⁴ and two guidelines⁸⁻⁹ were identified.

Systematic reviews and meta-analyses

The Cochrane systematic review by Kujan et al. (2005)⁵ assessed the effectiveness of screening methods in reducing mortality of oral cancer. A literature search was done between 1966 and September 2002 and a randomized controlled trial (RCT) study design was one of the main inclusion criteria of this systematic review.

There were no published RCTs examining toluidine blue, brush biopsy, or fluorescent imaging as tools for screening or as an adjunct method for screening. Only one RCT conducted in Kerala, India using conventional visual examination as a method for screening was included. The study reported that there was no statistically significant difference in death rate from oral cancer between the intervention group and the control group over six-year follow-up period. The sensitivity and specificity of the program were 81.5% and 84.8%, respectively. The positive predictive value was 39.6%. The three year survival rate was 57.5% in the intervention group and 38.8% in the control group (p>0.05, not statistical significant). This is the only the RCT showed clinical effectiveness of oral cancer screening by reporting mortality as primary health outcome.

Given the limitation of the evidence and methodological weaknesses of the included study, this systematic review concluded that there was “no evidence to recommend inclusion or exclusion of screening programs for oral cancer using visual examination in the general population”. ⁵

A systematic review on the effectiveness of screening for oral cancer and precancer by Downer et al. (2006)⁷ included 28 studies, but only one of these studies was an RCT (same RCT from India described in the systematic review above). Conventional oral examination was the method of screening. The authors found that the included studies showed “substantial heterogeneity

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regarding objectives and studies design, location and setting, numbers and characteristics of participants, screening personnel, methods of recruitment and types of data collected. A quality assessment was given to the included studies. In agreement with the Cochrane review, this review concluded that there are insufficient available data regarding the potential benefits associated with an oral cancer screening program.

A systematic review on screening for oral cancer and precancer by Downer et al. (2004) established a range of values for test performance (sensitivity and specificity) using visual examination. Eight studies were included. Meta-analysis using a random effects model revealed that the weighted pooled value of sensitivity was 84.8% (95% CI 73.0, 91.9), and the corresponding value for specificity was 96.5% (95% CI 93.0, 98.2). The included studies showed “substantial differences regarding target populations and their demographic characteristics, study designs, specified target lesions, categories and numbers of personnel undertaking screening and providing clinical examinations, and the amount of training received by the screeners.”

Subgroup analysis between studies using dentists as screeners and those using trained basic health workers showed no significant difference in the discriminatory ability of the test between these two groups.

The authors found no reports using the toluidine blue method as an aid in population screening of apparently healthy individuals for oral cancer and precancer.

**Review**

A review article by Lingen et al. (2008) systematically and critically examined the literature associated with current oral cancer screening and case-finding aids or adjuncts. Conventional oral cancer examination, brush cytology, toluidine blue, tissue reflectance and autofluorescence were critically examined in this review.

**a. Oral cancer examination**

The conventional oral cancer examination (COE), using normal (incandescent) light, has been the standard method for oral cancer screening. Although COE may be effective as a screening test (Table 1), there are some problems with this approach. First, 5-15% of the general population has oral mucosal abnormalities, which are clinically/biologically benign. Second, COE cannot discriminate between lesions that are progressive or become malignant and those non-progressive counterparts. Third, COE may miss the detection of precancerous lesions that appear clinically normal by CEO alone. Thus, while COE is a useful tool in detecting some oral cancer lesions, it does not identify all potentially premalignant lesions.

**Table 1: Studies of COE included in the review by Lingen et al.**

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<thead>
<tr>
<th>Study</th>
<th>Findings of the study</th>
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<td>Downer (2004)</td>
<td>This meta-analysis showed an overall sensitivity of 0.85 (95% CI 0.73, 0.92) and specificity of 0.97 (95% CI 0.93, 0.98).</td>
<td>COE has a satisfactory test performance for oral cancer examination. The included studies in this meta-analysis did not assess the effectiveness of the screening programs (i.e., mortality, which is the gold standard outcome of effectiveness)</td>
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Kujan (2003) Only one RCT from India was included in this systematic review. There was no evidence of reduced mortality with regard to oral cancer. Subsequent results at 9 years showed that there was a significant increase in survival among males who used tobacco. This RCT was the first clear evidence to support the efficacy of an oral cancer screening program.

COE = oral cancer examination

b. Brush cytology

The brush biopsy (CDx Laboratories) was designed for the interrogation of clinical lesions with low level of suspicion for carcinoma. However, when an abnormal result is reported, a scalpel biopsy must follow. Some strengths and weaknesses of studies that looked at this method are presented in Table 2. The technology appears to be promising. However, firm conclusions could not be reached until there are studies conducted in a cohort of subjects with class II lesions (innocuous) where both brush and scalpel biopsy are performed on each subject. This technique may be beneficial in patients with multiple lesions throughout the oral cavity and who are reluctant to consent for multiple scalpel biopsies.

Table 2: Studies of brush cytology included in Lingen et al.\textsuperscript{4}

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<td>Sciubba (1999)\textsuperscript{10}</td>
<td>The study used the combination of class I (clinically suspicious) and class II (innocuous) lesions. Only class I lesions underwent both brush and scalpel biopsy while class II lesions underwent brush biopsy. If positive test results were deemed indicative of cancer, the test showed 100% sensitivity with 100% specificity.</td>
<td>Strength: generalizability of the results, large population, blinding of pathologists who analyzed the brush and scalpel biopsies. Weakness: Scalpel biopsy was not performed in the majority of class II lesions, a cardinal rule for the evaluation of diagnostic test. No information regarding true sensitivity and specificity of the test within the class II lesions was reported.</td>
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<td>Svirsky (2002)\textsuperscript{11}</td>
<td>Of the 298 patients, 243 had abnormal brush biopsies. Among 55 cases that were brush biopsy negative, 4 had positive scalpel biopsies. A comparison of 80 patients who had both brush cytology and scalpel biopsy had a sensitivity of 92% and specificity of 94% for both positive and atypical results in detecting dysplasia and oral cancer.</td>
<td>Strength: The study design better reflects the actual use of this tool in the community, since the patients evaluated were derived from the general dentists who performed initial examination and brush biopsy. Weakness: The inclusion of class I patients would skew the calculations of sensitivity, specificity, and positive predictive value.</td>
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### Study

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<td>Poate (2004)¹²</td>
<td>Most of 112 patients were of class I. All patients with positive brush biopsy underwent scalpel biopsy. Patients with negative brush biopsy only underwent scalpel biopsy if the lesions were judged to be clinically suspicious. The sensitivity was 71%, specificity was 32% and positive predictive value was 44%.</td>
<td>Weakness: Patients were of class I, which were not the population intended for this technology. The gold standard scalpel biopsy was not performed in all patients, particularly class II patients. Thus the calculations of sensitivity and specificity were biased.</td>
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<tr>
<td>Christian (2002)¹³</td>
<td>The majority of the lesions were of class II. Of the 930 individuals screened, 93 lesions were found. Seven of these lesions were abnormal by brush biopsy, and four of the seven abnormal lesions had scalpel biopsies. Three of four showed dysplasia.</td>
<td>Strength: Population consists of type II lesions for which the technology was intended. Weakness: Fail to perform scalpel biopsies to all subjects. Thus, it is impossible to calculate sensitivity and specificity.</td>
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<td>Scheifele (2004)¹⁴</td>
<td>96 lesions with clinical diagnosis of oral leukoplakia (n=49), oral lichen planus (n= 18), or squamous cell carcinoma (n=13) underwent both brush and scalpel biopsies. The sensitivity and specificity were 92.3% and 94.3%, respectively.</td>
<td>Strength: this is the only study where both brush and scalpel biopsies were performed in all subjects. Weakness: Population seems to consist of both class I and II. Oral lichen planus and squamous cell carcinoma should not have been evaluated with brush biopsy.</td>
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### Toluidine blue staining

Toluidine blue (also known as tolonium chloride) is a dye that stains nucleic acids of abnormal tissues. It has been used for decades as an aid for the identification of mucosal abnormalities of the cervix and in the oral cavity.

Studies of toluidine blue had many problematic issues:

- No studies carried out in a primary care environment
- Data from studies in secondary care are not necessarily applicable to general population
- No randomized controlled trials
- Some studies only include carcinomas or dysplasia and some include both
- Histological diagnosis is rarely used as a gold standard
- Methods vary – single rinse, double rinse, ‘painting’
- Confusion over inclusion of equivocal (pale) staining as positive or negative
- High sensitivity, but low specificity (high false positive)

Despite those limitations, toluidine blue remains a useful technique as an adjunct to clinical examination (screening) and case-finding (diagnosis).
d. Tissue reflectance (ViziLite Plus, MicroLux DL)

Tissue reflectance involves rinsing the mouth with a 1% acetic acid solution followed by direct visual examination of the oral cavity using a blue-white light. Evidence that supports the use of this technology to aid the detection of oral premalignant lesions is currently quite limited. The published studies to date suffered from experimental design issues, especially the critical comparison to the diagnostic gold standard (scalpel biopsy). It is unclear that this technique could provide any additional benefit to the practicing clinician.

e. Narrow-emission tissue fluorescence (VELscope)

The autofluorescence of tissues is potentially useful for cancer detection. Fluorescent spectroscopy and fluorescent imaging technologies have been developed for cancer screening of many anatomic sites including the oral cavity.

The VELscope is a portable device and is being marketed for use in oral cancer screening. Under intense blue excitation light (400-460 nm), normal oral mucosa emits a pale green autofluorescence when viewed through a narrow band filter. In contrast, abnormal or suspicious tissue exhibits decreased levels of normal autofluorescence and appears dark relative to the surrounding healthy tissues.

Current published studies (Table 3) gave limited evidence regarding the ability of the VELscope to identify premalignant regions within class II lesions or to reveal cancerous lesions otherwise visually undetectable. However, the preliminary results of those studies are promising.

Table 3: Studies of VELscope included in Lingen et al. 4

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| Lane (2006) | This study reported the ability of VELscope to identify precancerous and cancerous lesions. Conventional oral examination followed by VELscope was conducted in 44 patients. Using scalpel biopsy as the gold standard, the device demonstrated 98% sensitivity and 100% specificity. It should be noted that all of the dysplasias and/or carcinomas were observed using incandescent light alone. | *Strength*: the device was directly compared to the gold standard (scalpel biopsy). It as a high degree of sensitivity and specificity  
*Weakness*: Small in sample size, the majority of lesions were of class I. |
| Poh (2007)  | This study reported three non-consecutive representative cases in which non-evident lesions were identified using VELscope.                                                                                                                                               | *Strength*: class II lesions  
*Weakness*: the individual cases represent anecdotal observations |
| Poh (2006)  | This study investigated the role of fluorescent visualization for the detection of surgical tumor margins for oral cancer when used in the operation room. Nineteen of 20 tumors demonstrated loss of autofluorescence that extended as much as 25 mm beyond the clinically evident tumors. | *Weakness*: Class II lesions identified within this work were found within the background of obvious class I lesions. As such, VELscope fails to demonstrate that it could identify de novo class II lesions |
In summary, the conventional oral examination (COE) has been used as the screening tool for detection of signs of oral cancer and precancerous lesions despite the fact that it can be problematic. Early cancers and precancers are heterogeneous and often rarely demonstrate the clinical characteristics observed in advanced cases. Various case finding tools with promising results have been developed, but no technology to date has shown that it improves the sensitivity or specificity of oral cancer screening beyond the COE alone. There is no strong evidence to suggest that these technologies could help the clinician to identify premalignant lesions before they are detectable by COE.\(^4\)

**Guidelines**

A Canadian guideline for early detection of oral cancer was written by a working group of the BC Oral Cancer Prevention Program for the College of Dental Surgeons of British Columbia in 2008.\(^8\) It provides clinical recommendations for dental practice in Canada, addressing opportunistic screening, that is, “screening in the context of clinical assessment linked to routine care, and give information about subjects who may be at higher risk”.\(^8\)

Oral cancer screening and mucosal lesion assessment consists of four steps:\(^8\)

1. Completion of patient history – general health history, oral habits and lifestyle involving tobacco use and alcohol consumption, and symptoms.
2. Visual screening examination – extraoral examination, intraoral examination (by conventional oral examination), lesion inspection and documentation.
3. Adjunctive visual tools – toluidine blue staining and direct fluorescent visualization. These techniques should be used as complementary and not a replacement for the conventional oral examination.
4. Diagnostic biopsy – the gold standard for diagnosing. It should be used on suspicious mucosal lesions persisting for more than three weeks.

The recommendation was based on one randomized controlled trial of visual screening for oral cancer in India, of which the mortality result showed no statistically significant difference between the intervention and control groups. However, screening significantly reduced deaths in users of tobacco and alcohol. The recommendation was also based on an economic analysis suggesting that high-risk opportunistic screening by a dentist might be cost effective. The authors of the guideline accept that there is no strong direct evidence of a benefit of oral cancer screening. The guideline will be updated on a regular basis.

A US guideline from HealthPartners Dental Group provides a model to assess a patient’s risk for developing oral cancer and recommends tools to identify oral cancers earlier in the course of the disease.\(^9\)

**Major recommendations:**\(^18\)

1. Risk assessment includes assessment of tobacco and alcohol use, history of oral cancer, immunodeficiency, sun exposure and age.
2. Oral cancer examination. It is recommended to use conventional visual examination including oral soft tissues, extra oral head and neck tissues, and head and neck lymph nodes. It is considered as a standard of care as part of a complete dental examination.
3. Oral tissue biopsy. It is the gold standard for diagnosis of oral cancers.
4. Screening tools such as toluidine blue, ViziLite and brush biopsy offer help in distinguishing which oral lesions should be biopsied, but none of them can be relied on to establish definitive diagnoses.

5. Once a diagnosis of oral cancer has been made, imaging studies may be undertaken to determine the extent of the disease. The imaging techniques include computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET) and ultrasonography.

The type of evidence supporting the recommendations was not specifically stated. No implementation strategy was provided.

Conclusions and implications for decision or policy making:

Both systematic reviews found that there was insufficient evidence to recommend the inclusion or exclusion of visual examination as a screening tool for oral cancer and precancerous lesions; although one RCT from India showed that the test was effective in the reduction in mortality in a high risk population (males who used tobacco). No technique or technology to date has provided definitive evidence to suggest that it improves the sensitivity and specificity of oral cancer screening beyond the conventional oral examination. There is no evidence to suggest that any of the technologies developed in the last decade could be used as screening tool. Both guidelines identified in this review have recommended the use of visual examination as the primary tool in oral cancer screening. Toluidine blue staining, direct fluorescent visualization and brush cytology may be used as adjunctive visual tools to determine which lesions are needed for scalpel biopsy (gold standard) to establish a definitive diagnosis.

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