REVIEW ARTICLE

ADJUVANT DIAGNOSTIC AIDS FOR ORAL CANCER DETECTION: A REVIEW

Authors:

[1]Anoop Kurian Mathew
[2]Jeethumol Shaji
[3]Shaul Hameed
[4]Asaf Aboobakker

[1]Reader and Head
Department of Oral Medicine and Radiology
Indira Gandhi Institute of Dental Sciences,
Nellikuzhy P.O., Kothamangalam, 686 691
Ernakulam District, Kerala, India

[2]Consultant Dentist
Dent Care Dental Lab Pvt Ltd, Muvattupuzha,
Ernakulam District, Kerala, India

[3]Assistant Professor
Maxillofacial Surgery and Diagnostic Science
College of Dentistry
Qassim University, Saudi Arabia

[4]Reader
Department of Oral Medicine and Radiology
Educare Institute of Dental Sciences,
Chattiparamba, Malappuram 676504, Kerala, India

Address for correspondence
Dr. Anoop Kurian Mathew
Reader and Head
Department of Oral Medicine and Radiology
Indira Gandhi Institute of Dental Sciences,
Nellikuzhy P.O, Kothamangalam, 686 691
Ernakulam District, Kerala, India
E mail: drakm2020@gmail.com

ABSTRACT

Oral cancer is considered to be a globally growing oral disease. Early diagnosis of oral cancer helps in improving cancer outcome by providing care at the earliest possible stage. Screening is a tool that is used to detect a disease in people without any signs or symptoms or examination of a group of asymptomatic individuals to detect those with higher probability of developing these conditions. Simple visual examination is being carried out as part of screening, but it is limited to subjective interpretation. As a result of this, various adjunctive methods have been suggested to enhance our ability to detect malignancy as well as areas of dysplasia which are not seen by naked eye. This paper highlights various methods of screening and assesses their value in identifying various premalignant and malignant diseases.

Keywords: Oral cancer, diagnosis, screening, dysplasia.

J Odontol Res 2020;8(1)26-31.

INTRODUCTION

Early diagnosis of oral cancer is one of the most efficient method to reduce the high mortality of such conditions. This can even lower the morbidity of these disease and its treatment, which is commonly associated with moderate or severe loss of function, asymmetry and low quality of life[1]. Therefore detecting these conditions at an early stage helps raising awareness among general public as well as improves access to oral health services.

Oral cancer or oral malignancy is always preceded by a precancerous lesion in oral mucosa. As reported by American Dental Association, identifying initial white or red patches within oral mucosa and removing them out is one of the most effective method to reduce its incidence and mortality. The various modalities of oral cancer detection are listed below.

Various modalities:

1. Visual examination:

A Conventional Oral Examination, using normal (incandescent) light, has long been the standard method for oral cancer screening. Conventional visual cancer screenings for some anatomic locations can be highly successful and includes assessment of high risk sites. A number of publications have suggested that Conventional Oral Examination may have limited value as a method for detecting pre-cancerous or early cancerous lesions[2]. Precancers and early stage cancers cannot be adequately identified by visual inspection alone and may be easily overlooked and neglected.

2. Vital Tissue Staining:

A. Toludine blue staining:

Toluidine blue as a vital tissue stain to aid in the early detection of the oral premalignant and malignant lesions. Tolonium chloride, (chemical name) more commonly referred to as TB, has been used for more than 40 years to aid in detection of mucosal abnormalities of the cervix and the oral cavity[3].Toluidine blue is a metachromatic vital dye that may bind preferentially to tissues undergoing rapid cell division (such as inflammatory, regenerative and neoplastic tissue), to sites of DNA change associated with potentially malignant disorders or both. The binding results in the staining of abnormal tissue in contrast to adjacent normal mucosa.

Diagnostic Aids for Oral Cancer Detection

TEST	PROCEDURE
Screening	Visual/Oral Examination
Vital Staining	Toludine Blue Staining Lugol's Iodine staining
Biopsy	Brush Biopsy Scalpel Biopsy
Light based systems	Vizilite (Chemiluminescence) VELscope (Autofluorescence) Optical Spectroscopy
Experimental	DNA Image Cytometry Saliva Testing Lab-on-a-chip
Imaging Modality	Optical Coherance Tomography

Screening procedure for detection of oral cancer using 1% tolonium chloride mouth rinse. Stains were prepared according to the recommendation by Mashberg.

Preparation - A 100 ml of tolonium chloride was freshly prepared each time by mixing 1 g tolonium chloride with 10 ml acetic acid, 4.19 ml absolute alcohol and 86 ml of distilled water while a 100 ml of 1% acetic acid rinse was prepared by diluting 1 ml of glacial acetic acid with 99 ml distilled water[4,5].

Procedure[6]

1. Oral examination and annotation of location, size, clinical characteristics, and photographing of the lesion.
2. Cleaning of the lesion with a cotton tip soaked in 10% H2O2 (Cleaning of lesion with water jet).
3. Cleaning of lesion with 1% acetic acid (dehydrates the mucosa by dissolving the
4. glycoprotein and for the elimination of saliva, food, or tissue remains).
5. Cleaning of lesion with water jet.
6. Application of 1% aqueous solution of toluidine blue with cotton tip for 30 seconds
7. Cleaning of lesion with water jet.
8. Application of 1% acetic acid with cotton tip for 30 seconds (for elimination of excess of stain).

B. Lugol's Iodine staining:

Lugols iodine consists of iodine, potassium iodide and distilled water. In contrast to Toluidine blue, Lugol's iodine is retained in normal squamous epithelial cells, but not in dysplastic or malignant epithelial cells of the cervix. Lugol's iodine solution produces a brown black stain by reaction of the iodine with glycogen. Normal mucosa contains higher amount of glycogen than abnormal mucosa and produces a brown-black stain. Glycogen content is inversely related to keratinisation. In the oral mucosa, the glycogen content varies with the keratinisation of the area of the mucosa.

Lugol's iodine when used with toluidine blue helped in delineating the inflammatory lesions and was the mean source in determining clinically the degrees of differentiation of malignant lesions as the poorly differentiated malignant lesions without glycogen content failed to show Lugol's iodine retention[7].

3. Oral Brush Biopsy:

Oral cells can be obtained by different physical systems of scraping the surface of the mucosa, by rinsing the oral cavity or even by taking a sample of saliva from the patients. Brush cytology (brush biopsy; Oral CDx) is an alternative to conventional exfoliative cytology for investigating persistent oral epithelial lesions not considered suspicious for carcinoma[8].

OralCDx kits consisted of

1. An oral brush biopsy instrument.
2. A precoded glass slide and matching test requisition form.
3. An alcohol/polyethylene glycol fixative pouch and a preaddressed container in which to submit the contents.

Applications of Brush biopsy:

- Detection of innocuous appearing but persisting mucosal lesions.
- Alternate for assessing lesions in patients who refuse scalpel biopsy.
- In combination with vital staining, may be useful for sampling multiple areas of patients previously treated patients with dysplasia or with Oral squamous cell carcinoma[9].
- Oral candidiasis, epithelial infections due to Ebsteinbarr virus and herpes virus.

4. Vizilite:

Based on the principle of 'Chemiluminescence', that is, emission of light from a chemical reaction. Chemiluminescent reactions emit light of varying degrees of intensity and lifetime, with colours that span the visible spectrum[10].

Vizilite kit:

• The Vizilite kit consisted of a Vizilite 1% acetic acid solution, Toludine Blue(TB) sticks and capsule, retractor and user instructions.

• The contents of the Vizilite1 1% acetic acid solution are purified water, acetic acid, sodium benzo-

ate, raspberry flavour, and base of propylene glycol and alcohol.

• A 100 ml of tolonium chloride was freshly prepared each time by mixing 1 g tolonium chloride with 10 ml acetic acid, 4.19 ml absolute alcohol and 86 ml of distilled water while a 100 ml of 1% acetic acid rinse was prepared by diluting 1 ml of glacial acetic acid with 99 ml distilled water.

Screening procedure for detection of oral cancer and PMD using Vizilite[11].

• Conventional examination of the oral cavity using dental chair light.

• Record location, size, morphology and surface characteristics of lesion(s).

• Photograph the lesion(s).

• Rinse mouth with 30 ml of 1% acetic acid and expectorate after 1 min.

• Activate Vizilite capsule and place it in the Vizilite retractor.

• Dim surgery lights and examine the oral cavity.

• Record and photograph any findings.

• Rinse mouth with water and expectorate after 20 s.

The acetic acid wash helps to remove surface debris and reportedly cause epithelial cells to dehydrate slightly increasing the relative prominence of their nuclei. Under blue white illumination, normal epithelium appears bluish in color, whereas abnormal epithelium appears distinctly white or acetowhite. The TB is used as a marking dye to help highlight lesions identified with the light source.

5. Optical Spectroscopy

Optical spectroscopy allows non-invasive physical and chemical characterization of biological tissues. The structural and chemical composition of cells and tissues strongly influences their optical features, and therefore alterations in the optical characteristics may indicate the presence of diseased tissue. Optical spectroscopy may provide possibilities in the early detection of cancerous tissues in humans[12].

6. Autoflurescence:

It is the fluorescence of tissues to which no chemical substances have been applied: it is the natural fluorescence of the tissue itself ('auto'). Fluorescence in general is the process by which excitation with light evokes the emission of light of a different (lower) wave length. When cells interact with light they become excited and re-emit light of varying colours (fluorescence) and this can be detected by sensitive spectrometers. All tissues fluoresce due to the presence of fluorescent chromophores (fluorophores) within them[13].

VELscope is an equipment designed to work under the principle of Fluorescence. It uses a specific wavelength of blue light, transmitted through a halide lamp, to excite tissue from the epithelial surface, down through the basement membrane, stopping at the stroma. The lighted tissue, in turn, emanates a green fluorescence (sometimes referred to as autofluorescence).The emitted fluorescence is not visible to the naked eye, but the VELscope hand piece filters out the blue light, so that only the green fluorescence remains. Differences in the degree of green reveal possible abnormalities. Healthy tissue appears pale, lime green, while abnormal tissue appears dark green to dark rust.

The proposed mechanism of tissue fluorescence is that mucosal tissues have a reflective and absorptive pattern based on naturally occurring fluorophores in the tissue. Tissue fluorescence in the oral cavity is variable and is affected by structural changes, metabolic activity, the presence of haemoglobin in the tissue, vessel dilatation and, possibly, inflammation. This variability has not been defined. Exposure to blue light spectra (400-460 nanometres) may maximize a differential profile in areas undergoing neoplastic change in which a loss of fluorescence visualization is reported[13].

VELscope is a portable unit that can be placed on a counter top or mobile cart to be transported to different operatories in an office or clinic. To prevent cross-contamination, VELscope comes with inexpensive disposable caps and sheaths that protect the patient, practitioner, and unit. A disposable retractor helps access to the oral cavity, and includes markings for measurement of the lesion. The FDA approved VELscope in 2006 as an adjunct to a conventional, incandescently lighted oral exam to aid detection of tissue abnormalities, such as cancer or

OPLs, not necessarily visible without additional technology. VELscope has also been approved for use by surgeons to help identify diseased margins of clinically visible lesions[14].

7. DNA Image Cytometry:

It determines the malignant potential of cells by measuring the ploidy status. Alterations in cellular DNA content is identified by means of computer assisted analysis. If genomic instability is appreciated, it marks a slight contribution towards cancer development and abnormal DNA content may distinguish the dysplastic lesions that can result in cancer[15].

8. Saliva Testing:

It is a non invasive technique that is alternative to serum testing. Saliva is often used as a diagnostic tool, as it is easy to collect and this testing may be an effective modality of cancer diagnosis as well as determining prognosis and monitoring post therapy status. Many reports mentioned that saliva may provide a cost effective practical approach for screening majority of people. This test may be used to detect specific salivary macromolecules, enzymes, cytokines, growth factors, MMP's, mRNA and DNA transcripts[16-18].

9. Lab-on -a Chip:

It is a microfluidics technology, which is the adaptation, miniaturization, integration and automation of analytical laboratory procedures into a single device or chip[19]. This chip uses a membrane associated cell proteins that are expressed on the cell membranes of dysplastic and cancer cells in order to detect cells with dysplastic features.

10. Optical CoheranceTomography:

Optical Coherance Tomography is a kind of non imaging modality which is non invasive. It can detect areas of inflammation, dysplasia and cancer.[20] It mainly records subsurface reflections to build a cross-sectional architechtural image of the tissue. It utilized gold nanoparticles to enhance the contrast in these images.[21] Studies need to be conducted to upgrade its reliability to provide a diagnosis for cancerous lesion, still not specific.

CONCLUSION

Oral health professionals may play a vital role in early diagnosis of oral cancer and should be considered as a priority health objective. Detection at an early stage can reduce complications related to various cancer therapies and can result in a better prognosis. Therefore, it is acknowledged that in addition to screening, there are other diagnostic adjuncts that are important in preventing oral cancer. Minor biopsy procedures can be effective for evaluating suspicious lesions that have malignant potential. Light based techniques mentioned above can be used along with oral screening as some lesions may be overlooked on conventional visual examination of the oral cavity. Early diagnosis may result in less aggressive treatment which can improve the quality of life as well as the survival rate.

REFERENCES

1. KH Awan.Oral Cancer: Early Detection is Crucial. J Int Oral Health 2014;6(5):1-8
2. Silverman S J. Early diagnosis of oral cancer. Cancer 1988;62(8):1796-9
3. Patton L, Epstein J, Kerr R. Adjunctive techniques for oral cancer examination and lesion diagnosis. A systematic review of literature. J Am Dent Asscoc2008;139:896-905.
4. Mansberg A. Toonium (toludine blue) rinse: A screening method for recognition of squamous cell carcinoma – continuing propective study of oral cancer. JAMA 1981;245:2408-10.
5. Mashberg A, Final evaluation of tolonium chloride rinse for screening of high risk patients with asymptomatic squamous cell carcinoma. J Am Dent Assoc 1983;106:319-23.
6. Onofre MA, Sposto MR, Navarro CM. Reliability of toludine blue action in the detection of oral epithelial dysplasia and in situ and invasive squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral

RadiolEndod2001;91:535-40.

7. Nagaraju K, Prasad S, Ashok L. Diagnostic efficiency of toludine blue with Lugol's iodine in oral premalignant and malignant lesions. Indian J Dent Res 2010;21(2):218-223.
8. Scuibba JJ. Improving detection of precancerous and cancerous oral lesions:computed assisted analysis of the brush biopsy – collaborative oral CDx study group. JADA 1999;130:1445-57.
9. John Kalmer. Advances in the detection and diagnosis of oral precancer and cancerous lesions. Oral Maxillofac Surg Clin N Am 2006;18:465-89.
10. Carlson R, Lewis SW, Lim KF. Seeing the light using chemiluminescence to demonstrate chemical fundamentals. Aust J Chem Ed 2000;14:51-53.
11. Ram S, Siar CH. Chemiluminescence as a diagnostic aid in the detection of oral cancer and potentially malignant epitjelial lesions. Int J Oral Maxillofac Surg 2005;34:521-27.
12. Veld, Vanderwaal, Sternberg, Roodenberg. The status of in vivo autofluorescence spectroscopy and imaging for oral oncology. Oral Oncol 2005;41(2):117-31.
13. Swinson B, Jerjis W, Narris P, Hopper C. Optical techniques in diagnosis of head and neck malignancy. Oral Oncology 2006;42:221-228.
14. Osuna T, Hopkins S. Oral cancer diagnostic technologies. CDHA Journal 24(1):1-17.
15. Bradley G, Odell EW, Raphael s, Ho J, Le LW, Benchimol S, Kamelreid S. Abnormal DNA content in oral epithelial dysplasia is associated with increased risk of progression to carcinoma. Br J Cancer2010;103(9):1432-42.
16. Nagler RM. Saliva as a tool for oral cancer diagnosis and prognosis.Oral Oncol 2009;45:1006-10.
17. Bagar G, Feinmesser R, Popovtzer A, NaglerRM.Salivaryanalysisin oral cancer patients:DNA and protein oxidation, reactive nitrogen species, and antioxidant profile. Cancer 2007;109(1):54-9.
18. Li Y, St John MA, Zhou X, Kim Y, Sinha U, Jordan RC, Eisele D, Abemayor E, Elashoff D, Park NH, Wong DT. Salivary Transcriptome diagnostics for oral cancer diagnosis. Clin Cancer Res 2004;10:8442-50.
19. Ziober BL, Mauk MG, Falls EM, Chen Z, Ziober AF, Bau HH. Lab-on-a-chip for oral cancer screening and diagnosis. Head Neck 2008;30(1):111-21.
20. Kim CS, Wilder-Smith P. AhnYC, Liaw AH, Chen Z, Kwon YJ. Enhanced detection of early-stage oral cancer in vivo by optical coherence tomography using multimodal delivery of gold nanoparticles. J Biomed Opt 2009;14(3):034008.
21. Jerjes W, Upile T, Conn B, Betz CS, McKenzie G, Radhi H, Vourvachis M, El maaytah M, Sandison A, Jay A, Hopper C. In vitro examination of suspicious oral lesions using optical coherence tomography. Br J Oral Maxillofac Surg 2010;48:18-25.