

ADJUNCTIVE METHODS FOR DIAGNOSIS OF ORAL SQUAMOUS CELL CARCINOMA

AN EVIDENCE BASED REPORT

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1.0 BACKGROUND AND PURPOSE AND DEFINITION OF PROBLEM

Oral cancer is 8th most common cancer worldwide (Petersen, 2005) with 274,000 cases reported in 2002 (Parkin, 2005). In the United States, 30,000 new cases are expected in 2005, two-thirds of them in males over 50 years old (ACS, 2005). Cancer in the oral cavity has one of the lowest five-year survival rates, currently at 59% (Greenlee, 2001). More than 90% of oral cancers are squamous cell in origin. Although the incidence of SCC has declined in the United States between 1975–1982 and 1991–1998 (Canto, 2002), it is still a very significant public health issue in south-central Asia where oral cancer is the 3rd most common malignancy (Petersen, 2005). Oral SCC is most likely to manifest on the tongue, lip or floor of the mouth (Canto, 2002), where the treatment (if successful) could have negative implications on aesthetics and function. Accordingly, an early diagnosis is crucial for obtaining timely and appropriate treatment, decreasing mortality rates and achieving the most favourable health outcome.

The primary step in oral cancer detection and diagnosis is patient history and thorough soft-tissue examination. If a suspicious lesion is discovered, it is biopsied and a histological examination of the sample is performed. Currently, a biopsy with histopathology is considered the gold standard for diagnosis of squamous cell carcinoma. However, a number of other adjunctive tests exist that are being used or could be used clinically as diagnostic tests for SCC. The purpose of this report is to provide evidence on the accuracy of these adjunctive tests, relative to biopsy, in diagnosing squamous cells carcinoma.

This report is tailored toward general dentists in private practice, and focuses on tests that are already available or could potentially be ordered by the general practitioner, either directly or by referral.

Note: The original research question was phrased "How accurate are adjunctive tests (other than biopsy) for diagnosing soft tissue oral lesions?" However, a preliminary search revealed an abundance of literature on tests aimed at diagnosing a variety of oral lesions. Consequently, a decision was made to narrow the question to squamous cell carcinoma (SCC) only, due to its life-threatening nature.

2.0 TARGET POPULATION

This evidence based analysis is aimed at patients suspected of having soft tissue oral squamous cell carcinoma. The soft tissues in the selected studies included, but were not limited to gingiva, buccal mucosa and tongue. Populations consist of both genders, and comprise a range of age groups with mean ages ranging from 40-80 years. Population sizes in the selected studies range from 27-945 people and several studies include associated risk factors such as tobacco use or alcohol use. Where possible, studies include matched control groups based on age and/or gender. Various ethnic groups are also included due to the variety of study locations. All of the selected studies compare diagnostic tests to the gold standard (histopathology), and included diagnostic statistics to compare specificity and sensitivity of the adjunctive test.

3.0 CLINICAL PROBLEMS ADDRESSED AND NOT ADDRESSED

This evaluation is limited to tests diagnostic of squamous cell carcinoma. Squamous cell carcinoma is a very significant public health issue, especially in south-central Asia where oral cancer is the 3rd most common malignancy (Epstein et al. 2002). Other types of oral lesions, such as ulcerations, lichen planus and hyperkeratosis, are not directly incorporated into this report.

Currently, the gold standard diagnostic test for oral cancerous lesions is biopsy. This report is aimed at evaluating other diagnostic tests and assessing whether any of these tests have potential advantages over biopsy in being less invasive or costly, while still attaining high accuracy in diagnosis.

4.0 CLINICAL FLEXIBILITY

All patients suspected of having oral SCC have to undergo biopsy to confirm the diagnosis. This could potentially lead to experimenter biases when evaluating the accuracy of the adjunctive diagnostic test.

5.0 STRUCTURE OF THIS REPORT

6.0

The results of this systematic review are presented in the following evidence-based report. The structure of the report is based on the template proposed at the RCDSO/CDHSRU workshop (Leake et al., 1996).

6.0 REVIEW OF EVIDENCE

6.1 *Search Strategy*

The following resources were used to identify relevant articles:

Ovid databases: Ovid Medline 1966- Feb 2006, All EBM Reviews, Ovid Medline In-Process etc.

- Limits: - 1990 to 2006
- English language
- Human
- Keywords used to identify existing diagnostic tests:
 - Diagnosis
 - Oral OR mouth
 - Cancer OR neoplasia
 - Squamous cell carcinoma OR SCC
- Keywords specific for imaging:
 - CT, MRI, PET
 - Advanced Imaging
 - Radiography
- Keywords specific for brush biopsy:
 - Brush biopsy OR OralCDx

- Keywords specific for toluidine blue:
 - Toluidine OR toluidine blue OR tolouium chloride
 - Vital stain OR vital dye
- Keywords specific for fluorescence:
 - Premalignant OR precancerous
 - Fluorescence
 - Spectroscopy

The search for additional potentially relevant articles included reference lists of articles already deemed relevant, review articles (although non-systematic reviews were excluded from the critical appraisal), the Oral Cancer Society website, and American Cancer Society website.

Additional guidance on the relevant topics was received through consultations with the residence students and specialists at the Pathology and Radiology departments at the University of Toronto and Dr. R.J. McComb, Oral Medicine and Pathology discipline head at the University of Toronto.

The search was limited to the articles available through University of Toronto Libraries.

6.2 Inclusion/Exclusion Criteria

During relevant article selection, the report concentrated on primary research articles focusing on diagnostic accuracy of an adjunctive test for oral SCC. The relevant studies were selected provided they met the following criteria:

- 1) reported specifically on the diagnostic capabilities of toluidine blue dye, brush biopsy, imaging or autofluorescence techniques;
- 2) were human, in-vivo studies;
- 3) provided statistical analysis (sensitivity, specificity, accuracy and/or ROC value).

When applicable, preference was given to studies that sought to differentiate between various grades of lesions, such as benign vs. (pre)malignant lesions, not just between healthy mucosa and malignant/cancerous lesions.

Articles that passed the abstract stage were independently scored by two group members using the Checklist for Assessment of Diagnostic and Predictive Tests. The articles that obtained the highest scores and met all aforementioned criteria were selected for inclusion in the evidence report.

7.0 SUMMARY OF EVIDENCE

7.1 Diagnostic methods for biopsy

Different adjunctive tests can help the dentist screen oral lesions for cancer during the examination procedure, however the current gold standard for diagnosing (pre)malignant oral lesions is surgical biopsy followed by histological analysis of the sample tissue. The goal of an oral biopsy is to provide a pathology lab a complete and accurate representation of the tissue in question, while minimizing trauma to the sample

site. There are various biopsy methods available such as needle biopsy, brush biopsy and scalpel biopsy. Treatment for a suspicious oral lesion begins only after positive histopathology of a surgically excised tissue sample. Although the majority of biopsies are performed by oral surgeons, general dental practitioners are qualified to perform an oral biopsy.

7.2 Diagnostic methods for staging and therapeutic progress

Various imaging modalities play a critical role in treatment planning and measuring progress in post therapeutic treatment. Dental radiologists recommend advanced imaging prior to biopsy for suspected malignancy pathologies. This is to avoid alterations of the field caused by a biopsy and allow for an unaltered specimen to be diagnosed. Prior to treatment of malignant pathologies, advanced imaging is utilized to assess staging and measure lymph nodal spread. This aids in surgical and radiation treatment and also measures baseline pathology. During and after treatment, advanced imaging modalities are employed to identify and measure the progress of treatment and whether any relapse has occurred. It is common practice for treated and cured patients to have annual imaging scans performed in an effort to catch any relapse early on.

7.3 Evidence Based Tables

See Appendix 1 for Evidence Based Tables.

7.31 EVIDENCE BASED TABLES FOR IMAGING STUDIES

The studies comparing the diagnostic ability of MRI, CT and PET for oral SCC showed similar conclusions. None of the aforementioned imaging modalities were more accurate than histopathological diagnoses (Ng et al., 2005; Yen TC et al., 2005). Moreover, a lack of agreement between studies was detected in terms of the accuracy of these diagnostic tests, with a range of accuracy between 75% - 94.2% depending on the imaging technique (Araki et al., 1997; Ng et al., 2005; Wiener et al., 2005; Yen TC et al., 2005). A significant trend noticed in the studies was that when two or three imaging modalities were used to diagnose rather than just one individual modality, the accuracy of SCC detection was significantly higher (Ng et al., 2005; Yen TC et al., 2005). In addition, studies that compared PET vs. MRI and CT concluded that PET diagnosis was more sensitive than CT and MRI, and thus prevented futile surgery in patients (Ng et al., 2005).

7.32 EVIDENCE BASED TABLES FOR BRUSH BIOPSY STUDIES

The evidence of the brush biopsy studies similarly concluded that the OralCDx technique can effectively screen questionable oral lesions. However the specificity and accuracy values were inconsistent for the Svirsky et al. 2002 report. This discrepancy was most likely caused by variability in oral lesion classification criteria. Each study created unique guidelines to categorize the degree of dysplasia among oral lesions. This lack of standardization introduced some variability in the results.

7.33 EVIDENCE BASED TABLES FOR TOLUIDINE BLUE STAINING STUDIES

The evidence for toluidine blue staining showed broad variability in specificity and sensitivity. Factors augmenting sensitivity and specificity included: 1) whether high-risk populations were studied, as

they would yield a higher specificity given the ability inability of toluidine to consistently diagnose pre-malignancy, 2) the lack of standardization for cut-offs of premalignancy versus cancer, 3) handling of equivocal tissue dye retention data, 4) whether dye application was commercial or laboratory preparation, multiple or single rinse or direct local dye application, 5) whether biopsy was taken from all subjects' lesions, regardless of stain retention, 6) whether trauma was considered. (Onofre et al., 2001, Fischer et al., 2004, Epstein et al., 2003).

The majority of literature asserts toluidine dye as having low specificity and a higher sensitivity, however the evidence from selected literature conflicts in this regard. The highest quality of evidence from Epstien et al (2003) indicated that toluidine blue is more sensitive than clinical exam alone in high risk patients, with sensitivity of 96.7% and specificity of 90.9%. These findings are in agreement with a meta-analysis of toluidine's effectiveness in detection of oral cancers (Rosenberg and Cretin, 1989). Epstein's study focused on a high-risk population, which may have buoyed specificity somewhat. Conversely, Onofre et al (2001) excluded 'obvious' malignancies, thereby lowering the specificity and sensitivity. Accordingly, since toluidine more readily marks malignancies than premalignancies, the sensitivity and specificity Onofre reported were much lower than literature, at 77% and 67% respectively. Zhang et al (2005) demonstrated, with fair quality evidence, that toluidine can identify high-risk characteristics of non-malignant lesions. However, like Epstien, Zhang et al studied only high-risk lesions in high-risk patients.

7.34 EVIDENCE BASED TABLES FOR AUTOFLUORESCENCE STUDIES

Autofluorescence-based tests rely on the presence of endogenous fluorophores found in the tissue matrix and cells to produce fluorescent emission in response to the exposure to light of specific wavelength. In the disease state, the concentration of fluorophores in tissues is altered, consequently allowing for the detection of such changes through means of autofluorescence spectroscopy or imaging. One problem with this technique is that the presence of blood or bacteria in and around the tissue can alter the fluorescence that is emitted by the tissue. Additional issues with this technique are that benign, pre-malignant and malignant lesions are variable in composition and may resemble one another.

The studies for both autofluorescence imaging and spectroscopy used variable excitation wavelengths leading to excitation of different fluorophores. This could be a cause of variability in the research findings, and there is currently no constant for this parameter.

The data on the accuracy of autofluorescence spectroscopy is conflicting. Although the technique is excellent at differentiating healthy mucosa from cancerous lesions, or healthy mucosa from any type of lesion, it falls short when trying to distinguish pre-cancerous from cancerous lesions (De Veld, 2005). While some studies obtained acceptably high sensitivity and specificity values, others have failed to prove the accuracy of the test. Furthermore, the studies which obtained promising results did have a number of associated limitations, such as small sample size and homogeneous data set restricted to lesions in the buccal mucosa of individuals with smoking and tobacco-chewing habit (Wang, 2003). Thus, these results should be regarded with caution.

The research on autofluorescence imaging is also inconclusive. Sensitivity values are very promising, but specificities often fall short (Betz, 2002). This is of concern, as unnecessary treatment of false positive results could be extremely detrimental to a patient's health. However, recent research using a red-to-blue intensity ratio to evaluate the imaging data has shown a high degree of accuracy in differentiating benign, precancerous and cancerous lesions (Zheng, 2004). Overall, autofluorescence imaging has the most potential to be used as a tool to scan the oral cavity for new lesions and for detecting invisible tumour extensions after removal (De Veld, 2005).

8.0 CLINICAL APPLICATION

8.1 Clinical Application of Imaging

Since general dentists do not have CT, MRI and PET machines available to them in their own practices, a referral to a dental radiologist is required for these diagnostic modalities. However, simple dental films and panoramic radiographs combined with visual inspection are usually the primary means of detecting oral pathology (van der Waal, 2005). Upon discovery of an abnormality by the general dentist, one option is to take a simple dental radiograph. If this abnormality can be diagnosed, then no other adjunctive tests are required. However, if the results are inconclusive, then further tests are required. Referral to a dental radiologist is an option to help determine the type and extent of the pathology (van der Waal, 2005). Imaging diagnostic modalities are for the most part non-invasive, except for the minimal radiation that passes through the patient. Regular dental radiograph machines and panoramic machines are essential to dentists in their practices, the cost per use is reasonable for this application. However, CT and MRI scans cost around \$300-1200 and may evoke psychological discomfort to claustrophobic patients. The high costs and regulatory requirements of these machines limit their availability mostly to hospital settings. These imaging modalities have proven to be extremely useful in health care when used in assisting histopathologic diagnoses, and will continue to improve with the progression of technology. Their use is intrinsic to successful surgical treatment and detection of relapsing malignancies.

8.2 Clinical Application of Brush Biopsy

The oral brush biopsy can be a fast, effective, and minimally invasive chair-side screening procedure. OralCDx (Computer assisted brush biopsy) may bridge the gap between clinical inspection and histological evaluation of oral lesions with epithelial abnormalities (Sciubba et al.1999, Svirsky et al. 2002). Studies suggest that OralCDx may be used as a screening tool for clinically benign appearing oral lesions if the following criteria are met: the test should benefit the patient sufficiently to justify its use over an alternate screening method, and the dentist must be able to identify eligible lesions and correctly administer the brush biopsy procedure (Scheifele et al. 2004, Svirsky et al. 2002). All positive and atypical results must be confirmed with a follow-up scalpel biopsy and characterized histologically (Scheifele et al. 2004, Sciubba et al.1999, Svirsky et al. 2002).

8.3 Clinical Application of Toluidine Blue Staining

Toluidine blue is a fast, minimally invasive and patient-accepted diagnostic aid (Patton, 2003), that has been in use for over thirty years. It has been the most widely studied aid in clinical detection of oral cancer and pre-cancer and its popularity and purported diagnostic value have waxed and waned over years considerably. Patton's systematic review (2003) of toluidine reported that when high-risk groups are targeted for screening, 2 to 3 times the number of lives would be saved, while only one quarter of the population would be screened. However, Patton's work also indicates that there is insufficient evidence to determine whether toluidine dye would improve oral cancer screening programs for the general population.

Notably, most studies cautioned that toluidine blue dye could be used as a diagnostic adjunct, but caution that it is not a substitute for clinical judgement or biopsy. As a rule false positives do not occur with obvious malignancies, and toluidine is highly accurate in this regard, perhaps serving to accelerate biopsy (Onofre, 2001). In the context of the aforementioned two points, as a general practitioner undertaking

clinical examination of a suspicious lesion, one may wish to use toluidine blue dye for a minimally invasive confirmation of diagnosis prior to biopsy, or to guide the biopsy excision.

It should be noted that recent research indicates staining of non-visible oral lesions that are histopathologically classed as premalignant are more likely to have a negative long-term outcome (cancer), so these sites should be more frequently monitored, while pre-malignant sites that do not stain have more positive outcomes (Zhang, et al). As it should be expected, clinicians should be adequately trained in the exact interpretation of results, as there are no studies supporting the use of toluidine blue dye at non-specialty practices or of diagnostic accuracy at general practitioner's office.

8.4 Clinical Application of Autofluorescence

In autofluorescence spectroscopy, the intensity of the fluorescence is recorded using a spectrometer and the data is analyzed using a chosen mathematical algorithm. In autofluorescence imaging, the fluorescence is recorded using a camera and the image is digitized and analyzed using a spectrophotometer. A mouth rinse containing 5-aminolevulinic acid is often used, which induces accumulation of the fluorescent protoporphyrin IX in neoplastic tissues (Zheng, 2004). With some training, it would be easy for a general dentist to use autofluorescence in the clinical setting.

Autofluorescence is not yet available to dentists as a diagnostic tool. However, if it does become available commercially, autofluorescence imaging could be used to scan the oral cavity for invisible lesions or to find an optimal site for biopsy (Betz, 2002). Clearly, biopsy would still be performed after this test.

Currently, the specific diagnostic equipment associated with autofluorescence is not available to general or specialist dental practitioners. For research purposes, most laboratories set up their own spectroscopes or used modified endoscopes. An accurate cost assessment is not available at this time, but it seems likely that the implementation costs (including machinery, software and training) would be high, whereas ongoing operation costs would be relatively low, especially since no specimens would have to be sent out to a lab for analysis as in biopsy.

9.0 COST VS. OUTCOME ASSESSMENT

Adjunctive diagnostic tests are not evaluated solely on their accuracy in diagnosis. They are also appraised by various other factors including their cost in relation to that of the gold standard. The adjunctive tests discussed in this report are either more costly or in a comparable price range in relation to conventional histopathological tests, and are not as accurate in diagnosis.

Note: Autofluorescence cost was estimated because this technology is not yet marketed and available for general use.

9.1 Abridged Technology Assessment Table

COMPARED TO BIOPSY THE TEST COSTS	COMPARED TO BIOPSY THE TEST WORKS		
	BETTER	THE SAME	WORSE
LESS			
THE SAME			<i>TOLUIDINE BLUE BRUSH BIOPSY</i>
MORE			<i>IMAGING AUTOFLUORESCENCE</i>

10.0 EVIDENCE BASED RECOMMENDATIONS

10.1 Recommendations for Imaging Studies

Due to the lack of availability of PET scans in North America, conventional CT and MRI scans will continue to play an intrinsic role in diagnosis of extent and staging of pathology. Due to their limitations in accurately diagnosing individual types of pathology, their use in determining spread and extent is quintessential during surgical treatment.

10.2 Recommendations for Brush Biopsy Studies

Studies support the use of brush biopsy as an adjunct to the oral examination. It is not intended to be a screening tool of obvious malignancies. Instead it is used to determine if a less suspicious oral lesion requires scalpel biopsy. (Scheifele et al. 2004). In this regard, the evidence supports brush biopsy as an accurate adjunctive test for oral squamous cell carcinoma.

10.3 Recommendations for Toluidine Blue Staining Studies

Literature indicates that evidence for toluidine blue as an accurate diagnostic adjunct is inadequate. There is insufficient evidence to categorically accept toluidine vital staining as a consistently accurate diagnostic adjunct, though in specific instances it may be very useful. The dental community requires more information to support toluidine's use as a regular screening tool in the general population. High false positives causing unnecessary patient alarm and unnecessary surgical biopsy and the economic burden of screening all patients detracts from its use. However, given the severe implications of undiagnosed SCC, our report would support the use of toluidine for targeting and screening select high-risk patient populations, such as males over 40 who regularly consume alcohol or use tobacco. In these populations good sensitivity and specificity has been demonstrated (Epstein et al., 2003). Toluidine dye may safely assist in primary biopsy site selection and identify lesions not found in clinical examination.

10.4 Recommendations for Autofluorescence Studies

Currently, autofluorescence spectroscopy cannot be deemed an accurate test for diagnosis of SCC due to conflicting findings reported by various investigators. Autofluorescence imaging may eventually be used to scan the oral cavity for invisible lesions in high-risk individuals (Betz, 2002) and for determining an optimal biopsy site once a lesion is found (Zheng, 2004).

11.0 RECOMMENDATIONS FOR FURTHER RESEARCH

Imaging: Current research focuses on improving the diagnostic accuracy of oral SCC metastasis to local regional lymph nodes. Due to limitations inherent in diagnostic imaging, i.e. lack of specific disease diagnosis, diagnostic imaging should be utilized as an adjunct to surgical treatment. Imaging has the ability to successfully identify regional lymph nodes that have been metastasized much easier than any other diagnostic instrument. Further research should continue to improve accuracy of bone and lymph node metastasis.

Toluidine Blue Vital Staining: Future research should address the accuracy of toluidine in identifying and predicting outcomes of premalignancy, as well as the accuracy of clinical visual exam with and without this adjunct. Definitive criteria for administration and interpretation must be standardized. Additional research might also address serial testing of toluidine in conjunction with other diagnostic tests for diagnosing oral squamous cell carcinoma, toluidine's effectiveness in a community setting, and its accuracy in particularly high-risk populations. Currently OraScan (Zila Medical) is undergoing phase III clinical trials in the United States.

Autofluorescence: Since autofluorescence is not yet available to the general dentist, it is clear that more research on its methods and clinical applications is needed. Future research could focus on better mathematical algorithms and analytical tools for the interpretation of data. Inclusion of other optical diagnostic methods (i.e. diffuse reflectance spectra) could also be considered in order to improve test performance. The manufacturing of specialized diagnostic equipment geared specifically towards oral SSC diagnosis is the ultimate goal of future research

Other: Furthermore the need for a non-invasive, accessible and highly efficient diagnostic test, has spurred research in the direction of Salivary Transcriptome Diagnostics (Yang Li et al., 2004). This new technology uses microarray analyses of patients' saliva specimens to detect salivary genes which have an altered expression due to oral cancer. Although this new technique is very promising, continued research is needed to detect new combinations of biomarkers (altered genes), in order to increase the accuracy of this screening method.

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APPENDIX 1: EVIDENCE BASED TABLES

Table 1: Evidence for accuracy of toluidine blue vital dye as a diagnostic adjunct

EVIDENCE BASED TABLES – TOLUIDINE												
Author	Population	Diagnostic Test	Compared to Gold Standard	Specificity	Sensitivity	Accuracy	PPV	NPV	LR+	LR-	Critical Appraisal Test	Conclusions
Zhang, et al. 2005 <i>Toluidine blue staining identifies high-risk primary oral premalignant lesions with poor outcome.</i>	162 patients in longitudinal follow-up study, 1996-2004 100 patients biopsied and tested with toluidine blue. Mean age 64 years 47% male 69% smokers (high risk behaviour) All were suspected of High-Risk primary oral premalignant lesions.	1% Toluidine Blue Dye OraScan by Zila Biomedical	YES	90.9	68.8	.81	.86	.78	7.6	.34	7C	<ul style="list-style-type: none"> -Toluidine blue preferentially stains lesions with high-risk clinical features -Toluidine-positive premalignant lesions have increased histologic progression -TD recognizes lesions with high-risk molecular patterns that correlate with outcomes -Predicts risk outcome for oral premalignant lesions with minimal or no dysplasia -Sensitivity Low (not in agreement with most findings) but high specificity -Selected high-risk lesions only, entering possible selection bias, but increasing standardized results. -Lacking ROC, Clear Sens, Spec.

<p>Onofre, MA et al., 2001</p> <p><i>Reliability of toluidine blue application in the detection of oral epithelial dysplasia and in situ and invasive squamous cell carcinomas.</i></p>	<ul style="list-style-type: none"> -50 patients, 56% male - Mean age 55 - 42-68 yrs old - Pts w potentially malignant epithelial lesions (PMELs) - Excluded biopsy refusal, abandonment, obvious invasive lesions or lesions w/o risk or suspicion of malignancy. - Excluded mechanical trauma. 	<p>1% toluidine blue dye 'standard'</p>	<p>YES</p>	<p>67.0</p>	<p>77.0</p>	<p>69.0</p>	<p>43.5</p>	<p>88.9</p>	<p>8B</p>	<ul style="list-style-type: none"> -TD staining is highly reliable for detecting in situ carcinoma because no false positives for these lesion types. -However TB is an adjunct and NOT a substitute for clinical judgement or biopsy. -Examiners should be experienced. Lacking ROC, not better than current standard.
<p>Epstein, et al. 2003</p> <p><i>The utility of toloum chloride rinse in the diagnosis of recurrent or secondary primary cancers in patients with prior upper aerodigestive tract cancer.</i></p>	<ul style="list-style-type: none"> - 620 patients - 80% male - 81 biopsied patients - 96 biopsy sites - Mean age 61.5 years - SCC in upper respiratory pathway, all suspicious lesions included - Excluded 30d past participation in a trial, Cancer Tx w/i 3mo, TC dye w/i 6 mo, pregnant or feeding, other preventive health problems 	<p>1% Toluidine Blue Dye (OraTest, Zila biomed.)</p>	<p>YES</p>	<p>90.9</p>	<p>96.7</p>	<p>92.7</p>	<p>82.8</p>	<p>98.3</p>	<p>9B</p>	<ul style="list-style-type: none"> - Tolonium chloride is a more sensitive technique than visual exam alone in detecting oral SCC and CIS in high risk patients with prior upper aerodigestive cancer. - Lacking ROC, not better than current gold standard.

Table 2 – Evidence for accuracy of Brush Biopsy as a diagnostic adjunct

EVIDENCE BASED TABLE – BRUSH BIOPSY												
Scheifele et al, 2004 <i>Journal of Oral oncology</i>	80 patients 47 males; 53yrs +-11y 33 females 64 yrs+-14y	Brush Biopsy Positive/ atypical	Yes	94.3	92.3	91.8	85.7	94.3	16	.08	9-B	Brush Biopsy meets basic criteria for diagnosis of clinically benign appearing oral lesions.
		Brush Biopsy/ Positive	Yes	97.1	61.5	87.5	88.9	87.2	21	.40	9-B	
Svirsky et al, 2002 <i>General Dentistry</i>	298 patients 151 female 146 male	Brush Biopsy Oral CDx	Yes	26.5	98.9	49.0	38.3	1.8	1.35	.04	8-B	Brush Biopsy indicated for O. lesions that lack suspicious clinical (cancerous) features.
Sciubba et al, 1999 <i>JADA</i>	945patients 502 female 443 male Age 18-83 Mean-55yr	Brush Biopsy OralCDx	Yes	92.9	100	95.0	87.9	100	14	0	8-B	Brush Biopsy can differentiate benign oral lesions from precancerous.

Table 3: Evidence for accuracy of Advanced Imaging as a diagnostic adjunct

EVIDENCE BASED TABLES - IMAGING												
<p>Araki et al, 1997</p> <p><i>CT of carcinoma of the upper gingiva and hard palate: correlation with the surgical and histological findings.</i></p>	<ul style="list-style-type: none"> - 27 patients (56% male) - 25-83 years old - Mean age 66 - SCC of upper palate - Excluded patients with tumours originating in maxillary sinus 	CT	Yes	89.0	64.0	75.0	85.3	71.2	14.9	.40	7-B	<p>CT was helpful for evaluation of tumor in the upper gingiva (soft tissue). Accuracy is fairly low and it is preferred that CT be used in combo with MRI or PET.</p>
<p>Ng et al., 2005</p> <p><i>F-FDG PET and CT/MRI in Oral Cavity SCC: A prospective study of 124 patients with histologic correlation</i></p>	<ul style="list-style-type: none"> 124 patients (98% male) - 26-82 years old - Mean age 40 yrs - SCC in a variety of sites: buccal mucosa, tongue. - Excluded patients with diabetes having fasting glucose >/= 200mg/mL 	PET	Yes	93.0	74.7	89.5	71.7	93.9	10.7	.27	9-B	<p>PET is superior to CT/MRI, but combined is better. Sensitivity is still not high enough to replace pathologic lymph node staging based on neck dissection. PET preferred over CT/MRI</p>
		CT and MRI	Yes	94.5	52.6	86.4	69.4	89.3	9.74	.50		
		combined	Yes	94.5	77.9	91.3	77.1	94.7	14.1	.23		
<p>Wiener et al, 2005</p> <p><i>Comparison of 16-</i></p>	<ul style="list-style-type: none"> -52 patients (35 M, 17 F) - 45-91 years old - mean age 63 yrs - SCC in various oral 	CT	Yes	95.5	71.4	92.3	71.2	95.5	15.8	.30	8-B	<p>MRI more accurate then CT for diagnosing primary SCC and tumour staging. Both methods not accurate to diagnose</p>

<i>slice MSCT and MRI in the assessment of SCC of the oral cavity.</i>	locations: alveolus, floor of mouth, hard palate, cheek mucosa	MRI	Yes	100	93.3	94.2	69.9	100	93.0	.07		lymph node metastasis MRI preferred over CT as first choice modality in primary SCC diagnosis
Yen TC, et al. 2005 <i>Staging of untreated SCC of buccal mucosa with 18F-FDG PET. Comparison with head and neck CT/MRI and histopathology.</i>	102 patients with buccal SCC - 97% male - Chang Gung memorial hospital, Taiwan	MRI/CT	YES	96.0	84.0	92.0	95.4	94.1	21	.17	9-B	PET is superior to CT/MRI in identifying cervical node metastases from buccal SCC. All 3 imaging techniques used in combo provides the highest accuracy.
PET + CT/MRI	YES	97.0	93.0	96.0	96.9	93.2	31	.07				

Table 4: Evidence for accuracy of Autofluorescence as a diagnostic adjunct

EVIDENCE BASED TABLES - AUTOFLUORESCENCE												
Betz et al, 2002	85 patients 34-82 years old (mean age 58.1)	AF	Yes	56.4	87.8	72.0	66.8	82.2	2.01	.22	7	- AF + PPIX distinguish between SCC and normal mucosa, delineate tumor margins
		AF + PPIX	Yes	51.3	100	76.0	67.2	100	2.05	0		
Zheng et.al, 2004	49 patients 23 men, 26 women range 31-85 years old (median age 60)	Ben/dys	Yes	96.0	92.0	94.0	96.0	92.0	23.0	.08	8	- 5-ALA induced PPIX- good differentiation between stages of SCC
		Ben/SCC	Yes	96.0	98.0	97.0	96.0	98.0	24.5	.02		
		SCC/dys	Yes	92.0	98.0	95.0	92.0	98.0	12.3	.02		
deVeld et al, 2004	155 patients 18-85 years old (mean age 50 years) 96 healthy volunteers 20-91 years old (mean age 57)	Healthy/lesion	Yes			81.0					7-B	- AF spectroscopy can differentiate between healthy/any lesion or specifically malignant lesion, not between benign/premalignant - No specificity reported, blinding not indicated
		Healthy/SCC	Yes			93.0						
		Ben/ premalig	Yes			65.0						
Wang et al, 2003	30 patients with oral submucous fibrosis, 39 with oral leukoplakia, 13 with SCC, 15 healthy All considered high-risk patients	Benign/premalig	Yes	81.0	96.0	82.0	88.0	93.0	20.0	0.2	8-B	- AF spectroscopy combined with PLS-ANN algorithm has high potential for diagnosis of premalignant/ malignant lesions. - Small sample size, homogeneous data set - Effect of moving cut-off pt not reported, small sample size