What about new ways of detecting potentially malignant lesions earlier?

Critical Evaluation of Diagnostic Aids for the Detection of Oral Cancer*

M Lingen, J Kalmar, T Karrison & P Speight

Oral Oncology 2008 Jan;44(1):10-22

University of Chicago, Ohio State University, University of Sheffield

* A position paper of the American Academy of Oral and Maxillofacial Pathology

True Positive and True Negative Requires a “GOLD STANDARD”

GOLD STANDARD for tissue diagnosis is a scalpel biopsy

Screening vs. Case-Finding

• Case-finding - a diagnostic test for a patient who has abnormal signs or symptoms (Class I)

• Screening - checking for a disease in a person who is symptom free (Class II)

Evidence of chemiluminescence enhancing intraoral examinations?

Let’s look at the scientific literature
Evidence of chemiluminescence enhancing intraoral examinations?

Literature was only for gynecological examinations until 2004

Strengths of this study

- Large sample size
- Consecutive patients
- One lesion detected by ViziLite (not stated what diagnosis was)

Weaknesses of this study

- Few cases with histologic correlation
- Can’t assess sensitivity, specificity or predictive value
- High false positives - suggests that sensitivity may be high but specificity and PPV are low

Evidence of chemiluminescence enhancing intraoral examinations?

“In our study we have examined only overtly obvious cases of oral cancer which do not require special screening tests for identification. In this respect, we have not been able to detect any case of early oral cancer (CIN) in normal-looking oral mucosa with this tool. The other shortcoming is the observed false positive rate of 6/31 lesions indicating the Vizilite® is non-specific and likely to result in many unnecessary biopsies”

S. Ram and C.H. Siar
Faculty of Dentistry
University of Malaya

Acetic Acid Wash and Chemiluminescent Illumination as an Adjunct to Conventional Oral Soft Tissue Examination for the Detection of Dysplasia: A Pilot Study

Huber MA, Bsoul SA, Terezhalmy GT
Quintessence International 2004: 35(5):378-84

- 150 consecutive patients
- Examined linea alba, leukoedema, hairy tongue, leukoplakia, traumatic ulcer, fibroma
- All 32 cases of leukoedema were positive (aceto-white) - False Positives
- 2 of 14 frictional keratoses were positive; No biopsies performed on “frictional keratoses”
- 3 Leukoplakias
- 1 biopsied = hyperkeratosis
- 2 brushed, 1 “atypical” biopsied = ulcer
- One lesion aceto-white lesion identified not clinically apparent

Chemiluminescence as a diagnostic aid in the detection of oral cancer and potentially malignant epithelial lesions

Ram, S. and Siar, C.H.
Int J Oral maxillofac Surg, 2005;34: 521-527

- Study was of already discovered lesions and 5 cases of normal oral mucosa
- Comparison to 1% toluidine blue mouth rinse
- Negatives were not biopsied
- High sensitivity, very low specificity (14.2% Vizilite® and 25% toluidine chloride)

This was not a study of efficacy for using Vizilite® as a screening method

The efficacy of oral lumenoscopy (ViziLite) in visualizing oral mucosal lesions.

Epstein JB, Gorsky M, Lonky S, Silverman S Jr, Epstein JD, Bride M.
Special Care Dentist 2006 Jul-Aug;26(4):171-4

College of Dentistry and Illinois Cancer Center, University of Illinois
All patients had history of previously-detected oral mucosal lesions - Not screening

2 occult lesions in separate patients with previous hx of squamous cell carcinoma - one recurrent Ca, one benign

The chemiluminescent light did not appear to improve visualization of red lesions, but white lesions and lesions that were both red and white showed enhanced brightness and sharpness.

Conclusion:
ViziLite examination did not significantly improve lesion detection compared to COE

Weakness:
Lack of standardized correlation of clinical findings to histopathologic diagnosis of lesional tissue

Clinical evaluation of chemiluminescent lighting: an adjunct for oral mucosal examinations

Kerr AR, Sirois DA, Epstein JB.

J Clin Dent
2006; 17(3):59-63

The Bluestone Center for Clinical Research, New York University College of Dentistry

Aim: Describe the utility of Vizilite® as an adjunct to visual examination, especially those lesions clinically suspicious for pre-cancer or cancer

501 patients with positive tobacco history

410 “suspicious” lesions in 270 patients by visual examination [suspicious for WHAT?]

127 lesions “suspicious” for oral cancer

98 were “aceto-white” + 6 not seen visually

77 (78.5%) were “suspicious” [what happened to 50 “suspicious” lesions?]

Results

Suggest that Vizilite®, when used as a screening adjunct provides additional visual information

“Leukoplakias” may be more readily observed

Only sharpness was significantly improved

Studies are underway to explore the clinical significance and predictive value of oral chemiluminescence lighting”

NO BIOPSIES WERE PERFORMED
THIS IS NO HELP WHATSOEVER - NO IDEA WHAT THE 6 LESIONS DETECTED BY VIZILITE WERE

A pilot case control study on the efficacy of acetic acid wash and chemiluminescent illumination (Vizilite™) in the visualisation of oral mucosal white lesions

Camile S. Farah, and Michael J. McCullough

Oral Oncology 2007 Sep;43(8):820-4

Department of Oral Medicine and Pathology, School of Dentistry, The University of Queensland, Brisbane QLD 4072, Australia

School of Dental Science, The University of Melbourne, Melbourne VIC 3000, Australia

Received 12 September 2006; revised 17 October 2006; accepted 18 October 2006; on-line pub. Dec. 2006
Strengths:
• All lesions were biopsied

Weaknesses:
• 2 diagnostic specialists performed all examinations
• Couldn’t directly compare clinical and histological findings for specific lesions

Aim: Assess efficacy in visualization of oral mucosal white lesions in a tertiary referral center
• 55 pts referred for existent white lesions [not screening]
• Vizilite® subjectively enhanced visualization in 26/55
• No significant difference in lesion SIZE, EASE OF VISIBILITY, OR BORDER DISTINCTIVENESS
• Could not distinguish between epithelial hyperplasia, dysplasia, carcinoma or inflammation
• All appeared “aceto-white”
• Did not change provisional diagnosis, nor alter biopsy site

Sensitivity 100%
Specificity 0%
Accuracy 18.2%

Sensitivity
\[ \frac{\# \text{ of true positive results}}{\# \text{ of those who have the disease}} \]

Specificity
\[ \frac{\# \text{ of true negative results}}{\# \text{ of those who are without the disease}} \]

Depends on a comparison to a “gold standard”

Positive Predictive Value
\[ \frac{\# \text{ of true positive results}}{\# \text{ of those who tested to have the disease}} \]

Negative Predictive Value
\[ \frac{\# \text{ of true negative results}}{\# \text{ of those who tested to be without the disease}} \]

Conclusions
( Farah and McCullough)
• Vizilite® does not aid in identification of malignant and potentially malignant oral lesions
• Does not discriminate between keratosis, inflammation, malignant or potentially malignant lesions
• Little if any benefit for lesions already detected
• High index of suspicion, expert clinical judgement and scalpel biopsy is still essential for proper patient care
Efficacy of the ViziLite System in the Identification of Oral Lesions

Oh, ES and Laskin, DM


School of Dentistry, University of North Carolina, Chapel Hill, NC

100 patients
39 males
61 females

Oral exam with incandescent light - 29 clinically undiagnosable lesions
Oral exam with acetic acid rinse - 3 additional clinically undiagnosable lesions
Oral exam with ViziLite - no additional clinically undiagnosable lesions

32 clinically undiagnosable lesions were examined with Oral CDx
2 were “atypical” and were biopsied
Neither was premalignant or malignant

Conclusions: “Although the acid rinse accentuated some lesions, the overall detection rate was not significantly improved. The chemiluminescent light produced reflections that made visualization more difficult and thus was not beneficial.”

32 clinically undiagnosable lesions were examined with Oral CDx
2 were “atypical” and were biopsied
Neither was premalignant or malignant

Conclusions: “Although the acid rinse accentuated some lesions, the overall detection rate was not significantly improved. The chemiluminescent light produced reflections that made visualization more difficult and thus was not beneficial.”

Vizilite® My opinion at this time

• Extra time and care using the system ARE VALUABLE
• Evidence of aiding detection of premalignant lesions is quite sparse
• Unclear what added benefit there is to practitioner
• Cannot discriminate indolent lesions from biologically worrisome

Vizilite® My opinion at this time

Not worth charging the patient extra money over a standard visual and tactile exam

• Vizilite® is NOT approved by the ADA Council on Scientific Affairs
• If you do the Vizilite® exam, how would you justify charging your patient based on peer reviewed evidence?

• Well-controlled clinical trials are needed that specifically investigate the ability of Vizilite® to detect precancerous lesions that are invisible by COE alone. Studies needed for combined Vizilite® and toluidine blue dye.
• If such discrimination can be confirmed, it would support the use of this technology as a true screening device
VELscope®
A Magic Wand for the Community Dental Office?
Observations from the British Columbia Oral Cancer Prevention Program
Laronde D, Poh C, Williams P, Hislop T, Zhang L, MacAskill C, and Rosin M.
J Canadian Dent Assoc Sept 2007 (73)7; 607-609
• Loss of fluorescence occurs in many benign mucosal conditions, such as geographic tongue, aphthous ulcers (sic) and tissue trauma.
• Training in communication skills directed at reducing patient anxiety related to abnormal screening result is also important.

VELscope®
• The use of the device encouraged greater attention to oral cancer screening in their practices, leading to the identification of lesions that may have been otherwise overlooked.

Conclusions
• FV has the potential to be an adjunctive screening tool that facilitates the discrimination of soft tissue changes requiring follow-up.
• It will not replace conventional clinical examination.
• Although evidence supports its use in high-risk clinics, its value in general practice remains to be determined.
• No current evidence that using FV in general dental practice saves lives, but regular use of a high quality screening examination could make a difference.

VELscope®
Evidence-Based Decision-Making: Should the General Dentist Adopt the Use of the VELscope for Routine Screening for Oral Cancer?
Balevi B
J Canadian Dent Assoc Sept 2007 (73)7; 603-606
• 4 clinical papers reviewed and critically appraised, 2 case studies, 2 observational studies
• All studies included patients seen in referral clinics that are specialized in the diagnosis and management of oral pathology
• Risk of test-referral bias

VELscope®
• 2 case studies demonstrated potential benefit during follow-up of already diagnosed (high-risk) patients to check for new lesions
• 2 observational studies may be giving an artificially high true-positive rate (sensitivity) and true-negative rate (specificity) because of “spectrum bias”
• No evidence this device can distinguish between oral cancer and aphthous ulcers (sic), lichen planus, pemphigoid, etc.
• No long-term evidence that this device actually saves lives
• It is important to consider the potential risk of harm from a false-positive reading
• No assessment of inter-observer and intra-observer agreement

VELscope®
Shortcomings
• Currently, neither the scientific evidence nor the level of clinical skill justifies the routine use of the VELscope in a general dental practice
• The device is more likely to detect the more common abnormal oral tissue lesions than oral cancer
• No intra- and inter-operator agreement has been verified

VELscope®
Conclusions
• No evidence that routine use saves lives
• Concern about the risk of harm if routinely used
• Routine use is premature
• VELscope may be of value in a clinic that is specialized in management of oral cancer
VELscope®

My opinion at this time

• Best use is in determining margins for excisions of premalignant lesions
• Could be useful in screening if shortcomings cited in the article can be corrected

Cell-based sensor for analysis of EGFR biomarker expression in oral cancer

Shannon E. Weigum, Pierre N. Floriano, Nicolaos Christodoulides and John T. McDevitt
Lab Chip, 2007, 7, 995 - 1003

A cell-based sensor to detect oral cancer biomarkers, such as the epidermal growth factor receptor (EGFR) whose over-expression is associated with early oral tumorigenesis and aggressive cancer phenotypes.

The lab-on-a-chip (LOC) sensor utilizes an embedded track-etched membrane, which functions as a micro-sieve, to capture and enrich cells from complex biological fluids or biopsy suspensions.

• Immunofluorescent assays reveal the presence and isotype of interrogated cells via automated microscopy and fluorescent image analysis.
• Using the LOC sensor system, with integrated capture and staining technique, EGFR assays were completed in less than 10 minutes with staining intensity, homogeneity, and cellular localization patterns comparable to conventional labeling methods.

• These results support the LOC sensor system as a suitable platform for rapid detection of oral cancer biomarkers and characterization of EGFR over-expression in oral malignancies. Application of this technique may be clinically useful in cancer diagnostics for early detection, prognostic evaluation, and therapeutic selection

Examples of what you can do with the LOC

• Real-time PCR; detect bacteria, viruses and cancers.
• Immunosassay; detect bacteria, viruses and cancers based on antigen-antibody reactions.
• Dielectrophoresis detecting cancer cells and bacteria.
• Blood sample preparation; can crack cells to extract DNA.
• Cellular lab-on-a-chip for single-cell analysis.
• Ion channel screening

Salivary diagnostics for oral cancer

David T. Wong
J Calif Dent Assoc. 2006 Apr;34(4):303-8

• Two salivary proteins, interleukin (IL)-8 and thioredoxin, that can discriminate between saliva of oral cancer and control subjects.
• IL-8 is significantly elevated in saliva of oral cancer patients and is highly discriminatory of detecting oral cancer in saliva (n = 64) with a receiver operator characteristic (ROC) value of 0.95, sensitivity 86% and specificity 97%.
• Other results suggested that saliva thioredoxin is a validated biomarker for oral cancer detection
Biopsy versus other methods of analyzing oral tissues

The Brush Test® is a “case-finding” test, not a “screening test”

Brush Test®
exfoliative cytology

**PROS**
- No anesthesia
- Patient acceptance

**CONS**
- Negative results are not biopsied
- No research on negatives
- Negative results were not tested against the “gold standard”

Brush Test®
exfoliative cytology

**PROS**
- No anesthesia
- Patient acceptance

**CONS (continued)**
- Extremely high number of false positives
**Brush Test® exfoliative cytology**

**PROS**
- No anesthesia
- Patient acceptance

**CONS**
- No ability to detect dysplasia by architecture
- No baseline histology if future biopsies are done

(continued)

**Brush Test® exfoliative cytology**

ADA Council on Scientific Affairs

All Oral CDx “atypical” or “positive” results must be confirmed by incisional biopsy and histology to completely characterize the lesion.

**Brush Test® exfoliative cytology**

ADA Council on Scientific Affairs

Persistent lesions, even with negative results, must receive adequate follow-up evaluations.

**Brush Test® exfoliative cytology**

ADA Council on Scientific Affairs

Persistent lesions, even with negative results, must receive adequate follow-up evaluations.

**Brush Test® exfoliative cytology**

ADA Council on Scientific Affairs

Persistent lesions, even with negative results, must receive adequate follow-up evaluations.

**Brush Test® exfoliative cytology**

ADA Council on Scientific Affairs

Shows promise

Study needed with a large cohort of Class II subjects with brush and biopsy of ALL subjects

Brush Test® may be beneficial:
1. Multiple lesions, particularly in someone with no history of oral cancer
2. Non-compliant patient who is unlikely to come back for a follow-up exam or accept an immediate biopsy

Judicious use in these scenarios may be clinically useful