European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 07, Issue 05, 2020

Non-invasive Techniques for Detection of Oral Potentially Malignant Disorders (OPMDs) - Detect Early to Treat Early- A Review

S Swathi[1], Swetha P[2], Ravikanth Manyam[3]

[1]*Post graduate, Department of Oral Pathology, Vishnu Dental College.*
[2]*Professor, Department of Oral Pathology, Vishnu Dental College (Corresponding Author)*
[3]*Professor & HOD, Department of Oral Pathology, Vishnu Dental College*

Abstract:
Oral potentially malignant disorders (OPMDs), the group of conditions with the risk of malignancy being present in a lesion or condition either at the time of early diagnosis or future date. Oral carcinoma is a major global, health care issue with high morbidity and mortality rates to date. Leukoplakia, Erythroplakia, Palatal lesion associated with reverse smoking, Oral Lichen Planus, Oral Sub Mucous Fibrosis, Actinic Keratosis, Discoid Lupus Erythematosus are other OPMDs. The aetiology varies from exogenous factors such as tobacco and various autoimmune disorders or inherited genetic aberrations. Early detection of the lesion is essential to prevent malignant transformation, and also to improve the chances of the patient's survival. Though tissue biopsy and histological assessment is the gold standard diagnosis for OPMDs, in recent years, demand for non – invasive adjunctive diagnostic techniques are increasing for early detection. With this in view, the early diagnostic methods were divided into 3 main categories such as vital Staining, light-based detection systems, and optical diagnostic technologies. Among the recent developments in optical imaging systems, the tissue autofluorescence, optical coherence tomography have been proved to be considerably efficient. These techniques have proven valuable for screening and monitoring OPMDs. Awareness should be created in public in employing screening methods that are non-invasive, robust and economic thereby it would enhance early detection of oral cancer which gives a positive impact on patient's survival. This review explains the sensitivity, specificity and limitations as well as their advantages, disadvantages and clinical applications of these techniques and to identify which one is better advisable and adaptable for all population groups.

Keywords: Oral potentially malignant disorders, Sensitivity, Specificity, Vital Staining, Light-based detection, Optical based detection systems.

1. INTRODUCTION

Despite advances in cancer therapies, oral malignancies have high mortality and morbidity rates due to varied reasons. Oral potentially malignant disorders (OPMDs) are a group of conditions, which include leukoplakia, erythroplakia, oral lichen planus, oral submucous fibrosis, palatal lesions associated with reverse smoking, actinic keratosis, and discoid lupus erythematosus. OPMDs occur due to exogenous factors like tobacco, autoimmune disorders or inherited genetic aberrations are prone to increased risk for malignant transformation to oral cancer with a low survival rate for not being diagnosed at early stages [1],[2]. Oral Squamous cell Carcinoma (OSCC) is one such OPMD with a challenging note to diagnose at an early stage accounting with an overall 5 year survival rate since decades. Regardless of standard scalpel biopsies with the histopathological examination, these are invasive and incompliant with a high degree of intra and inter-observer variability. Hence new non-invasive adjunctive diagnostic techniques like vital Staining, light-based detection systems, and optical imaging systems like tissue autofluorescence imaging, optical coherence tomography have been proven efficient and becoming popular for screening and monitoring OPMDs[3]. This review gives an overview of promising new commercially available non-invasive adjunctive diagnostic techniques early detection and diagnosis of OPMDs. Vital Staining is an efficient chair-side diagnostic technique helps in identifying the clinically non-apparent lesions with a focus on cells with high

ISSN 2515-8260 Volume 07, Issue 05, 2020

reproductive rate, thereby indicating the most suitable area for biopsy used in staining tissues and cells with a range of pigments (table I). Although this method is easy to use, it is not conclusive and commonly used as an adjunctive diagnostic tool [4]. Light-based detection systems hand-held diagnostic technique using special light sources to detect the abnormal metabolic and structural changes occurring in mucosal

diagnostic systems offer better advantages based on biochemical changes rather than tissues with different absorbance & reflectance properties [11] (table II) Optical based visual or microscopic changes in cellular tissue morphology with quantitative information that can be rapidly analyzed to yield a diagnosis, even in the hands of a non-expert [15] (table III).

Nowadays, advanced research using salivary biomarkers were exploring. Salivary mRNA's and Interleukin 6 are most widely used in differentiating OSCC with epithelial dysplasia[19], [20]. Patients with OPMDs are often encountered in clinical settings. The challenge of the clinician lies in detecting the oral mucosal abnormality with malignant potential at the earliest stage to improve the productive longevity of the individuals. Early detection is necessary before it progresses into cancer and also for disease management. Early detection is the best way of improving the quality of life & survival rates for oral cancer patients worldwide. Presently, there is no widely accepted technique for the application of non-invasive methods in the detection and diagnosis of OPMDs. More research studies on large no of subjects are needed using these non-invasive detection techniques due to its limited evidence. Long term follows up also helps in understanding the efficacy of these detection techniques.

.

Stains	Principle	Sensitivity	Specificity	Advantages	Limitations	Interpretation
Toluidine blue	High affinity for acidic compounds, stains the cells or tissues blue with greater nucleic acid content [5]	38-100%	9-100%	Sensitive, chair-side, rapid, Low cost **Disadvantages** High false-positive rates	Lack of sufficient randomized control trials evidence and long-term prospective data can further improve our understanding.	Adjunctive aid for dental care providers in clinical assessment of OPMDs and selection of the biopsy site. Positive - Lesions with dark blue color Negative - lightly or faintly stained areas
Methylene blue	Stains tissue with large quantities of nucleic acids	90-91.4%	66.6-69%	Sensitive, chair-side, rapid, Low cost **Disadvantages** High false-positive rates	False positive rates reported due to the retention of stain in traumatic and inflamed areas [6]	To screen oral malignancy in high-risk cases.
Rose bengal	Tetrachloro and tetraiodo derivative of fluorescein [7]	90-100%	73.7-89.09%	Sensitive, chair-side, rapid, Low cost **Disadvantages** High false-positive rates	Very few studies have been conducted so far to assess the efficacy of this method in detecting oral PMDs	To diagnose ocular surface disorders, detection of OPMDs and oral cancer.
Lugol's iodine	Reaction of iodine with glycogen present within the cytoplasm, which is visualized by color change	87.5-94.7%	83.8-84.2%	Sensitive, chair-side, rapid, Low cost **Disadvantages** High false-positive rates	Gingiva and hard palate have high keratinization and lack of glycogen, stain can't be localized [8]	Adjunctive aid in selection of biopsy site and clinical assessment of OPMDs. Normal mucosa - Mahogany or brown due to its high glycogen. No stain/Pale - Dysplastic lesions when compared with the surrounding tissue.

Table I: Vital Staining
Table II: Light-based detection systems

Light based	Principle	Sensitivity	Specificity	Advantages	Limitations	Interpretation
Chemi-luminescence	Produce bluish-white light with a wave length of 430-580nm, absorbed by normal cells and reflected by abnormal cells that have a higher nuclear-cytoplasmic ratio(12).	ViziLite: 77-100% ViziLite Plus(ViziLite& toluidine blue): 77.3%, Microlux/ DL: 77.8 – 94.3%	ViziLite: 0-84.6%(11) ViziLite Plus: 27.8% Microlux/ DL: 70.7 – 99.6%	Effective chair-side, Rapid, high sensitivity in diagnosing OPMD's and Oral cancer. **Disadvantages** Low specificity	Fails to detect oral red patches.	Presence of an "ace to white" lesion after a one-minute rinse with 1% acetic acid solution is considered as positive(11).
Velscope	Hand held device, aids in visualization of oral mucosal changes by activating tissue Auto-fluorescence.	30–100%	15–100%	Rapid, chair-side & easy to operate **Disadvantages** Moderate false-positive rates.	Insufficient evidence that it can distinguish between dysplastic/ cancerous tissue from inflammatory oral lesion; frequent false positive results.	Normal cells exhibit pale green fluorescence whereas abnormal cells appear dark due to loss of auto fluorescence(13).
Photodynamic diagnosis	Based on the fluorescence generated by administration of an exogenous photo-activated compound that accumulates in cells with malignant potential,			Real-time & cost-effective **Disadvantages** Strict patient management, high false-positive rates.	Low specificity – 50–99%,(14) longer time required for the test.	Tissues exhibiting fluores-cence are considered to possess malignant potential

	followed by appropriate photo-irradiation.					

Table III: Optical based systems

Optical based	Principle &procedure	Sensitivity	Specificity	Advantages	Limitations	Interpretation
Optical Coherence Tomography (830nm)	Uses "L" shape probe upto 1mm of depth for 0.2seconds produces cross sectional images of tissue with a high spatial resolution of 10-20um, enables optical biopsy & provides immediate and localized diagnostic information.(15)	62-85%	51-81%	High sensitivity& specificity. Cross sectional images of the normal/abnormal tissues can be obtained without biopsy **Disadvantages** Examines only a very small area at a time	Only small area can be examined at a time because of probe size	Produces imaging of near surface abnormalities in complex tissues
Raman Spectroscopy (vibrational spectroscopy of tissue)	Provides real time histology information about molecular composition of tissue used in analysis of biological tissue to know the exact localization, extent and borders of lesion with spatial & high resolution(16)	86%	94%	Can be used by non-specialists with suitable diagnostic algorithms. No reagents are required, as based on a fingerprint of the biochemical composition **Disadvantages** Time consuming	Difficulty of capturing inherently weak tissue Raman signals and the relatively slow speed of spectrum acquisitions	
Narrow	Highlights	97.7%	98.9%	Advantage of	Chronic	Abnormal

Band Imaging (Novel method of imaging)	abnormalities in superficial vasculature of mucosal lesions so that precancerous or cancerous lesions can be identified more easily(17)			detecting superficial cancers when compared to conventional techniques. **Disadvantages** Moderate false-positive rates	infections & postoperative radiotherapy may lead to false positive results	vasculature will be seen as scattered spots with well demarcated borders
Colposcopy	Direct oral microscope with focal length of 200 mm providing 3-dimensional image of tissue surfaces. 3-5% Acetic acid and iodine solution are applied to the surface to improve the visualization of abnormal areas(18)			High resolution, good magnification and illumination. Detects lesions at an early stage with an accuracy of 80-90%. **Disadvantages** Expensive	Technique sensitive and expensive	High grade lesions: Persistent duller shade of white & straighter, sharper outlines with well-defined borders Low-grade lesions: Translucent or bright white& fade quickly& have feathery margins and irregular borders.

CONCLUSION: Considering all the non-invasive techniques, the dentist/clinician should be aware of the best method that can be applied in routine chairside practice. It is essential for the method to be accurate and economical. More research has to be conducted using a larger sample size on the available techniques to determine the best technique. Previous literature comparing the sensitivity, specificity and cost of the available methods, toluidine blue, ViZiLite, and VELScope have shown to be reasonable in clinical practice. Recently developed optical imaging techniques the best detection techniques but are expensive. As toluidine blue has high sensitivity but low specificity, hence it can be used as an adjunctive tool for early detection. It can be used along with ViZiLite and VELScope, for accurate results. Early referral and collaboration with dental professionals and owing to these various advances, able to provide quick and efficient care to the patients, thus improving their quality of life and in the prevention of specific health hazards and also reduces the possibility of further complications. Future directions are to identify those at risk of cancer, saliva in advanced genomic, proteomic technologies, alignment of optical imaging technologies with biomarker strategies, automation & objective point of care diagnostics.

REFERENCES

[1] J Liu, D., Zhao, X., Zeng, X., Dan, H., & Chen, Q. (2016). Non-invasive techniques for detection and diagnosis of oral potentially malignant disorders. Tohoku Journal of Experimental Medicine, 238(2), 165–177.

[2] Warnakulasuriya, S., Johnson, N.W. & van der Waal, I. (2007) Nomenclature and classification of potentially malignant disorders of the oral mucosa. J. Oral Pathology and Medicine., 36, 575-580

[3] Madhura, M. G., Rao, R. S., Patil, S., Alhazmi, Y. A., Jafer, M., Habib, S. R., & Awan, K. H. (2020). Minimally invasive procedures for the recognition and diagnosis of oral precancer and cancer. Disease-a-Month, 1–5.

[4] Panta, P. (2019). Oral cancer detection: Novel strategies and clinical impact. Oral Cancer Detection: Novel Strategies and Clinical Impact, 1– 314.

[5] Singh D, Shukla RK. Utility of toluidine blue test in accessing and detecting intra-oral malignancies. Indian J Otolaryngol Head Neck Surg. 2015;67:47–50.

[6] Mascitti, M., Orsini, G., Tosco, V., Monterubbianesi, R., Balercia, A., Putignano, A., Santarelli, A. (2018). An overview on current non- invasive diagnostic devices in oral oncology. Frontiers in Physiology, 9(OCT), 1–8.

[7] Petruzzi M, Lucchese A, Baldoni E, Grassi FR, Serpico R. Use of Lugol's iodine in oral cancer diagnosis: an overview. Oral Oncol 2010;46:811–3.

[8] Mittal N, Palaskar S, Shankari M. Rose Bengal staining– diagnostic aid for potentially malignant and malignant disorders: a pilot study Indian J Dent Res. 2012;23:561–4.

[9] Nagi, R., Reddy-Kantharaj, Y. B., Rakesh, N., Janardhan-Reddy, S., & Sahu, S.

(2016). Efficacy of light-based detection systems for early detection of oral cancer and oral potentially malignant disorders: Systematic review. Medicina Oral Patologia Oral y Cirugia Bucal, 21(4), e447–e455.

[10] Ram S, Siar CH. Chemiluminescence as a diagnostic aid in the detection of oral cancer and potentially malignant epithelial lesions. Int J Oral Maxillofac Surg. 2005;34:521-7.

[11] Kerr, A.R., Sirois, D.A. & Epstein, J.B. (2006) Clinical evaluation of chemiluminescent lighting: an adjunct for oral mucosal examinations.

J. Clin. Dent., 17, 59-63.

[12] McNamara KK, Martin BD, Evans EW, Kalmar JR. The role of direct visual fluorescent examination (VELscope) in routine screening for potentially malignant oral mucosal lesions. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;114:636-43.

[13] Chang CJ , Wilder-Smith P . Topical application of photofrin for photodynamic diagnosis of oral neoplasms. Plast Re- constr Surg .

2005;115:1877–1886

[14] Sharwani A , Jerjes W , Salih V , MacRobert AJ , El-Maaytah M , Khalil HS , et al. Fluorescence spectroscopy combined with 5- aminolevilinic acid-induced protoporphyrin IX fluorescence in detecting oral premalignancy. J Photochem Pho- tobiol B . 2006;83:27–33 a .

[15] Green, B., Cobb, A.R., Brennan, P.A. & Hopper, C. (2014) Optical diagnostic techniques for use in lesions of the head and neck: a review of the latest developments. Br. J. Oral Maxillofac Surg., 52, 675-680

[16] Carreras-Torras, C., & Gay-Escoda, C. (2015). Techniques for early diagnosis of oral squamous cell carcinoma: Systematic review.

Medicina Oral, Patologia Oral y Cirugia Bucal, 20(3), e305–e315.

[17] Nguyen, P., Bashirzadeh, F., Hodge, R., Agnew, J., Farah, C.S., Duhig, E., Clarke, B., Perry-Keene, J., Botros, D., Masters, I.B. & Fielding,

D. (2013) High specificity of combined narrow-band imaging and autofluorescence mucosal assessment of patients with head and neck cancer. Head Neck, 35, 619-625

[18] Biopsy, K. (2014). Colposcopy - A Novel Diagnostic Technique for Oral Mucosal Lesions. Journal of clinical and Diagnostic Research2014, October: Volume 8(10) 25–28.

[19] PM. Pavani, N., Srinivas, P., Rani Kothia, N., & Chaitanya Chandu, V. (2018). Recent Advances in the Early Diagnosis of Oral Cancer: A Systematic Review. International Journal of Medical Reviews, 4(4), 119–125.

[20] Wong DT. Salivary diagnostics powered by nanotechnologies, proteomics and genomics. Journal of American Dental Association 2006; 137(3): 313–32