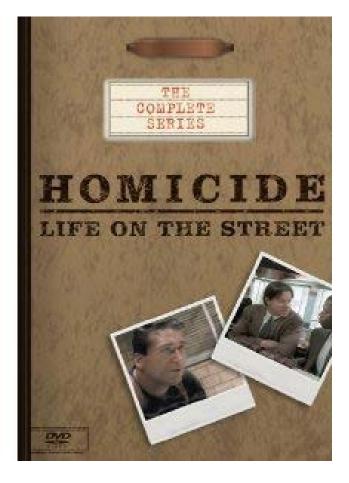
Oral Cancer Screening

Donita Dyalram DDS, MD Assistant Professor Associate Program Director Maxillofacial Oncology/Microvascular Surgery Department of Oral Maxillofacial Surgery University of Maryland



THE FINAL SEASON

JANUARY 6, 9 PM









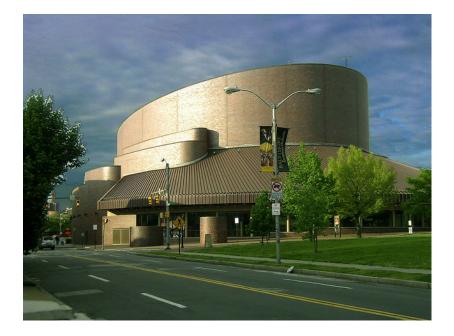
TownMapsUSA.com







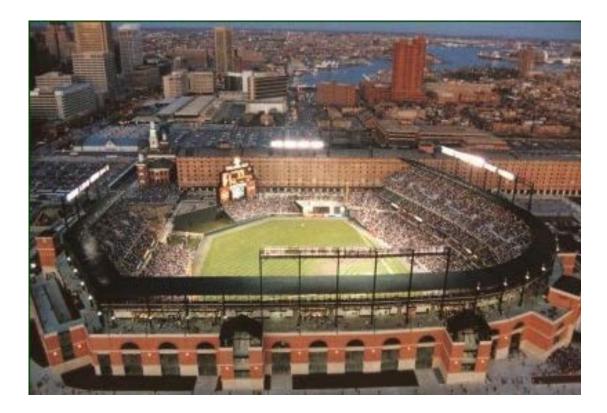














Cal Ripken Jr. Iron Man; 2,131











FIRST DENTAL COLLEGE

BALTIMORE COLLEGE OF DENTAL SURGERY, FIRST DENTAL COLLEGE IN THE WORLD. CHARTERED BY THE GENERAL ASSEMBLY OF MARYLAND MARCH & 1840. FOUNDERS WERE HORACE H HAYDEN. M.D. D.S. AND CHAPIN A HARRIS, M.D. D.S. S. THE ASSEMBLY STIPULATED BY ACT OF CONSOLIDATION APRIL 9. 1924. THAT THE NAME OF THE COLLEGE SHALL BE PRESERVED AS A DEFINITE DEPARTMENT OF THE UNIVERSITY OF MARYLAND' THE NAME ADOPTED BALTIMORE COLLEGE OF DENTAL SURGERY. DENTAL SCHOOL UNIVERSITY OF MARYLAND' TABLET IN HOPKINS PLAZA. SIX BLOCKS EAST. MARKS ORIGINAL SITE OF THE COLLEGE.













Thank you to Dr. Robert Ord

Lecture Goals

- How to conduct a head and neck exam
- Pre-Malignant Lesions
- Risk of transformation of pre-malignant lesions
- Management of Pre-malignant lesions
- Use of Adjunctive techniques in detecting high risk lesions of the oral cavity
 - Toludine Blue
 - Lugol's Iodine
 - Chemiluminesence
 - Oral CDX

- Worldwide: 640, 000 new cases each year
- US: 41,380 new cases each year (oral cavity and pharynx)
- Maryland: Approximately 650 new cases each year
- Deaths: 7,890 (oral cavity and pharynx)
- Approximately 50% of will survive 5 years

• National Cancer Institute, 2013

 "Historically the death rate associated with this cancer is particularly high not because it is hard to discover or diagnose, but due to the cancer being routinely discovered late in its development."

- This holds true today
- Oral Cancer Foundation

 It is estimated that approximately \$3.2 billion is spent in the United States each year on treatment of head and neck cancers.

Head and Neck Exam



















Premalignant Lesions

► Leukoplakia

► Erythroplakia

► Lichen Planus

- Most common precancer, represents 85% of all precancers
- Increases with age, 8% of men>70 years and 2% of women >70 years
- Prevalence in men increases 10 fold from the 4th to 7th decade
- Commonest sites include buccal mucosa, alveolar mucosa and lower lip

► Malignant transformation 1% - 17%

► Average 3% - 6%

• Author Cases F.U. % Cancer • Pindborg 1968 248 3.9 4.4% • Silverman 1968 117 1-11 6.0% 1970 **187** • Kramer 4.8% Bánóczy 1977 670 6.0% 9.8 • Silverman 1984 257 17.5% 7.2 Lind 1987 **157** 9.3 8.9% \bullet • Schepman 1998 166 12.0% 2.5

Risk Factors for Transformation of Leukoplakia

- Multiple genetic alterations dictate the frequency and pace of progression to cancer.
- Genetic progression does NOT imply a uniform orderly progression through various stages of histologic progression
- Earliest alterations target genes on chromosomes 3p, 9p21, and 17p13 and LOH at 9p21 may precede histologic evidence of dysplasia

Risk Factors for Transformation of Leukoplakia

- Systematic review of biomarkers in oral dysplasia, identified 2550 studies, 288 scrutinized, 247 excluded due to cross sectional design, 28 excluded poor f.u. so data extracted from 13 longitudinal studies.
 - Identified four biomarkers:-
 - LOH 3p+/-9p, survivin, MMP9 and DNA content significantly increase the risk for malignant progression.

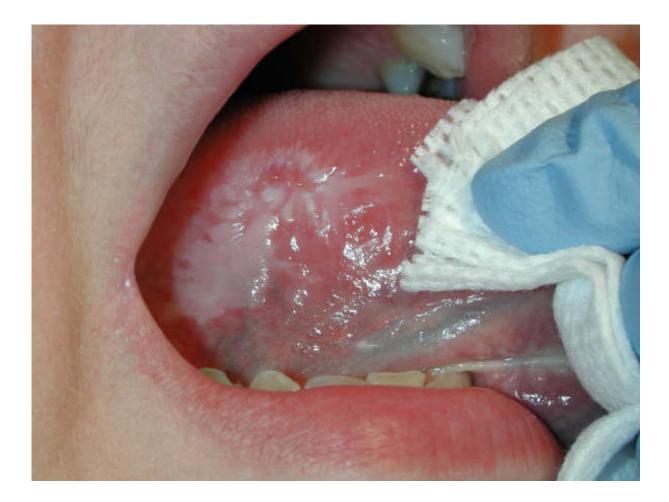
Smith J et al Oral Oncol 2009

Risk Factors for Recurrence of Leukoplakia

- ► Use of Cell Cycle Analysis with Cyclin A, B1 and Ki67
- ► 40 patients, moderate severe dysplasia
- Significant progression risk with values exceeding the median was
 - p 0.02 Cyclin A
 - p 0.01 Cyclin B1 and
 - p 0.025 Ki67

Thompson et al BJOMS 2008

Risk Factors for Transformation of Leukoplakia



Risk Factors for Transformation of Leukoplakia

- ► Female patients
- ► Site
- ► Appearance
- ► Dysplasia
- ► Candida
- ► Syphilis
- Habits (Non Smokers)

Sublingual Keratosis

Approximately 50% malignant change Kramer et al

• B.D.J. 1978

Site Dysplasia/Carcinoma

- Floor of mouth 43%
- Lateral Tongue 24%
- Lower Lip

24%

Waldron/Shafer Cancer 1975







Speckled Leukoplakia

► Mixed red and white lesion

Malignant potential 44% and a dysplasia rate of 51%

Pindborg et al 1963





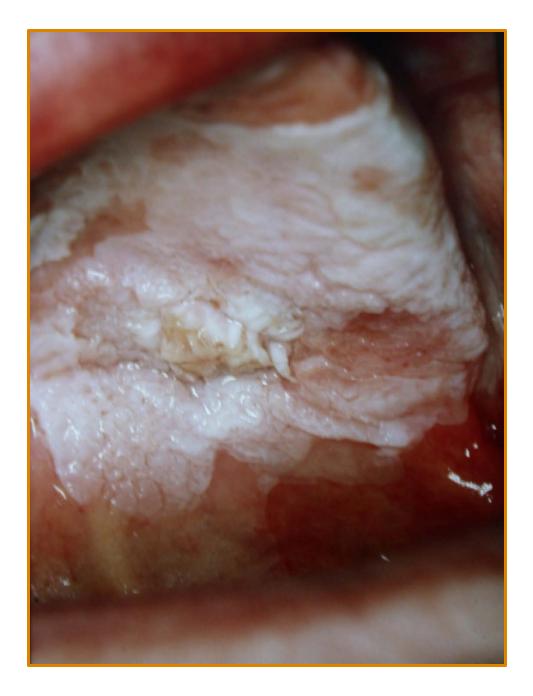


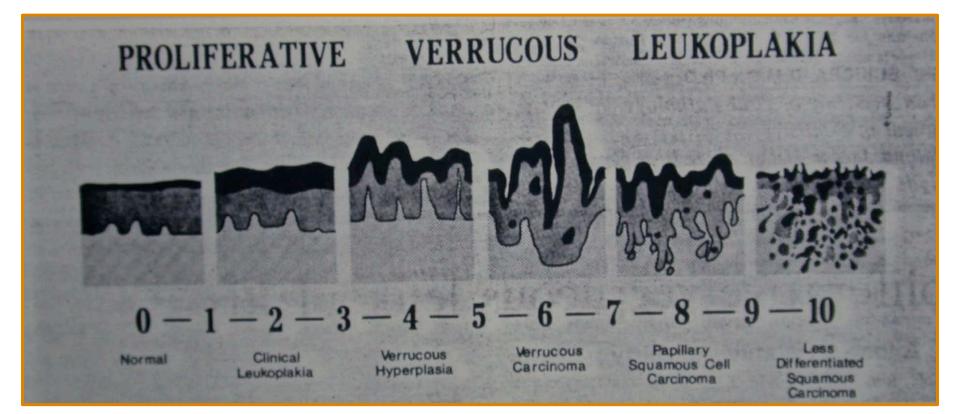
Proliferative Verrucous Leukoplakia

- ► 30 cases
- ► 9 changed to Verroucous Carcinoma
- ► 12 changed to Papillary Carcinoma
- ► 5 changed to Squamous Carcinoma

Hansen et al. 1985











Oral Epithelial Dysplasia (OED)

- 3256 cases of oral leukoplakia showed 19.9% with some degree of dysplasia.
- Within the dysplasia subgroup:
 - 3.1% of patients had squamous cell carcinoma,
 - 4.6% had severe dysplasia/CIS, and
 - 12% were mild to moderate dysplasia.

Waldron and Schaffer 1975

Oral Epithelial Dysplasia (OED)

- 240 pts. (f.u. up to 20 yrs) 33 (13.8%) Carcinomas
- Excision of OED 65 pts.

53 (81.6%) Cured 4 (6.2%) Carcinomas

No treatment OED 91 pts.
 16 (17.6%) Improved
 14 (15.4%) Carcinomas

Lumerman et al. Oral Surg. Oral Med. Oral Path. 1995



Oral Epithelial Dysplasia (OED)

Architecture

- Irregular epithelial stratification
- Loss of basal cell polarity
- Drop shaped rete pegs
- Increased number mitotic figures
- Abnormally superficial mitoses
- Premature keratinization in single cells (dyskeratosis)
- ► Keratin pearls within rete pegs

Cytology

- Abnormal variation in nuclear size (anisonucleosis)
- :- in nuclear shape (nuclear pleomorphism)
- :- in cell size (anisocytosis)
- :-in cell shape (cellular pleomorphism)
- > nuclear-cytoplasmic ratio
- ► > nuclear size
- Atypical mitotic figures
- > number and size of nucleoli

Inter-examiner reliability in diagnosing of oral epithelial dysplasia

- ► Exact Agreement with 50.5%
- ► Within one Histologic Grade 90.4%
- ► Dysplasia vs. Non dysplasia 81.5%

Abbey et al Oral Surg. Oral Med. Oral Path. 1995

Habits

Stomatitis NicotinaSmoking / Alcohol

- Benign
- Increased risk OED

Morse et al, Cancer Epid., Bio., Preven. 1996

Pipe Smoking



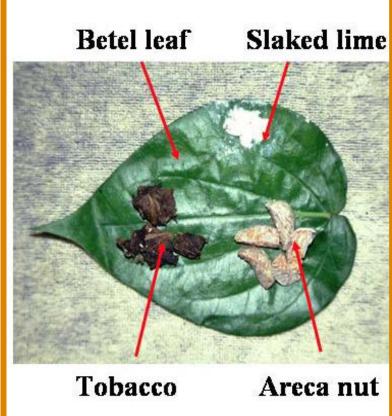


Smokeless Tobacco









Oral Sub-mucous Fibrosis

- Epithelial atrophy
- ► Keratosis and
- ► Dysplasia in up to 25% of cases

► 7% change to SCC over 17 years.

Murti PR et al 1985.

Management of Leukoplakia

- History & Examination
- ► CBC / Candida Scrape
- Photograph / Diagram
- Biopsy (Toluidene Blue/Lugols Iodine)
- ►Laser
- ► Cryotherapy
- ► Topical FU
- ► Surgery
- Medical Therapy

Management of Leukoplakia

- Surgery:- recurrences 15-35% (margins, salivary ducts, widespread lesions)
- CO² Laser:- recurrence 7-38% and malignant transformation 1-2%. Excision on non-keratinized mucosa and ablation on keratinized (post biopsy)

Redi and Shafer 2006

Management of Leukoplakia

- Can we prevent malignancy by treating premalignant lesions??
- 11-14% of mild dysplasias surgically or non-surgically treated develop carcinoma and 11% of lesions with no dysplasia.
- 20% of patients with non-homogenous leukoplakia develop SCC post-surgery which is more than those without surgery.
- Does surgical removal increase the risk of cancer? Holmstrup et al Oral Oncol 2006 Holmstrup Oral Oncol 2009

 "A fiery red patch that cannot be characterized clinically or pathologically as any other defined lesion."

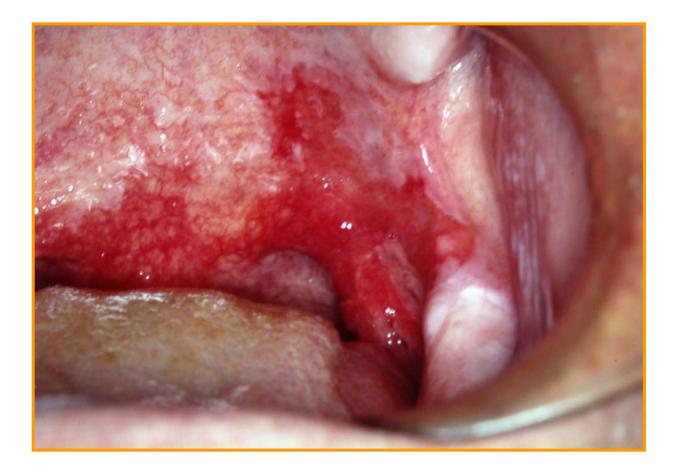
Pindborg et al 1997

- Incidence:
- 9 cases of 50,915 (0.02%) Mehta et al 1971
- 58 cases of 64,345 (0.09%) Shafer/Waldron 1975

▶91% show Severe Dysplasia, CIS or Invasive Carcinoma

Floor of mouth 49%
Soft palate / Ant-Pillar / RMF 31%
Lateral tongue 17%







Lichen Planus vs. Lichenoid Dysplasia



Clinical Controversies in Oral & Maxillofacial Surgery

- ► Oral Lichen Planus:
 - A benign lesion

Eisenberg,E.

- ► Oral Lichen Planus:
 - A potentially premalignant lesion

Silverman, S.

JOMS 58(11) 2000

- 223 Published cases of malignant transformation of OLP
- Only 15 of 223 sufficiently documented
- Lack of risk factor history, lack of biopsy of OLP, site remote from OLP, etc.

Krurchkoff et al. J. Oral Pathol 1978

 Meta-analysis of the literature of 28 studies confirmed transformation in 10 of 28 (34%)

 However, they identified salient documentation deficiencies similar to Krutchkoff et al which weakened the credibility of many of the follow up studies

van der Meij et al 1999

	Author	Patie	nts	F.U	Transformation
	Silverman et al	1991	214	10 years	5 (2.1%)
D	Barnard et al	1993	241	10 years	8 (3.3%)
D	Silverman/Bahl	1997	95	6.1 years	3 (3.2%)
	Garcia-Pola et a	al 1999	210	1-10 years	4 (1.9%)

- 723 patients with oral Lichen Planus (biopsy proven)
- 75% Female: 25% Male
- Oral cancer: 6 patients 0.8%
- All Cancers: erosive / erythematous
 Eisen, D. J. Am. Acad Dermatol 2002

Adjunctive Techniques





Adjunctive Techniques

► Toluidene Blue Staining

► Lugol's Iodine

Oral CDX Brush Biopsy

► Chemiluminescence



- Toluidine Blue
- Topical Application
- False positive 5.7%
- False negative 2.5%

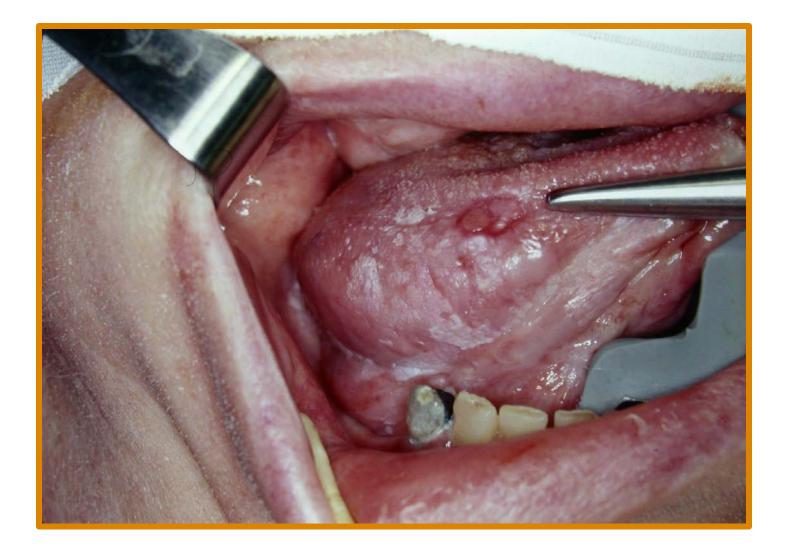
Mashberg A. JADA 1983

Toluidine Blue

Rinse Mouth20 secondsRinse Mouth20 seconds1% acetic acid1% acetic acidDry w/ gauze gently2 minutesSwab area with Toluidene Blue2 minutesRinse Mouth1 minute1% acetic acid1% acetic acid

Toluidine Blue Stain







Toluidine Blue

- Systematic review of 77 studies only 14 evaluated the ability to detect occult SCC
- ► No randomized controlled trials
- ► None conducted in a primary care setting
- Most were case series by specialists on high risk patients
- ► Overall Sensitivity 78-100%, Specificity 31-100%



Lugol's Iodine

- Cells in the intermediate and superficial layers of oral mucosa contain glycogen.
- These cells take up iodine and stain mahogony brown
- Dysplastic cells and carcinoma do not stain with Lugol's iodine

Lugol's lodine

- Standard 1cm margin resection of oral cancer 32% dysplasia/CIS/carcinoma at the margin
- ► In the Lugol's iodine group 4%

McMahon et al Brit J OMFS 2010

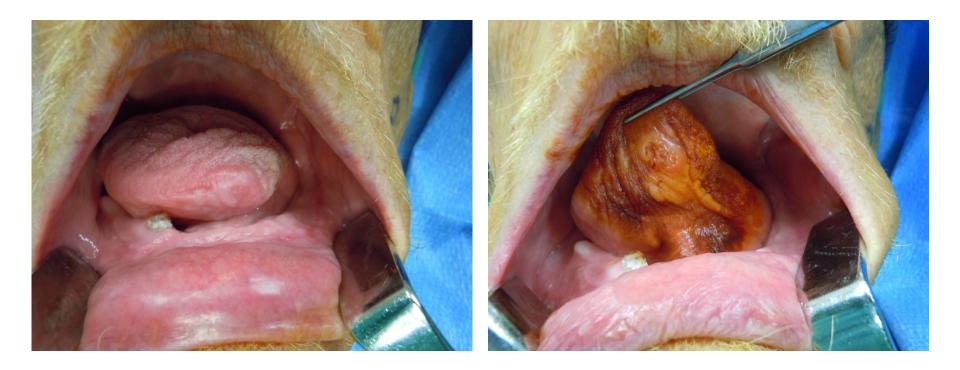


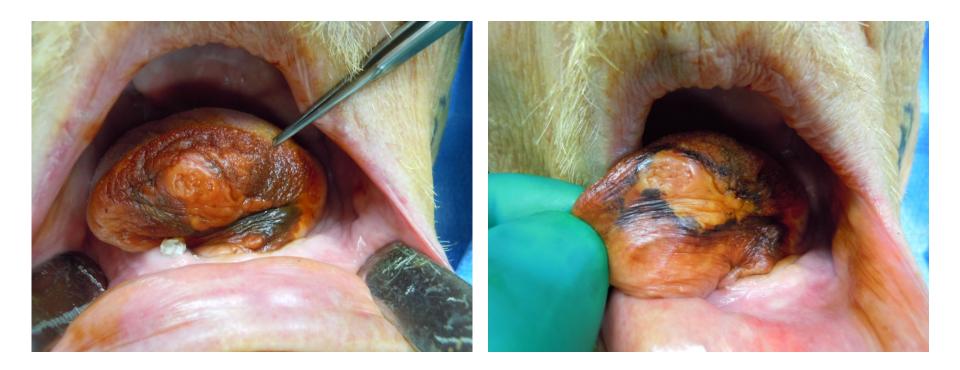


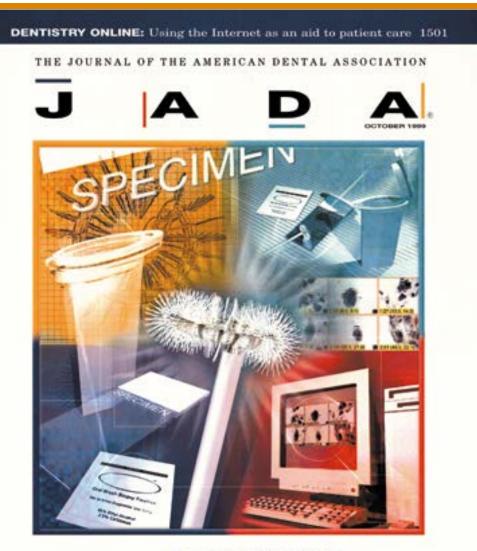












DETECTING ORAL CANCER Computer-assisted analysis of oral brush biopsy 1445

AMALGAM vs. RESIN-MODIFIED GLASS IONOMER CEMENT Comparing their effectiveness in Class II restorations 1459

NIGHTGUARD VITAL BLEACHING Assessing dentin color changes 1485

OralCDx Testing

<u>Three Components</u>

- Optimal Sample Oral Brush Biopsy
- Optimal Search Computer-assisted inspection specifically designed for the oral mucosa
- Optimal Interpretation Laboratory exclusively engaged in and specialty trained in computerassisted oral brush biopsy analysis

OralCDx MULTICENTER U.S. TRIAL

- Participants: Oral Medicine, Oral Pathology and Oral Surgery Departments at 35 major U.S. Academic Dental Centers
- ► 945 patients enrolled
- Cover story in <u>Journal of the American Dental</u> <u>Association (JADA)</u> October, 1999

U.S. Multicenter Clinical Trial - Sensitivity Data

- If an oral lesion would be found to be precancerous or cancerous using scalpel biopsy and histology, would it also be detected using OralCDx?
- OralCDx <u>correctly detected every lesion</u> diagnosed as precancer or cancer using scalpel biopsy and histology (n=131)
- ► Measured False Negative Rate = 0%
- ► Statistical Sensitivity > 96% p<.05

U.S. Multicenter Clinical Trial -Specificity Data

- What is the probability that a histologically benign lesion will not have an abnormal OralCDx result?
- ► 100% (196/196) for "positive" CDx results
- ► 92.9% (182/196) for "atypical" CDx results
- ► Statistical Specificity for "positive" > 97%, p < .05
- ► Statistical Specificity for "atypical" > 90%, p < .05

Summary of OralCDx

- Overcomes the obstacles that have impeded early oral cancer detection
 - the limitations of the oral cavity examination: no more guessing about which lesions require surgical biopsy
 - the tendency to delay referral of patients for scalpel biopsies: all abnormal CDx results require scalpel biopsy
 - the hesitation of patients to comply with follow-up surgical biopsy: patient compliance extremely high after abnormal CDx result

Summary of OralCDx

- Many more dentists are carefully screening their patients and testing lesions that would have been overlooked in the past
- The accuracy of CDx, as established in the multicenter clinical trial, has now been corroborated by experience with many thousands of patients from general practice settings
- As of 2/2004, 4500 dysplasias and carcinomas were detected by brush biopsy

Scheifele et al. Oral Oncology 2004

► 103 patients Oral CDX compared to biopsy

- ► Sensitivity 92.3%, Specificity 94.3%
- Major limitations were sampling bias
- Conclusions Figures agree with previously published data and support the use of OralCDX as a screening tool of oral lesions

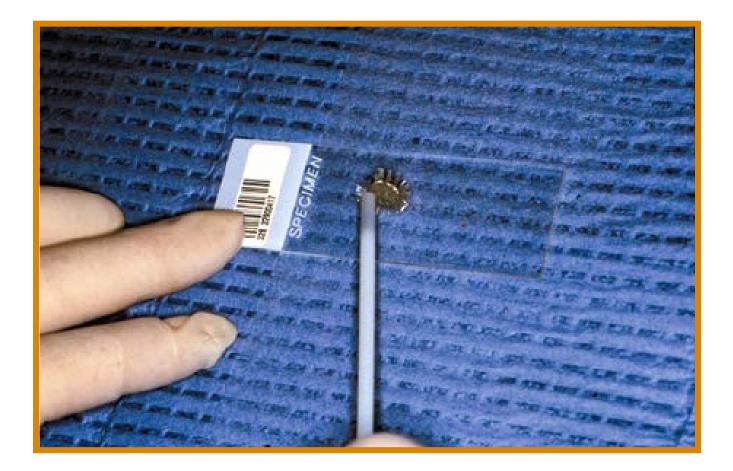
The Brush Biopsy Technique

- Topical or local anesthesia is not required minimal or no pain
- Tear open the fixative package prior to performing the brush biopsy
- Slightly moisten the biopsy brush with water or the patient's saliva if the lesion is dry

The Brush Biopsy Technique

- The flat surface or cylindrical edge of the biopsy brush is placed against the surface of the lesion
- Apply firm pressure against the surface of the lesion while rotating 10 times or more
- Pink tissue or microbleeding indicates that the brush has penetrated to the desired depth, the basement membrane





Slide Preparation Procedure

- Fold the fixative pack in half and squeeze the <u>entire</u> contents onto the glass slide, saturating all cellular material with the fixative
- After 15 to 20 minutes, the alcohol component of the fixative will evaporate, and the slide will be ready for shipment

OralCDx Brush Biopsy A Fail-Safe Procedure

- OralScan Laboratories automatically confirms the adequacy of each brush biopsy specimen and determines if cells from all three layers of the epithelium have been sampled
- Inadequate specimens, which most commonly result from either insufficient pressure or too few rotations of the brush, should be repeated - lab analysis repeated at no charge

The OralCDx Computer

- Neural network-assisted inspection specifically designed to detect oral epithelial precancerous
- and cancerous cells
- Originally developed for missile defense
 Image analysis process is performed utilizing a specially designed and trained image processor
- Every brush biopsy specimen is analyzed for:
 - Abnormal cellular morphology
 - Signature spectral abnormality of the keratin protein
 - Cytometric evaluation of nuclear DNA content

OralCDx Results

Classification

- "negative": no cellular abnormalities
- Abnormal Results:
- "positive": definitive cellular evidence of epithelial dysplasia or carcinoma
- "atypical": abnormal epithelial changes warranting further investigation



Oral Brush Biopsy OralCDx[®] Test Report

Confidential Patient Information If you received this transmission in error please contact OralScan Laboratories Toll Free 877-672-5722

>) -(020414A

Dr.
Biopsy Date:
Rcv Date:
Phone:
Fax:
PN:

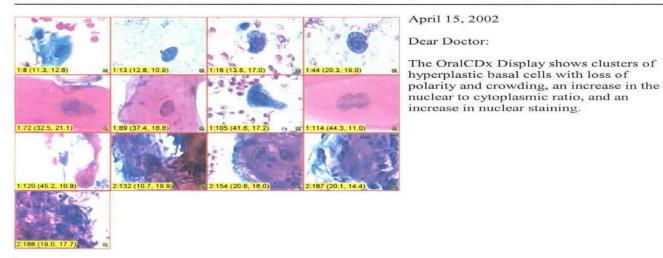
Patient: Sex: DOB: SS#: Lesion Site: Lateral Tongue Case:

Microscopic Description: Mild atypia

Cellular Representation: Superficial, intermediate, and basal cells

OralCDx Result:

Atypical epithelial cells-warranting further investigation



If this report is a fax, then the original report with color images will be forwarded.

Sincerely,

Dr. Matthew Klein Cytopathologist (Electronically Signed)

ORALSCAN LABORATORIES, INC. 2 EXECUTIVE BLVD. SUFFERN, NY 10901 PHONE 845-369-7096 FAX 845-369-7082 LABORATORY DIRECTOR DR. STEPHEN FRIST CLIA# 33D0952202

The Brush Biopsy in Practice

- JADA Study: March, 2002
- ► 930 dentists and dental hygienists were examined
- ► 10% had a benign appearing oral lesion
- ► All lesions brush biopsied
- ► 3 lesions proven precancerous

40 new/recall patients in your practice = 4 lesions per week



The OralCDx[®] Computer-assisted, Oral Brush Biopsy Analysis Method is accepted as an effective adjunct to the oral cavity examination in the early detection of precancerous and cancerous oral lesions. All OralCDx[®] "atypical" and "positive" results must be confirmed by incisional biopsy and histology to completely characterize the lesion. Persistent lesions, even with negative results, must receive adequate follow-up evaluations.

Council on Scientific Affairs, American Dental Association

What to Expect in Your Practice

	Known benign entities	Harmless appearing, white or red spots of unknown origin	Highly suspicious lesions
Presentation			
Frequency in average dental practice	Several times each day	About twice a week	Once or twice each year
Action	Observe or treat	Brush biopsy	Scalpel biopsy

Data Against Oral CDX

- 298 cases OralCDX, 4 false negatives, and 150 false positives. Svirsky et al. Gen Dent 2002
- 100 cases 84% false positives, specificity 3.4%. Rick G. M. letter Oral Surg, Oral Med, Oral Pathol 2003
- 115 cases 3.5% false negatives (mean delay to scalpel biopsy 117 days) Potter et al JOral Maxillofacial Surg 2003

Potate et al Oral Oncol. 2004

- ► 112 patients Oral Medicine Clinic
- Sensitivity dysplasia/CA 71.4%
- ► Specificity 32%
- ▶ PPV 44.1%, NPV 60%
- Conclusion Not all potentially malignant disease is detected with this non-invasive procedure

CDX Brush Biopsy

142 scalpel biopsies from atypical (149) and positive (3) brush biopsies

PPV only 7.9% overall, False positives as high as 92.1%

Bhoopathi et al Cancer 2009

CDX Brush Biopsy

Oral Cytology Revisited. In order to improve validity of brush biopsy combine it with other techniques DNA analysis, immuno-cytochemical and molecular analysis can improve sensitivity up to 100%

Mehrotra et al J Oral Pathol Med 2009

CDX Brush Biopsy

- Prospective blinded study 186 brush biopsies
- Sensitivity for OSCC 88.5% and high risk lesions 86.4%
- OSCC <20mm sensitivity 78% so less reliable for small lesions

Koch et al Clin Oral Investig 2010





Chemiluminescence

- ► 410 lesions (270 patients >40yrs. + tobacco)
- ► 127 clinically suspicious, 98 CL+
- ► 77 of 98 CL+ (78.5%) clinically suspicious
- ► 6 CL+ not clinically seen
- Leukoplakias more likely to be CL+ than erythroplakias (p<0.01)</p>

Kerr et al J Clin Dent 2006

Chemiluminescence

▶46 lesions, 14 OSCC, 26 premalignant lesions, 6 benign, 5 normal mucosa.

 Vizilite Tolonium Chloride (Rinse)

- Sensitivity 100% 70.3%
- Specificity 14.2% 25.0%
- Accuracy 80.6% 64.5%
- 15 lesions and 5 normals **No Biopsy**

Ram and Siar Int J Oral Mxafac Surg 2005

Chemiluminescence

- 134 patients. Vizilite did not improve detection over COE. Epstein et al Spec Care Dent 2006.
- 100 consecutive cases, incandescent light, rinse with 1% acetic acid and Vizilite. Vizilite provided no additional benefit made exam more difficult. Oh and Laskin JOMS 2007.

Head Neck. 2012 Jun;34(6):856-62. doi: 10.1002/hed.21834. Epub 2011 Aug 4.

Efficacy of tissue autofluorescence imaging (VELScope) in the visualization of oral mucosal lesions.

Farah CS, McIntosh L, Georgiou A, McCullough MJ.

The University of Queensland, School of Dentistry and University of Queensland Centre for Clinical Research, Brisbane, Herston, Queensland 4029, Australia. c.farah@uq.edu.au

Abstract

BACKGROUND: Technology that highlights potentially malignant oral lesions in a highly sensitive and specific manner will aid clinicians in early diagnosis of these conditions. This study assessed the efficacy of direct tissue autofluorescence imaging Visually Enhanced Lesion Scope (VELScope) in the detection of oral mucosal lesions.

METHODS: One hundred twelve patients referred with a potentially malignant oral mucosal lesion were examined under routine incandescent light, and then with VELScope, noting loss of autofluorescence and presence of blanching. Incisional biopsies were performed to provide definitive histopathological diagnoses.

RESULTS: VELScope enhanced the visibility of 41 lesions and helped uncover 5 clinically undetected lesions. VELScope examination alone showed a sensitivity of 30% and a specificity of 63%. Its accuracy at identifying dysplasia was 55%.

CONCLUSION: VELScope examination cannot provide a definitive diagnosis regarding the presence of epithelial dysplasia. Loss of autofluorescence is not useful in diagnosing epithelial dysplasia in its own right without relevant clinical interpretation.

The role of direct visual fluorescent examination (VELscope) in routine screening for potentially malignant oral mucosal lesions

Kristin K. McNamara, DDS, MS,^a Brent D. Martin, DMD,^b Erik W. Evans, DDS, MD,^c and John R. Kalmar, DMD, PhD,^d Columbus and Cincinnati, Ohio The Ohio State University and University Of Cincinnati Health Center

Objective. Direct visual fluorescent examination (DVFE) is a proposed adjunct to conventional oral examination (COE). We evaluate the benefit of DVFE in screening for potentially malignant mucosal lesions in a general population of patients presenting for dental care.

Study Design. A total of 130 patients were evaluated by COE followed by DVFE. Areas clinically suspicious by COE or with positive DVFE (visual fluorescence loss [VFL]) underwent surgical biopsy. Association between COE and DVFE was assessed and compared with histopathology.

Results. A total of 42 subjects had one or more areas of VFL, yet histologic evidence of premalignancy/malignancy was only identified in a single individual. Further, one lesion negative by DVFE exhibited epithelial dysplasia. DVFE was statistically different from scalpel biopsy (P = .0001). No difference was found between COE and scalpel biopsy (P = 1.0). **Conclusions.** Results suggest that COE is more valid than DVFE at discriminating benign mucosal alterations from premalignancy and do not support use of DVFE as an oral cancer screening adjunct. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114:636-643)

Tex Dent J. 2012 May;129(5):471-80.

Adjunctive diagnostic aids in oral cancer screening: an update.

Huber MA.

Department of Comprehensive Dentistry, University of Texas Health Science Center at San Antonio, Dental School, San Antonio, Texas 78229, USA. huberm@uthscsa.edu

Abstract

During the past decade, several adjunctive aids have been introduced to the marketplace with the promoted goal of improving the dental practitioner's ability to screen for and identify oral premalignant and malignant lesions (OPMLs). These products include the OralCDx Brush Test, ViziLite Plus with TBlue, Microlux, VELscope Vx, Sapphire Plus, Identafi, and the DOE Oral Exam System. They are all marketed as aids for the clinician to use in addition to, not in lieu of, the accomplishment of a conventional oral examination (COE). Studies addressing the efficacy of these products when used in the general practice setting to screen for OPMLs are limited and conflicting. The ability to discriminate between truly dangerous OPML against the milieu of benign mucosal lesions remains a concern and further research is necessary to determine the true value of these products as marketed to the general practitioner. The attainment of a complete history and the accomplishment of a thorough and disciplined COE remains the foundation upon which the practitioner assesses the patient for OPMLs. Findings deemed suspicious or equivocal should be referred to an expert for further assessment or undergo immediate biopsy, while findings deemed innocuous should be re-evaluated within 2 weeks and referred to an expert for further assessment or undergo biopsy if still present.

