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Review Article

Diagnostic Aids for Oral Cancer: Detect Early to Treat Early

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Abstract

Oral cancer is ranked at the sixth position with the 5 years survival rate still remaining at 50% or even less with squamous cell carcinoma still being the most common form. Primary line for cancer screening is achieved through a subjective visual examination, further intensifying public attentiveness concerning the relevance of routine intra-oral examination and the development of diagnostic aids that can be used by the oral health care professionals to swiftly identify oral premalignant lesions.

Keywords: Oral Cancer; Diagnostic Aids; Brush Biopsy; Tissue Fluorescence

Introduction

Oral cancer is ranked at the sixth position with the 5 year survival rate still remaining at 50% or even less with squamous cell carcinoma still being the most common form [1]. The recurrence of oral cancer even after a rigorous follow up is not a rarity and still manifests as a major problem even after treating cancer.

Research over the years has helped in early diagnosis of cancer which not only helps in early detection but also in management and a favorable diagnosis which is the aim of each and every individual [1].

Even though there are many etiologic factors for oral cancer, tobacco (smoking and smokeless form) and alcohol still remain the primary agents for the disease process [2].

World Health Organization (WHO) has emphasized the importance of the knowledge of healthcare professionals which will help in early diagnosis as visual examination is still the primary method of screening.2 Over the years various other diagnostic methods have been added for the process of diagnosis, however they are just adjunctive to the screening methods [3].

Conventional oral examination

Conventional oral examination has drawbacks such as false positive findings which makes other diagnostic modalities the need of the hour. White lesions sometimes diagnosed falsely as leukoplakia is a disaster for the patient as it is a potentially malignant lesion.4 As only some of them get converted into cancer [4,5].

Brush biopsy

OralCDx Brush Test System is another diagnostic modality which is used on clinical suspicion of malignancy in respect to the lesion. When a positive outcome is reported, a biopsy of the suspicious lesion is reccomended.2,4 Also they are very helpful for diagnosis of multiple lesions and also in those patients in whom scalpel biopsies may not be feasible [4].

Vital tissue staining

Tolonium chloride (Toluidine blue) is used as a diagnostic stain as it stains mitochondrial DNA, dysplastic cells with increased DNA content or modified DNA in carcinogenic cells [5]. The application of toluidine blue which is a metachromatic dye recognizes malignant alterations and potential areas of high-grade dysplasia.

Lugol's solution on the contrary is used to stain the normal cells, generating a brownish black stain, this is a result of glycogen reaction with iodine, which helps in lining the abnormal cells.

The combination of Lugol's iodine and toluidine blue reduces the possibility of false positive results and the site for biopsy is demarcated precisely [6].

Rose Bengal staining

5, 6, 7-tetrachloro-2′, 4′, 5′, 7′- tetraiododerivative of fluorescein, also known as the rose Bengal stain can be used as a screening tool to detect oral precancerous lesions [7]. Du., *et al*. concluded in a study that RB staining may be better than toluidine blue staining [8].

Chemiluminescence

Chemiluminescence [commercially available as ViziLite (Zila, Batesville, AR, United States)] is an intraoral examination diagnostic tool to increase recognition, assessment and scrutinizing of oral mucosal aberrations in patients with increased possibility of malignant transformation.[3] Disposable chemiluminescent light packet is used in ViziLite plus whereas the MicroLux unit utilizes a light source which is battery-powered and reusable. The usage of acetic acid (1%) wash is done to eliminate superficial residues and to improve the conspicuousness of nuclei of the epithelial cells, perhaps as an outcome of slight dehydration of the cells.

Normal epithelium appears lightly bluish under blue-white illumination whereas aberrant epithelium looks noticeably white in appearance (acetowhite) [4].

The usage of a disposable chemiluminescent light stick which is conveniently hand-held for single time is done that emanates varied light at wavelengths of 430, 540 and 580 nm.[9] Light is absorbed by usual epithelium that appears dark while precancerous conditions and lesions emerge whitish. The alteration in color is correlated to distorted thickness of epithelium and the Greater nuclear substance and matrix of mitochondria that specially reflects light in the precancerous lesions and conditions, however the distinction between cancerous, benign and inflammatory oral lesions cannot be done [9,10].

Another disadvantage is its increased cost, reduced specificity, increased frequency of false positives, leading to unwarranted biopsies [9]. Vizilite has been found to be more accurate in detecting leukoplakia's than erythroplakia's and red lesions [12]. Future research is essential to evaluate the sensitivity and specificity of vital tissue staining with respect to histopathological and clinical attributes and to establish its accurate practicality for standard intra-oral examinations of the oral cavity [13].

Narrow-emission tissue fluorescence

The usage of tissue auto fluorescence in the examination and identification of premalignant conditions in the cervix, skin and lung has been suitably verified.[9] When tissues are exposed to a light of particular wavelength, there is auto fluorescence of cellular fluorophores after excitation (Fluorescence imaging). A visual examination of variation in colors is observed due to cellular changes that modulate fluorophores' concentrations affecting the absorption of light in the cells [4].

Visually Enhanced Lesion Scope (VELscope system; LED Dental Inc., White Rock, B.C.) comprises of light source (wave length: 400-460 nm) and a component (manual) to assist in detailed examination or inspection [13]. Typically, oral mucosal tissues emanate an auto-fluorescence light of green color but anomalous oral mucosal lesions absorbs the auto-fluorescent light and emerge as darker areas [13]. However its routine usage is not corroborated since there is an increased specificity, expense and the absence of scientific verification [13].

A recent research revealed that the VELscope was beneficial in substantiating oral premalignant lesions like leukoplakia and erythroplakia. However, the difference between greater-risk and lower-risk lesions could not be done [14]. However, VELscope system is displaying promise due to its efficiency in identifying mucosal lesions and their borders that are covert to intra oral clinical inspection under white light [2,15].

Confocal *in-vivo* microscopy

Confocal reflectance microscopy is an optical technology that delivers comprehensive descriptions of tissue structure and morphological characteristics of cell trans-epithelium in real time [16]. Confocal *in vivo* microscopy assists the compilation of pathological level high resolution imaging from the tissue for disease recognition in cell biology with an advantage of optical sectioning [17]. *In vivo* confocal images from the oral cavity show the distinctive characteristics like variability in nucleus findings that can recognize malignancy from normal oral mucosa [6,17].

Tissue fluorescence spectroscopy

Illumination of the oral cavity tissues with the use of UV-Visible light region result in the absorption of photons by fluorophores. It results in the excitation of fluorophores that causes emission of lower energy photons which are perceived as fluorescence from the mucosal surface [18].

The auto fluorescence spectroscopy system contains an optical fibre which is small and similarly generates wavelengths of variable excitations and consists of a spectrograph that collects the continuums of reflected fluorescence from the cellular structures and analyses the received information on a computer [2,15]. A study revealed that 405 nm wavelength excitation best differentiates normal oral mucosa with oral premalignant lesions [19]. However, a disadvantage is the reduced specificity in recognition of potentially malignant conditions. Auto fluorescence is typically caused by protoporphyrin and the variable concentration of blood components that vacillates proportionately during cancerous progression and retrogression.[20] The addition of fluorescence-reflectance or dual digital systems, backscattered light analysis and ultraviolet spectra can overwhelm the disadvantages of auto fluorescence [18].

Cell and tissue markers

Epithelial growth factor (EGF), Cyclins, AgNOR, bcl_2 and telomerase are the different tumor markers that have been evaluated [21]. Other tumor suppression markers and anti-tumor response like Retinoblastoma protein, p53 and Cyclin-dependent kinase inhibitors also are evaluated [21]. Angiogenic biomarkers CD105 and Eph receptor tyrosine kinases (Ephs), vascular EGF and four hypoxia biomarkers (GLUT-1, carbonic anhydrase IX, hypoxia inducible factor 1a, and erythropoietin receptor) were also identified as biomarkers [22].

The matrix metallo-proteins are proteases typically expressed by invasive cancers and the contiguous stroma and their expression has often been reviewed in various studies [23].

Colposcopy

Colposcopy, a medical diagnostic technique used to scrutinize the vaginal, vulval and cervix tissues under illuminated light with a magnified view of the area of interest [24]. Three-dimensional images of the tissue surfaces are viewed on a monitor screen, scanned with a portable video. The use of a green/blue filter enables the assessment of changes in the vascularity and color quality, as unfiltered white or yellow light diminishes the dissimilarity concerning the adjoining tissue and the arterioles. A 70-98% accuracy is reported for the recognition of oral mucosal alterations in oral premalignant lesions [24,25].

Salivary biomarkers

Numerous salivary proteins like α-amylase, interleukin 8, tumor necrosis factor-α, Statherin, CA 125, Endothelin-1, CD44, Catalase, Cyclin D1, CEA, Maspin, Lactate dehydrogenase and Transthyretin have been evaluated [26]. Limitations such as the absence of calibration for the method of salivary sample collection, variability in processing and storing; extensive whimsicality concentrations of probable oral cancer biomarkers in saliva of both the non-malignant individuals and oral cancer cases are the few defies in the use of saliva as salivary biomarkers [26].

ELASTOGRAPHY

The elasticity of the lymph node helps to set apart the malignant enlargement from an inflammatory enlargement. The displacement of the tissue structure and its assesment, can evaluate the damage caused [6].

Surface enhanced raman spectroscopy

A factual, pronounced - precise and profound procurement of the molecular tissue structure due to the particular interaction of cellular molecules with photons is obtained with the raman spectroscopy [27]. The spectral characters of lipids, nucleic acids and proteins function as precise Raman biomarkers to differentiate between malignant and normal oral mucosal area [27]. Drawbacks such as non acquistional imaging requires expensive equipment with the process, further the lack of spatial information and multifaceted algorithms to discern the various categories of tissues [18].

Optical coherence tomography

It is an overall cross-sectional tissue structural representation of subsurface images which are recorded. Distribution of polyethylene glycol linked gold nanoparticles that are antibody-conjugated helps in the distinction of the *in-vivo* images of cancerous lesions in oral cavity in a hamster model [28].

Positron emission tomography

Fluorodeoxyglucose-positron emission tomography (FDG-PET) examination demonstrates precise and prognostic significance while defining lymphatic condition. This aids in timely assessment and diagnosis of oral malignancy in affected patients [6-29]. PET/computed tomography (CT) can find and discriminate between

the surgical and radiation-induced variations from residual or recurrent neoplasia's because cancerous cells uphold greater FDG for lengthier intervals of time as compared to infectious and inflammatory structures.

Bio-nanochip

Recently, a novel bio-nanochip (BNC) sensor which is a fast oral-cytology test that amalgamates the power of cytological morphometric examination with quantification of neoplastic biomarkers was documented [31]. Generally, microfluidics technology (lab-on-achip) is the adjustment, miniaturization, amalgamation, and automation of analytical laboratory procedures into a solitary chip [28]. The conducted study on quantitative BNC method to oral cytology effectively revealed cancerous and pre-cancerous conditions in a short time duration (< 45 min) [31]. The recognition of cancerous cells in the BNC sensor utilized membrane-related cell proteins that are especially present on the cellular membrane structure of neoplastic cells [32].

Conclusion

Lack of knowledge in respect to the various indications, clinical presentation and predisposing reasons for cancers of the oral cavity and are considered to be responsible for the diagnostic delay. Primary line for cancer screening is achieved through a subjective visual examination, further intensifying public attentiveness concerning the relevance of routine intra-oral examination and the development of diagnostic aids that can be used by the oral health care professionals to swiftly identify oral premalignant lesions.

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