Chairside Investigations of Premalignant Lesions: Review Article

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INTRODUCTION

Oral squamous cell carcinoma is the most common oral and maxillofacial malignancy, and its morbidity and mortality rates are still high in most countries. The incidence of oral cancer worldwide is around 500000 new cases every year, accounting for approximately 3% of all malignancies, thus creating a significant worldwide health problem.[1]

Premalignant lesions are morphologically atypical tissue which appear abnormal when viewed under the microscope, and which are more likely to develop into cancer than normal tissue. A precancerous condition is a condition involving abnormal cells which are associated with an increased risk of developing into oral cancer.

The purpose of this review article is to enumerate the most common oral premalignant conditions that progress into OSCC. Also in there is a review of the non-invasive detection techniques that are currently used for early diagnosis of premalignant lesions by dentists and other health care workers.

Commonly seen premalignant disorders are leukoplakia, erythroplakia, palatal lesions associated with reverse smoking, oral lichen planus, oral submucous fibrosis, actinic keratosis, and discoid lupus erythematosus. Early detection and diagnosis of these lesions are important for cancer prevention and disease management. In recent years, there has been a growing and persistent demand for new non-invasive, chairside investigation techniques that enables early detection and diagnosis of oral cancers.

The chairside investigation techniques for detection of premalignant conditions can be broadly classified under four categories :

1. Vital staining with a solution
2. Light-based detection systems
3. Optical diagnostic technologies
4. Salivary biomarkers.

The clinical stage at the time of diagnosis is the most important predictor of recurrence and mortality in oral cancer patients. So there is a great importance in early detection and management of oral precancerous lesions.

IMPORTANCE OF EARLY DETECTION

There is general agreement that the clinical stage at the time of identification is that the most vital predictor of return and mortality in carcinoma patients. The time to identification is influenced by multiple clinical and sociodemographic variables, as well as patient reluctance to consult a health-care skilled because of lack of access to health care, particularly in patients with low socioeconomic standing, yet as skilled delay in designation and treating the malady. 40 Studies have shown that dentists and alternative health-care suppliers area unit in desperate want of general instructional updates in carcinoma bar and early detection, as they're derelict within the provision of oral examinations and within the detection of early oral cancers. Clinicians will improve patients' survival rates if a cancerous lesion is detected at associate early stage, or if a precursor lesion (dysplasia) is discovered and treated before malignant progression. 41 a significant challenge for early identification of the at-risk tissue is our restricted ability to differentiate oral malignant tumor lesions at high risk of progressing into invasive SCC from those at low risk. 42 Thus, the bar of carcinoma and its associated morbidity and mortality, hinges upon the first detection of oral malignant tumor lesions, providing microscopic anatomy analysis and resulting treatment reckoning on the stage of identification. Early detection and screening for carcinoma has the potential to decrease the morbidity and mortality of malady, however strategies for screening haven't been tested fortunate. Though a typical routine carcinoma examination needs a 90-s visual and tactile examination, too few practitioners and dentists particularly area unit conducting these exams.[2,3,4,5]

NON- INVASIVE TOOLS FOR EARLY DETECTION

Recent advancements in carcinoma analysis have semiconductor diode to the event of doubtless helpful diagnostic tools at the clinical and molecular level for the first detection of carcinoma. The gold commonplace for car-

cinoma identification remains tissue diagnostic test with histologic assessment, however this method desires a trained health-care supplier, and is taken into account invasive, painful, high-ticket and time overwhelming. 43 Recent clinical diagnostic tools for early detection of carcinoma embrace tolonium chloride or toluidine blue dye, Oral CDx brush diagnostic test kits, secretion nosology and last optical imaging systems. betting on the kind of sunshine and also the imaging approaches used, optical imaging of the oral tissues will observe smallest changes at intervals the tissues, like alterations in tissue design and composition; expression of specific biomarkers, vascularity / angiogenesis and perfusion; microanatomy and tissue boundary integrity (e.g., potential invasiveness of lesions).[5,6,7,8,9]

TOLUIDINE BLUE

Toluidine blue (TB) may be a member of the thiazine group of metachromatic dyes, which binds to DNA and is partially soluble both in water and in alcohol. Theoretically, dysplastic and malignant cells have higher macromolecule content than normal, and thus, staining of suspicious lesions with this dye can aid recognition of mucosal changes. TB has been used as an important stain to spotlight potentially malignant oral lesions since the first 1980s. A positive staining of TB may appear as a dark purplish blue. TB check seems to be sensitive (97.8%-93.5%) however less specific (92.9%-73.3%), primarily as a result of high false-positive results. 48,49 Recently, molecular studies on TB stained lesions rumored a link between malignant neoplastic disease and LOH at 3p and 17p, whereas abnormality resulted in LOH at 9p. The presence of LOH has additionally been rumored in high frequency of TB-stained lesions while not or with low grade dysplasia[10,11,12.]

ORAL CDx

Oral CDx brush biopsy uses the concept of exfoliative cytology to supply a cytological evaluation of a cellular dysplastic changes. The oral CDx provides an entire transepithelial sample because the brush extends deep within the epithelial layers. On a glass slide, cytological oral epithelial samples are fixed and which is stained with modified Pap test. Then analysed microscopically via computer-based imaging system. However, although exfoliative cytology and brush biopsy techniques are helpful in establishing a more definitive diagnosis of already visible lesions, they're of no value in detecting mucosal changes that aren't readily visible to the eye. Advances within the development of automated cytomorphometric methods combined with genetic and proteomic profiling may provide the specified tools to refine screening strategies within the future. A scalpel biopsy remains suggested if there's clinical suspicion of a lesion no matter the Oral CDx result.[13,14,15,16]

Chemiluminescence: ViziLite

This imaging device has been approved to be used within the us by the Food and Drug Administration since November 2001. It involves the utilization of a hand-held, single-use, disposable chemiluminescent light stick that emits light at 430, 540 and 580 nm wavelengths. the utilization of the sunshine stick is meant to enhance the visual distinction between normal mucosa and oral white lesions. Normal epithelium will absorb light and appear dark whereas hyperkeratinized or dysplastic lesions appear white. The difference in color might be associated with altered epithelial thickness, or to the upper density of nuclear content and mitochondrial matrix that preferentially reflect light within the pathological tissues. Using ViziLite with TB in recent study showed that the bulk of lesions with a histological diagnosis of dysplasia and carcinoma in place were detected and mapped in high risk patients. Another new chemiluminescence device (MicroLux DL; Zila, Batesville, AR, USA) has been introduced as an adjunct tool for oral lesion identification but few studies are published to assess its effectiveness in detecting precancerous lesions.[17,18,19]

VELSCOPE SYSTEM

For the screening and diagnosis of premalignant lesions within the skin lungs and cervix has been well documented using the tissue autofluorescence. This approach is already in clinical use within the lung.[20]

Using the tissue autofluorescence concept for diagnosis of dysplastic lesions within the mouth hinges on the changes within the structure and metabolism of the epithelium and therefore the subepithelial stroma when interacting with light. Specifically, loss of autofluorescence in dysplastic and cancerous tissue is believed to reflect a posh mixture of alterations to intrinsic tissue fluorophore distribution, thanks to tissue remodeling like the breakdown of the collagen matrix and elastin composition also as alterations to metabolism like the decrease in flavin adenine dinucleotide concentration, and increase the reduction sort of nicotinamide adenine dinucleotide related to progression of the disease.[21,22,23] Further, these structural changes in tissue morphology are related to alterations not only within the epithelium but also within the lamina propria (e.g., thickening of epithelium, hyperchromatic and increased cytoplasmic/nuclear pleomorphism, or increase microvascularity). The latter changes cause increased absorption and/or scattering of sunshine, which successively reduces and modifies the detectable autofluorescence signal.[25]

In the past decade, several sorts of autofluorescence technology are developed for inspection of the oral mucosa. In partnership with British Columbia Cancer Agency, LED Medical Diagnostics Inc markets the hand-held VELscope System. it's an easy hand-held fluorescence visualization tool for the direct visualization of tissue fluorescence, and it's quick and straightforward to use. the location of interest is viewed through the instrument eye piece. Normal oral mucosa appears pale green thanks to the tissue autofluorescence resulting from stimulation with intense blue light excitation at 400-460 nm wavelength. In contrast, dysplastic and malignant lesions will appear darker than the encompassing healthy tissues as they need decreased autofluorescence.[26,27,28]

Two recent studies emphasized the controversial use of this technique for early diagnosis. One study, demonstrated that VELscope examination didn't provide a definitive diagnosis regarding the presence of epithelial dysplasia, which loss of autofluorescence isn't useful in diagnosing epithelial dysplasia without relevant clinical interpretation. Whilst the other study shown that the VELscope was good in confirming the presence of leukoplakia, erythroplakia and other oral mucosal lesions, but the device was unable to discriminate high-risk from low-risk lesions.[29]

IDENTAFI 3000

The combination of the anatomical imaging with fiber optic, fluorescence and confocal microscopy is the Identafi 3000 technology which is used to map and delineate the lesion precisely. The advantage of this device over the Velscope is its small size and straightforward accessibility to all or any tissues within the mouth[30]. Besides detection of autoflurescence almost like the Velscope system (Figure 2b), this device also examines tissue reflectance which is predicated on the premise of detecting changes in angiogenesis with green-amber light (540- to 575-nm wavelength) illumination (Figure 2c). The amber light is assumed to reinforce the reflective properties of the oral mucosa, allowing a distinction between normal and abnormal tissue vasculature. Increased angiogenesis may be a known process during oral carcinogenesis and carcinoma progression.[31,32] It's important to develop imaging technology for evaluating the status of tumor angiogenesis.

A recent study using the Identafi 3000 for screening of 124 subjects, demonstrated a sensitivity of 82% and a specificity of 87% in differentiating between neoplastic and non-neoplastic oral conditions. Results seemed to vary between sampling depths, and keratinized vs. non-keratinized tissues. Another study using quantitative fluorescence imaging in 58 patients with oral lesions and 11 normal volunteers, showed that

healthy tissue might be discriminated from dysplasia and invasive lesion with 94.9% sensitivity and 96.1% specificity within the training set, and with 100% sensitivity and 92.4% specificity within the validation set. Further clinical studies are needed in diverse populations to guage fully the clinical usefulness of this promising technology.[33,34,35]

SALIVA AS A DIAGNOSTIC TOOL

Saliva from patients has been utilized in a completely unique thanks to provide molecular biomarkers for carcinoma detection. Saliva may be a mirror of the body, reflecting virtually the whole spectrum of normal and disease states and its use as a diagnostic fluid meets the stress for a cheap, non-invasive and accessible diagnostic tool.[36,37]

Discovery of analytes in saliva of normal and diseased subjects suggests a really promising function of saliva as an area and systematic diagnostic tool. The power to research saliva to watch health and disease may be a highly desirable goal for oral health promotion and research. So far, saliva has been wont to detect caries risk, periodontitis, carcinoma, carcinoma, exocrine gland diseases and systemic disorders like human immunodefficiency virus and hepatitis C virus.[38] However, thanks to lack of data of disease markers and an overall low concentration of those markers in saliva in comparison to serum, the diagnostic value of saliva has not been fully realized. However, nowadays, sensitive and high-throughput assays like DNA microarray, mass spectrometry and nanoscale sensors can measure protein and RNA markers at low concentrations in saliva, thus expanding the utility of saliva as a diagnostic tool.[39,40,41,42]

CONCLUSION AND FUTURE DIRECTIONS

Dentists' knowledge and education in detecting carcinoma at its precancerous phase is that the key to stop its progression to later stages. so as to enhance early detection, it's imperative to extend the health-care providers' depth of data about carcinoma, their risk factors and therefore the commonest oral precancerous conditions. Future research also can be directed towards establishing appropriate clinical practice standards for early detection exams. Currently, the new innovative visual-based techniques show promising results, but lack strong evidence to support their effectiveness in early detection. Their utilization in clinic practice remains anecdotal. Limitations that hinder their wide use include lack of methodologically sound clinical trials, their correlation with histological alterations and therefore the impact these techniques wear a patient's survival and risk of disease recurrence.

REFERENCES

1. Johnson NW, Warnakulasuiya S, Gupta PC et al. Global oral health inequalities in the incidence and outcomesfor oral cancer: causes and solutions. Adv Dent Res 2011; 23(2): 237–246.
2. Ho MW, Risk JM, Woolger JA, et al. The clinical determinants of malignant transformation in oral epithelial dysplasia. Oral Oncol. 2012;48 10:969–976. [PubMed] [Google Scholar]
3. Messadi DV, Wilder-Smith P, Wolinsky L. Improving oral cancer survival: the role of dental providers. J Calif Dent Assoc. 2009;37 11:789–798. [PMC free article] [PubMed] [Google Scholar]
4. Steele TO, Meyers A. Early detection of premalignant lesions and oral cancer. Otolaryngol Clin N Am. 2011;44 7:221–229. [PubMed] [Google Scholar]
5. Nair D, Pruthy R, Pawar U, et al. Oral cancer: premalignant conditions and screening—an update. J Can Res Therap. 2012;8 Suppl 1:s57–s66. [PubMed] [Google Scholar]
6. Fedele S. Diagnostic aids in the screening of oral cancer. Head Neck Oncol. 2009;1:5–10. [PMC free article] [PubMed] [Google Scholar]
7. Epstein JB, Silverman S, Jr, Epstein JD,

et al. Analysis of oral lesion biopsies identified and evaluated by visual examination, chemiluminescence and toluidine blue. Oral Oncol. 2008;44 6:538–544. [PubMed] [Google Scholar]

8. Lingen MW, Kalmar JR, Karrison T, et al. Critical evaluation of diagnostic aids for the detection of oral cancer. Oral Oncol. 2008;44 1:10–22. [PMC free article] [PubMed] [Google Scholar]

9. Rosin MP, Poh CF, Guillard M, et al. Visualization and other emerging technologies as change makers for oral cancer prevention. Ann NY Acad Sci. 2007;1098:167–183. [PubMed] [Google Scholar]

10. Patton LL, Epstein JB, Kerr AR. Adjunctive techniques for oral cancer examination and lesion diagnosis: a systematic review of the literature. J Am Dent Assoc. 2008;139 7:896–905. [PubMed] [Google Scholar]

11. Su WW, Yen AM, Chiu SY, et al. A community-based RCT for oral cancer screening with toluidine blue. J Dent Res. 2010;89 9:933–937. [PubMed] [Google Scholar]

12. Awan KH, Yang YH, Morgan PR, et al. Utility of toluidine blue as a diagnostic adjunct in the detection of potentially malignant disorders of the oral cavity—a clinical and histological assessment. Oral Dis. 2012;18 8:728–733. [PubMed] [Google Scholar]

13. Sciubba JJ. Improving detection of precancerous and cancerous oral lesions. Computer-assisted analysis of the oral brush biopsy. U.S. Collaborative OralCDx Study Group. J Am Dent Assoc. 1999;130 10:1445–1457. [PubMed] [Google Scholar]

14. Rick GM. Oral brush biopsy: the problem of false positives. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96 3:252–258. [PubMed] [Google Scholar]

15. Svirsky JA, Burns JC, Carpenter WM, et al. Comparison of computer-assisted brush biopsy results with follow up scalpel biopsy and histology. Gen Dent. 2002;50 6:500–503. [PubMed] [Google Scholar]

16. Scheifele C, Schimdt-Westhausen A, Detrich T, et al. The sensitivity and specificity of the OralCDx technique: evaluation of 103 cases. Oral Oncol. 2004;40 8:824–828. [PubMed] [Google Scholar]

17. Huber MA, Bsoul SA, Terezhalmy GT. Acetic acid wash and chemiluminescent illumination as an adjunct to conventional oral soft tissue examination for the detection of dysplasia: a pilot study. Quintessence Int. 2004;35 5:378–384. [PubMed] [Google Scholar]

18. Kerr AR, Sirois DA, Epstein JB. Clinical evaluation of chemiluminescent lighting: an adjunct for oral mucosal examinations. J Clin Dent. 2006;17 3:59–63. [PubMed] [Google Scholar]

19. Epstein JB, Gorsky M, Lonky S, et al. The efficacy of oral lumenoscopy™ (ViziLite®) in visualizing oral mucosal lesions. Spec Care Dent. 2006;26 4:171–174. [PubMed] [Google Scholar]

20. McIntosh L, McCullough MJ, Farah CS. The assessment of diffused light illumination and acetic acid rinse (Microlux/DL) in the visualisation of oral mucosal lesions. Oral Oncol. 2009;45 12:227–231. [PubMed] [Google Scholar]

21. Lam S, MacAulay C, Palcic B. Detection and localization of early lung cancer by imaging techniques. Chest. 1993;103 1 Suppl:12S–14S. [PubMed] [Google Scholar]

22. Park SY, Follen M, Milbourne A, et al. Automated image analysis of digital colposcopy for the detection of cervical neoplasia. J Biomed Opt. 2008;13 1:014029. [PubMed] [Google Scholar]

23. Kennedy JC, Pottier RH. Endogenous protoporphyrin IX, a clinically useful photosensitizer for photodynamic therapy. J Photochem Photobiol B. 1992;14 4:275–292. [PubMed] [Google Scholar]

24. Ebihara A, Liaw LH, Krasieva TB. Detection and diagnosis of oral cancer by light-induced fluorescence. Lasers Surg Med. 2003;32 1:17–24. [PubMed] [Google Scholar]

25. Schantz SP, Kolli V, Savage HE, et al. In

vivo native cellular fluorescence and histological characteristics of head and neck cancer. Clin Cancer Res. 1998;4 5:1177–1182. [PubMed] [Google Scholar]

26. Sweeny L, Dean NR, Magnuson JS, et al. Assessment of tissue autofluorescence and reflectance for oral cavity cancer screening. Otolaryngol Head Neck Surg. 2012;145 6:956–960. [PMC free article] [PubMed] [Google Scholar]

27. Lane PM, Gilhuly T, Whitehead P, et al. Simple device for the direct visualization of oral-cavity tissue fluorescence. J Biomed Opt. 2006;11 2:024006. [PubMed] [Google Scholar]

28. Poh CF, Ng SP, Williams PM, et al. Direct fluorescence visualization of clinically occult high-risk oral premalignant disease using a simple hand-held device. Head Neck. 2007;29 1:71–76. [PubMed] [Google Scholar]

29. Balevi B. Evidence-based decision making: should the general dentist adopt the use of the VELscope for routine screening for oral cancer. J Can Dent Assoc. 2007;73 7:603–606. [PubMed] [Google Scholar]

30. Camiles F, Mcintosh L, Georgiou A, et al. Efficacy of tissue autofluorescence imaging (Velscope) in the visualization of oral mucosal lesions. Head Neck. 2012;34 6:856–862. [PubMed] [Google Scholar]

31. Awan KH, Morgan PR, Warnakulasuriya S. Evaluation of an autofluorescence based imaging system (VELscopeTM) in the detection of oral potentially malignant disorders and benign keratosis. Oral Oncol. 2011;47 4:274–277. [PubMed] [Google Scholar]

32. Roblyer D, Kurachi C, Stepanek V, et al. Objective detection and delineation of oral neoplasia using autofluorescence imaging. Cancer Prev Res. 2009;2 5:423–431. [PMC free article] [PubMed] [Google Scholar]

33. Folkman J, Watson K, Ingber D, et al. Induction of angiogenesis during the transition from hyperplasia to neoplasia. Nature. 1989;339 6219:58–61. [PubMed] [Google Scholar]

34. Hasina R, Lingen MW. Angiogenesis in oral cancer. J Dent Educ. 2001;65 11:1282–1290. [PubMed] [Google Scholar]

35. Schwarz RA, Gao W, Redden Weber C, et al. Noninvasive evaluation of oral lesions using depth-sensitive optical spectroscopy: simple device for the direct visualization of oral-cavity tissue fluorescence. Cancer. 2009;115 8:1669–1679. [PMC free article] [PubMed] [Google Scholar]

36. McGee SA, Mirkovic J, Mardirossian V, et al. Model-based spectroscopic analysis of the oral cavity: impact of anatomy. J Biomed Opt. 2008;13 6:064034. [PMC free article] [PubMed] [Google Scholar]

37. Koch FP, Kaemmerer PW, Biesterfeld S, et al. Effectiveness of autofluorescence to identify suspicious oral lesions-a prospective, blinded clinical trial. Clin Oral Investig. 2011;15 6:975–982. [PubMed] [Google Scholar]

38. Forde MD, Koka S, Eckert SE, et al. Systemic assessments utilizing saliva: part 1 general considerations and current assessments. Int J Prosthodont. 2006;19 1:43–52. [PubMed] [Google Scholar]

39. Pesce MA, Spitalnik SL. Saliva and the clinical pathology laboratory. Ann NY Acad Sci. 2007;1098:192–199. [PubMed] [Google Scholar]

40. Li Y, St John MA, Zhou X, et al. Salivary transcriptome diagnostics for oral cancer detection. Clin Cancer Res. 2004;10 24:8442–8450. [PubMed] [Google Scholar]

41. Wong DT. Towards a simple, saliva-based test for the detection of oral cancer, oral fluid (saliva), which is the mirror of the body, is a perfect medium to be explored for health and disease surveillance. Expert Rev Mol Diagn. 2006;6 3:267–272. [PubMed] [Google Scholar]

42. Wong DT. Salivary diagnostics powered by nanotechnologies, proteomics and genomics. J Am Dent Assoc. 2006;137 3:313–321.