Review Article

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Light-based headways: An innovation in oral cancer espial

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Abstract:

Oral cancer is one of the most common malignancies in the world, mainly because of the widespread consumption of tobacco and related products. Early detection is very important in the management of oral cancer. However, when the lesion is detected in the oral cavity, it is at a much advanced stage for effective management, resulting in morbidity and mortality. A majority of deaths related to cancer are due in part to late diagnosis. In order to improve the clinical outcome of oral cancer, early detection is very important. One of the emerging technologies in the early detection of oral cancer is the use of noninvasive in vivo tissue imaging that captures the molecular changes at high resolution to improve the detection capability of oral cancer at an early stage.

Key words:

Early detection, oral cancer, noninvasive diagnostic aids

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Introduction

Oral cancer is a multistep, multipathway, and multifocal process extending over a period of 10-20 years, where a majority of carcinomas are assumed to be preceded by readily detectable visible changes of the oral mucosa.[1] Oral cancer is any malignant neoplasm that is found on the lip, floor of the mouth, cheek lining, gingiva, palate, and/or in the tongue.[2] Cancer is one of the major threats to public health in the developed countries and more so in developing countries according to WHO report as depicted in Table 1[3,4] Worldwide, cancers of the oral cavity and pharynx are the sixth most common type.[5] The incidence of oral cancer worldwide is around 500,000 new cases every year, accounting for approximately 3% of all malignancies, thus creating a significant worldwide health problem.[1] The incidence of oral cancer is highest in India and in South and Southeast Asian countries. The most common form of oral cancer is squamous cell carcinoma (SCC), which accounts for 90-95% of all cancers of the oral cavity. It is among the top three types of cancers in India. In India, 20 per 100,000 population are affected by oral cancer, which accounts for about 30% of all types of cancer. Over five people in India die every hour because of oral cancer.[2] The international agency for research on cancer has predicted that India's incidence of cancer will increase from 1 million in 2012 to more than 1.7 million by 2035. This indicates that the death rate will also increase from 680,000 to 1-2 million in the same period.[2] High incidence of oral cancer in India is attributed to a number of etiological factors. Severe alcoholism, use of smoke and smokeless tobacco, betel-nut chewing, and human papilloma virus (HPV) are the most common risk factors for oral cancer. In addition, oral cancer may also occur due to poor dental care and poor diet.[2] The occurrence of oral cancer is most frequent after the age of 40 years, with a peak at 60 years of age. It also affects males twice as often as females. Recently, several studies have suggested that head and neck cancers, particularly tongue cancer, are increasing in young adults both nationally and internationally.

The incidence of oral cancer has risen in the past decade and is usually recognized when symptomatic and at a late stage. The overall 5-year survival rates for oral cancer have remained low at approximately 50% for the past decades and have remained among the worst of all cancer death rates, considerably lower than that for colorectal, cervix, and breast origin. This is due to the lack of training of health professionals for early detection and diagnosis. Despite significant advances in cancer treatment, the early detection of oral cancer and its curable precursors remains the best way to ensure patient survival and improved quality of life.

The purpose of this review article is to summarize the noninvasive detection techniques that are currently being marketed to aid general dentists and other health-care providers for the early diagnosis of potential cancerous lesions.

Table 1: Incidence of oral cavity cancer (ICD-10: C00-C08) among all ages of male and female

Incidence	Male	Female
≥6.9	India, Pakistan, Sri Lanka, Burma, Russia	India, Pakistan, Sri Lanka, Bhutan, Namibia
3.3-6.8	Argentina, Norway, Sweden, Thailand, Afghanistan	Australia, Afghanistan, Saudi Arabia, Thailand, Burma
≤3.2	China, Mexico, Nigeria, Iran, Saudi Arabia	Russia, Sweden, China, Iran, south Africa

Age-standardized rate (ASR) per 100,000 world standard population.

Importance of Early Detection

There is general consensus that the clinical stage at the time of diagnosis is the most important predictor of recurrence and mortality in oral cancer patients. The time of diagnosis is influenced by multiple clinical and sociodemographic variables, including patient reluctance to consult a health-care professional due to lack of access to health care, especially in patients with low socioeconomic status, as well as professional delay in diagnosing and treating the disease. Dentists and other health-care providers are in desperate need of systemic educational updates in oral cancer prevention and early detection as they must become the first level of manpower in the detection of early oral cancers. A major challenge for the early diagnosis of at-risk tissue is our limited ability to differentiate oral precancerous lesions at high risk of progressing into invasive SCC from those at low risk. Thus, the prevention of oral cancer and its associated morbidity and mortality hinges upon the early detection of oral precancerous lesions, allowing for histological evaluation and subsequent treatment depending on the stage of diagnosis. Early detection and screening for oral cancer has the potential to decrease the morbidity and mortality of the disease, but methods for screening have not proven successful. Although a typical routine oral cancer examination requires a 90-s visual and tactile examination, very few practitioners and dentists in particular are conducting this examination.[1]

Noninvasive Tool for Early Detection

Recent advancements in oral cancer research have led to the development of potentially useful diagnostic tools at the clinical and molecular level for the early detection of oral cancer. The gold standard for oral cancer diagnosis remains tissue biopsy with histological assessment, but this technique needs a trained health-care provider and is considered invasive, painful, expensive, and time consuming. Recently, noninvasive light-based screening methods have becomeavailable for the early detection of malignant or premalignant lesions. Depending on the type of light and the imaging approaches used, optical imaging of the oral tissues can detect minimal changes within the tissues, such as alterations in tissue architecture and composition, expression of specific biomarkers, microanatomy, tissue boundary integrity (e.g., potential invasiveness of lesions), vascularity/angiogenesis, and perfusion.[1] Light-based systems enhance the visual inspection of intraoral tissues and help distinguish healthy areas versus potentially malignant lesions occurring at the submucosal layers and therefore not readily visible to the naked eye.[6] Following are the currently available innovative light-based techniques used for the early detection of oral cancer:

ViziLite

It involves the use of a handheld, single-use, disposable chemiluminescent light stick that emits light at 430, 540, and 580 nm wavelengths. ViziLite Plus with TBlue system requires a 30 s acetic acid prerinse that dehydrates the tissue.[3] The use of this light stick is intended to improve 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 could be related to altered epithelial thickness or to the higher density of nuclear content and mitochondrial matrix that preferentially reflect light in the pathological tissues.[1] The reported sensitivity of ViziLite ranged from 0[7] to 84%[8,9], and the specificity ranged from 15[9] to 91%.[8] When ViziLite was compared with Toluidine Blue, it showed better diagnostic values; however, it did not provide additional diagnostic value compared to the conventional clinical examination. ViziLite provided better specificity results than VELscope, but its sensitivity was lower. The principle utilized in ViziLite (Zila Pharmaceuticals, Phoenix, Arizona) has limitations such as (a) low specificity (b) not distinguishing inflammatory/benign/malignant lesions, and (c) questionable diagnostic value as there is a lack of histopathological correlation.[3]

VELscope (Visually Enhanced Lesions Scope)

It is a simple handheld device that uses the principle of fluorescence for the direct visualization of tissue fluorescence. It is quick, easy to use, easy to carry, allows for broader intramural imaging, and is cordless (utilizing a 12 h battery).[1] It does not require a dimmed light and can be used under incandescent light.[6] The site of interest is viewed through the instrument eyepiece. VELscope has a higher intensity for a better visualization; an external camera attachment was added to facilitate a photo documentation of suspicious lesions during the examination.[6] To differentiate between normal and abnormal mucosa, the tissue is exposed to different wavelengths (400-460 nm) of light. The excited tissue responds via autofluorescence due to cellular fluorophores. The abnormal tissue has a different fluorophore concentration leading to a color change. The normal mucosa glows as pale green whereas the abnormal mucosa absorbs fluorescence and acquires a dark magenta, brown, or black color. The system uses a small optic fiber that does not cover the entire mouth and hence presents a limitation to be used in very small mucosal areas.[3] Its sensitivity ranged from 30[10] to 100%[11], and specificity ranged from 16[12] to 97.4%.[10] The diagnostic values of the conventional clinical examination and VELscope provided comparable results.

Identafi 3000

The Identafi 3000 technology combines anatomical imaging with fluorescence, fiber optics, and confocal microscopy to map and delineate precisely the lesion in the area being screened.[1] It uses three lights: (i) white; (ii) violet (405 nm), both of which work via tissue reflectance and fluorescence; and (iii) amber (560 nm) light that helps in the visualization of vascular architecture.[3] The advantage of this device over the VELscope is its small size and easy accessibility to all tissues in the oral cavity. Besides the detection of autofluorescence similar to the VELscope system, this device also examines tissue reflectance that is based on the premise of detecting changes in angiogenesis with green-amber light (540-575 nm wavelength) illumination. The amber light is thought to enhance the reflective properties of the oral mucosa, allowing a distinction between normal and abnormal tissue vasculature. Increased angiogenesis is a known process during oral carcinogenesis and oral cancer progression. It is important to develop imaging technology for evaluating the status of tumor angiogenesis.[1] Identafi fluorescent light makes abnormal lesion appear dark brown or black, and healthy tissues reflect as blue fluorescence areas.[6] The study showed sensitivity and negative predictive values equivalent to the conventional clinical study, that is, 50 and 98%, respectively. However, the specificity and positive predictive values were lower than what was reported for the conventional clinical examination, 81 versus 98% and 11 versus 50% for the specificity and positive protective value of Identafi and the conventional test, respectively.

PET SCAN (positron emission tomography) with FDG (fluorodeoxyglucose)

PET SCAN can be used for the delineation of extent and detection of regional lymph node and distant metastasis of an unknown primary tumor origin or synchronous second primary tumor.[13] PET imaging is performed with a dedicated PET scanner. The scanner's septa allows examinations in either a 2D or 3D mode. All patients were made to abstain from food and drink for 6 h before undergoing PET. Prior to the examination, FDG/kg body weight is to be administered intravenously. After intravenous injection of FDG, the patients are kept at rest in a quiet, dimly lit room for at least 40 min. Talking, walking, or other physical activities are avoided to reduce muscle uptake. The time between tracer administration and the start of the PET scan varies between 53 and 110 min (average 64 min). PET's currently available data from various studies demonstrated large variations in sensitivity and specificity for FDG PET in the detection of cervical lymph node metastasis in head and neck cancers. These ranged from 67 to 96% for sensitivity and from 82 to 100% for specificity.[14] There are some limitations that are unique to PET with FDG including artifacts, false positivity in posttreatment phase due to inflammation and granulation tissues, and so on.[13]

In addition to the false-positive results associated with inflammation, FDG uptake in nodes reactive to recent biopsy or inflammation resulting from the ulceration of the primary tumor is a source of false-positive or equivocal activity in the lymph nodes.[15]

Table 2: Unique features of new light-based devices for the detection of oral cancer

Light-based devices	Unique features
ViziLite[3]	• Works on chemiluminescent light to check the keratinization • Require pre-rinse for 30 s to dehydrate tissue • Lacks histopathological correction
VELscope[1]	• No pre-rinse required • Works on the principle of tissue fluorescence
Identafi 3000[3]	• Works on the principle of reflectance and fluorescence • Visualization of vascular architecture[3]
PET Scan with FDG[11,12]	• Examine in a 2D or 3D mode • Time consuming • Complicated procedure[12] • Chances of false-positive results[11]
Contact Endoscopy[16]	• Quick procedure • No radiation exposure • Can not give clear image of cells beyond most superficial layer[16]

Contact Endoscopy

Contact endoscopy is a noninvasive tool that allows the surgeon to see cellular detail in vivo and provide instantaneous diagnosis. It can scan large areas quickly. It is simple and has high sensitivity, specificity, and accuracy.[16] Contact endoscopy is simply a magnifying endoscope that, when placed in direct contact with the mucosal surface, delivers images at 60 or 150 magnification. To provide contrast, methylene blue (MB) is applied topically to stain nucleic acids. Cell nuclei stained dark blue are visible against the lightly stained cytoplasm. Neoplastic cells are strongly stained by MB because of their high mitotic rate. Furthermore, blood vessels are stained by MB, which can be used to identify the formation of new vessels resulting from angiogenic processes. By examining and interpreting these features, it is possible to make histologic interpretations in vivo. Wardrop *et al*.[17] described how invasive carcinoma can be diagnosed by identifying tortuous vessels within the lamina propria lying deep to an epithelium that bears the histologic features of cellular atypia. Furthermore, by interpreting the degree of atypia within these cells, it is possible to grade the severity of dysplasia. Some limitations of contact endoscopy include the following: at high magnification, the image resolution obtained by contact endoscopy is significantly affected by glare from light reflected by cells not in focus. As a result, contact endoscopy cannot give clear images of cells beyond the most superficial layers of the epithelium, since tumor margins exist in three dimensions, which prevents the accurate distinction between carcinoma in situ and invasive carcinoma.[18] The unique features of new light-based devices for the detection of oral cancer are shown in Table 2.

Conclusion

Mortality due to oral cancer is raising high as consumption of tobacco is on an exponential growth. The major reason

behind is the easy availability of these products to the wider population at an early age. The only technique apart from educating the cases is to target the population at risk and make them undergo regular health checkup.

The early detection of cancer is of utmost importance in the overall management of potentially malignant lesions like oral cancer. As several newer, sensitive, and noninvasive techniques are available, early cancer detection must be made more effective involving a larger segment of the population who are especially at a greater risk of developing cancer.

There are recent advances in cancer detection that need to be made available not only to the individuals from urban settlements but also to the individuals from rural settlements. Light-based headway products like ViziLite, VELscope, and Identafi are portable and can reach the doorstep while contact endoscopy provides instant diagnosis. PET scan can provide lymph node metastasis but requires a large amount of time.

In spite of the biopsy, considered as the gold standard, there is a need to diagnose the condition at the earliest for which such new techniques are the need of the hour.

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