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RESEARCH ARTICLE

OPTICAL ADJUNCTIVE AIDS IN EARLY DETECTION OF ORAL CANCER – A REVIEW

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ABSTRACT

Despite having advances in treatment, prognosis for patients with oral cancer remains poor. Early diagnosis and treatment remains key to improved patient survival. Traditional methods of screening oral malignancies involve a conventional oral examination with digital palpation. A number of optical aids have been developed to assist the clinician to detect abnormalities and in early diagnosis of oral cancer. This review will discuss the use of optical systems and highlight the role of optical imaging such as chemiluminescence, auto fluorescence, optical coherence imaging etc in early diagnosis.

INTRODUCTION

Oral cancer is the sixth most common malignancy worldwide. Around 300000 patients are estimated to have oral cancer worldwide with prevalence rate of 1.30%. In developing countries oral cancer is third most common type of cancer (GuptaN *et al*., 2016). In India it ranks 6th most common malignancies with prevalence rate of 0.17% (Ajay *et al*., 2018). According to the India fact sheet of GLOBOCAN 2018, cancer of the lip and oral cavity showed a huge increase of 114.2% with 56,000 cases in 2012 that increased to 119,992 in 2018. The majority (84% - 97%) of oral cancers are squamous cell carcinoma. Despite advances in cancer therapies, the five-year survival rate for oral cancer has remained at approximately 50% over the past three decades (Warnakulasuriya *et al*., 2009). Thus, early detection and diagnosis of neoplastic changes in the oral cavity would pave the way for better prognosis. Currently, first line of screening of oral cavity abnormalities is performed by visual inspection, which is subjective. Clinical endoscopic examination and invasive needle biopsies followed by histopathological analysis remains the gold standard for diagnosis and surveillance of oral cavity cancer. However, these conventional techniques have their own limitations such as: (i) difficulty to distinguish benign from malignant lesions; (ii) difficulty in determining margin of lesions; (iii) can be subjective, especially during histopathological analyses; and also (iii) tissue biopsies can be invasive and painful for the patients(Olivo *et al*., 2011).

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Considering these facts, it is imperative that a new rapid and accurate diagnostic method for early oral cavity cancer detection is much needed to reduce the resulting mortality rate (Olivo etal., 2011). Given the difficulty of detecting oral cancer early and the prevalence in developing nations , any technique that improves the diagnosis should also improve the screening ability among large population. Therefore, optical techniques that are robust, accurate, of low cost, portable and easy to handle can be used effectively for clinical applications. Epstein *et al*. suggested that further research into adjunct visualisation technologies is required to improve the reliability of clinicians in screening for malignant and potentially malignant disorders (Epstien Betal.,). It is known that early detection of oral cancer and recurrence can enhance survival rates and improve overall quality of life. Light-based methods such as VELscope and ViziLite, optical spectroscopy employ native tissue characteristics such as fluorescence and reflectance to identify abnormal regions. This paper critically appraises the literature regarding these optical systems and discusses their application in the oral cavity, as well as highlighting other approaches to optical imaging.

OPTICAL DIAGNOSTIC TECNIQUES INCLUDES

Chemiluminiscence
Autofluoroscence
Raman spectroscopy
Narrow band imaging
Optical coherence spectroscopy

Chemiluminiscence

The ViziLite kit contains a vial of 1% acetic acid solution, a capsule, a retractor and the manufacturer's instructions (LiuD

et al ., 2016) .The capsule has an outer shell of flexible plastic and an inner vial of fragile glass. To activate it, the capsule is bent to break the glass vial, so that the chemical products react with each other and produce bluish-white light with a wave length of 430-580 nm that lasts for around 10 min. The specific wavelength is absorbed by normal cells and reflected by abnormal cells that have a higher nuclear-cytoplasmic ratio. The presence of an "ace to white" lesion after a one-minute rinse with 1% acetic acid solution is considered as positive. The absence of such findings is considered as negative. ViziLite positive lesions are considered to be abnormal oral mucosa. ViziLite shows high sensitivity in detecting oral PMDs and oral cancer. Commercially available chemiluminescence techniques include ViziLite, ViziLite Plus, Microlux/DL and Orascoptic DK. The main difference between these techniques is that ViziLite and ViziLite Plus involve a single use chemiluminescent stick, while Microlux/DL and Orascoptic DX provide a blue-white light-emitting diode (LED) fiber-optic light (LiuD *et al* ., 2016).

However, these studies often involved only patients with mucosal lesions that were previously visualized under conventional light. Some studies found that ViziLite could not differentiate between keratotic or inflammatory oral PMDs and oral cancer (Farah and McCullough 2007; Ram and Siar 2005). It preferentially detected leukoplakia but might fail to spot red patches (Epstein *et al*. 2006; Kerr *et al*. 2006; Awan *et al*. 2011b; Rashid and Warnakulasuriya 2015). In short, the evidence supporting the use of Vizi Lite for the early detection of oral PMDs is actually quite insufficient. Some studies compared the efficacies of Vizi Lite and TB staining for the diagnosis of oral PMDs and oral cancer, reporting that Vizi Lite was relatively more reliable compared to TB staining (Rajmohan *et al*. 2012; Vashisht *et al*. 2014). The manufacturer of ViziLite is now marketing an updated product called ViziLite Plus. The only difference between the Plus and the earlier version is that the lattercontains a TB staining solution. TB can further delineate ViziLite-positive lesions, thus improving the specificity. Microlux/DL shares the basic principles of ViziLite. The oral cavity is examined with a battery-powered LED fiber-optic source that emits a blue-white light (Liu *et al* ., 2016).

Ibrahim *et al*. 2014 conducted a study on 599 tobacco users, using biopsy as the gold standard, the sensitivity and specificity of Microlux/DL in detecting oral PMDs were 100% and 32.4%, which indicated that it seemed useful for enhancing lesion visibility, but couldn't discriminate between benign and malignant lesions) (Liu *et al* ., 2016). Microlux/DL is also a poor discriminator for inflammatory, traumatic, and malignant lesions (McIntosh *et al*. 2009). The Orascoptic DK system also requires an acetic acid rinse and a three-in-one, battery-operated, hand-held LED instrument to improve the visualization of oral lesions (Patton *et al*. 2008). There is no published evidence regarding its utility in oral PMD detection (Liu *et al*., 2016).

VEL scope: The VELscope is a hand held device that can enhance the visibility of oral mucosal abnormalities by activating tissue autofluorescence. Autofluorescence is due to the presence of endogenous fluorophores in cells, which produce a fluorescent emission when exposed to light of a specificwavelength. Within the oral mucosa, the most relevant fluorophores are nicotinamide adenine dinucleotide and flavin adenine dinucleotide in the epithelium, and collagen cross-links in the stroma. Mucosal abnormalities can alter the absorption and scattering properties of light as a result of changes in tissue architecture and concentrations of fluorophores. At these excitation wavelengths, normal cells show a pale green fluorescence when viewed through a filter, while abnormal cells show a loss of autofluorescence and appear dark. According to Huber etal several commonly occurring conditions, such as mucosal pigmentations, ulcerations, irritations, and gingivitis showed a loss of fluorescence under VEL scope. Blood hemoglobin can also reduce fluorescence. If a dark area appears during direct fluorescence visualization, the oral lesion must be considered as suspicious and clinical examination should be repeated by applying some pressure to remove blood from the target area. If normal green fluorescence returns after this pressure, the lesion is likely to have an inflammatory component (Kois *et al*., 2006).

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Kois and Truelove (2006) proposed that positive lesions need to be followed up with great caution; if they do not resolve within two weeks, further assessment and biopsy are generally recommended. In short, the results should be interpreted with caution, bearing in mind the frequent occurrence of false positive results (Kois *et al*., 2006).

Raman Spectroscopy: Raman spectroscopy is a vibrational spectroscopic technique that relies on the inelastic scattering of light, usually from a laser in the visible, near-infrared, or near-ultraviolet range. The vibrational changes in tissue parallel the Variations in chemical characterization and molecular structure in the sample. Raman Spectroscopy performs vibrational spectroscopy of the tissue content, thus providing immediate real-time histology (LiuD *et al*., 2016).When a sample is irradiated with intense monochromatic light, phenomena such as absorption, scattering, and reflection occur. Most of the scattered photons have the same frequency of the incident light (Rayleigh scattering) while a small proportion (one in ten million) are inelastically scattered, i.e. with a frequency different from the incident photons; this phenomenon is termed as Raman effect. When the frequency of the scattered light is lower than the frequency of incident photon, the process is called Stokes shift. If the frequency of scattered photon is higher than incident photon, the process is called anti-stokes shift (Liu *et al* ., 2016).

Raman spectroscopy has been successful in differentiating normal tissue from premalignant and malignant tissue in a range of non-oral tumor types, including brain, breast, Lower gastrointestinal tract, nasopharynx, skin, lung, and Cervix. In vivo Raman spectroscopy has Shown efficacy in the detection of normal tissue, PMDS, Cancer, and even of early changes such as cancer field effects or malignancy-associated changes in the oral cavity (Liu *et al* ., 2016). However, the clinical applications of Raman spectroscopy have been limited by both the difficulty of capturing inherently weak tissue Raman signals and the relatively slow speed of spectrum Acquisitions. Because of the technological limitations, research using Raman spectroscopy has Mostly been confined to either ex vivo studies of tissue samples or in vivo studies in animal models (Liu *et al* ., 2016).

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Narrow band imaging: Narrow-band imaging (NBI) is based on the depth of light penetration. The narrow-band blue light with a short wavelength (415 nm) penetrates into the mucosa and highlights the superficial capillaries as brown in color, while another wavelength (540 nm) identifies prominent vessels in the submucosal layer as cyan. The reflected light is captured by a monochromatic charge-coupled device located at the tip of the endoscope; a colored composite image is then created by the image processor, which is displayed on a high-definition video screen. Potentially malignant and malignant lesions have distinct microvascular morphologies, as angiogenesis occurs at an early stage of carcinogenesis. Under NBI, these lesions appear as scattered spots with well-demarcated borders. NBI highlights abnormalities in the superficial vasculature of mucosal lesions so that precancerous or cancerous lesions can be identified more easily. Yang *et al*. (2012) showed that NBI is a promising non-invasive tool for the evaluation and management of oral leukoplakia. NBI can capture the twisted elongation of intrapapillary capillary loops (IPCL). IPCL pattern destruction can be a useful indicator of the severity of oral leukoplakia (Yang *et al*., 2012).

Optical coherence spectroscopy: Optical coherence tomography (OCT) is an evolving optical technology that produces cross-sectional images of tissue with a high spatial resolution of 10-20 µm . It has most often been compared with ultrasonic imaging. Both technologies employ back-scattered signals reflected from different layers within the tissue to reconstruct structural images, with the latter measuring sound rather than light . The high spatial resolution of OCT enables "optical biopsy" and provides immediate and localized diagnostic information. This technique is capable of imaging tissue depths of up to 1-2 mm and is thus considered suitable for imaging oral mucosal lesions, as the normal human oral mucosa is very thin, ranging from 0.2-1 mm(LiuD *et al* ., 2016). Wilder-Smith *et al*. 2009 did study on 50 patients with suspicious lesions, including oral leukoplakia and erythroplakia, the sensitivity and specificity of OCT were 93-97%, showing the excellent capability of in vivo OCT for the detection and diagnosis of oral PMDs and oral cancer(Wilder-Smith *et al*., 2009). In another ex vivo study, Jerjes *et al*. (2010) confirmed the feasibility of using OCT to identify architectural changes in an abnormal lesion area; unfortunately, it was unable to provide a diagnosis or to differentiate between lesions (Jerjes *et al*., 2010). Moreover, there are still limitations regarding the application of OCT: (1) a histopathologist is needed to interpret the result, which is subjective, as OCT does not provide quantitative information; (2) only a small area can be examined at a time, because of the small size of the OCT probe .Several types of particulate contrast agent, such as air filled microbubbles, engineered microspheres, and gold nanostructures, have been developed to improve the OCT image by enhancing the intensity of backscattered light from the tissue .In addition, an OCT system can be readily combined with nonlinear optical modalities, such as two-photon excited fluorescence and second-harmonic generation. These combined techniques have been found to yield increased sensitivity and specificity in the diagnosis of oral dysplasia and cancer.

Conclusion

Early detection of oral premalignant lesions and early neoplastic changes may be the most effective means to improve survival and quality of life for oral cancer patients. The main contribution of optical imaging is to highlight oral lesions and to assist the physicians to better locate the surgical margins. Studies reported in this article supports the concept that optical imaging can be a very useful tool for the early detection and diagnosis of oral lesions. As the technology and techniques evolve, imaging modality may progressively reduce the need for biopsy, define surgical margins, and provide a direct evaluation of the effectiveness of oral cancer. A diagnostic technique capable of performing optical biopsy for non-invasive pathological diagnosis of cancer in situ and in real time should prove to be a powerful diagnostic modality in clinical medicine that will likely be a significant clinical advance with considerable impact on patient management.

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