REVIEW

ORAL CANCER DIAGNOSIS- THE PATH TREADED AND THE WAY AHEAD

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ABSTRACT

Oral cancer is a fatal disease and constitutes a major health problem in developing countries representing the leading cause of death. Though it occurs in middle aged and elders, an alarming number of this malignancy is also being documented in younger adults. A significant number of these develop from potentially malignant lesions like leukoplakia, erythroplakia, lichen planus and oral submucous fibrosis. Early diagnosis and prompt treatment offer better diagnosis for the patient. This article aims to review the current and future trends in diagnostic aids of oral cancer.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the sixth most common cancer for both sexes worldwide. Every year it accounts for more than 300,000 cases worldwide, more than 30,000 cases in the United States and more than 3,000 cases in Canada. The 5-year survival rate for oral SCC has remained at approximately 50% for the past several decades.

Oral medicine with respect to diagnostic decision making has seen remarkable advances over the years. Technical advances from biochemistry, immunology, histopathology, molecular biology, and optical physics have come together to radically change the way diagnosis is arrived at or confirmed which in earlier times was difficult to achieve.

At present, clinical examination and histopathological studies are the standard diagnostic methods to ascertain whether biopsied material is a precancerous or cancerous lesion. Identification of high-risk oral premalignant lesions and intervention at premalignant stages could constitute one of the keys to reducing the mortality, morbidity and cost of treatment associated with SCC.

ORAL CANCER DIAGNOSTIC AIDS

Vital Tissue staining

Toluidine blue staining is considered to be a sensitive adjunct tool for invivo identification of early oral squamous cell carcinoma (OSCC) and high-grade dysplasia. Toluidine blue is an acidophilic metachromatic dye that selectively stains acidic tissue components such as DNA and RNA. Sensitivity of this technique ranges from 0.78 to 1.0 while specificity yields to 0.31-1.0.

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The sensitivity, specificity, and accuracy of using 3-5% acetic acid (used for cervical cancer screening) for oral cancer examination were reported to be 83.33%, 84.21%, and 83.64%, respectively. The sensitivity for use of methylene blue dye (used to detect gastric, prostate and bladder cancers) when used for oral cancer screening was 90%, the specificity 69%, positive predictive value 74%, and negative predictive value 87%.

**Photodiagnosis and tissue fluorescence imaging**

Malignancy related biochemical and morphologic changes perturb tissue absorption, fluorescence and scattering properties. Thus biochemical information can be obtained by measuring absorption/reflectance, fluorescence or Raman scattering signals. Several light based adjunctive aids have been employed to aid in the diagnosis of oral cancer which include chemiluminescence, tissue fluorescence imaging, and tissue fluorescent spectroscopy.

The term “chemiluminescence” refers to the emission of light from a chemical reaction. In this system, a nontoxic blue-white chemiluminescent light of 490-510nm wavelength is shone into mouth and tissue reflectance is observed. Under this light, dysplastic tissues with enlarged nuclei, highlighted by dehydration with acetic acid, appear “aceto white”. The accuracy of this technique to detect oral cancer and potentially malignant epithelial lesions is 80.6% as compared to 64.5% of toluidine blue.

Epithelial and stromal changes in tissues alter their ability to emit fluorescence after stimulation with an intense light. Velscope operates on this principle by emitting a cone of light in the blue spectrum (400-460nm) into the oral cavity causing fluorophores in the oral tissue to excite and fluoresce which can be viewed through a narrow band filter embedded in the instrument. The reported sensitivity and specificity values are significantly lower ranging from 30% to 92% and 15.3% to 77%, respectively.

**Brush Biopsy**

Oral brush biopsy also known as the Oral CDx Brush Test is a chair side diagnostic procedure consisting of a kit containing a stiff bristle brush, a glass slide, a form, a fixative (alcohol/polyethylene glycol), and a container for sending samples to the oral CDx lab. This test works by placing the brush on one spot and rotating it until it produces hemorrhagic spots. The sample obtained is then fixed on a glass slide and sent to the laboratory.

A multicenter study comparing oral brush biopsy with scalpel biopsy reported specificity rates to be 100% for “positive” oral CDx results and 92.9% for “atypical” oral CDx results. The sensitivity rate for oral CDx was also reported as 100%. Emerging Trends

Recently, an increased amount of effort has been made to develop less invasive early diagnostic modalities for oral cancer, of which the in vivo high-resolution imaging of oral epithelial tissues using novel optical systems and the chemical analysis of saliva show great promise as valuable tools. Advanced optical systems for in vivo imaging, such as optical coherence tomography (OCT) and confocal reflectance endomicroscopy, are designed to image cell and stromal morphology for noninvasive clinical diagnosis in real time. However, the contrast between neoplastic and normal tissues is often too low to be of any clinical value.

Optical coherence tomography is a new high resolution optical technique capable of providing cross sectional imaging of biological tissue. They utilize a fibre optic probe with an imaging depth range of 2-3mm. It provides real time structural imaging based on low coherence interferometry, using broadband light to provide cross sectional, high resolution subsurface tissue images. The sensitivity and specificity in diagnosis statistics can reach 82 and 90% respectively. However significant challenges to the use of diagnostic spectroscopy include the often low signal to noise ratio, difficulty in identifying the precise source of signals, data quantification and establishing definitive diagnostic milestones and endpoints.

Opto-acoustic tomography is a novel medical imaging method that uses optical illumination and ultrasonic detection to produce images of deep tissues based on their light absorption. The development of a molecular-based contrast agent composed of gold nanoparticles conjugated to a monoclonal antibody that improves opto-acoustic tomography imaging potentiates its use in imaging deep tumours in early stages of cancer or metastatic lesions.

Raman spectroscopy is another technique that has been used to study cancer-related chemical changes in both cancers tissues as well as biofluids. Saliva contains many macromolecules such as proteins and nucleic acids giving a Raman signature. However, Raman spectra from saliva are inherently weak, making interpretation difficult. Metallic nanoparticles have recently been investigated to overcome the limitations of these imaging and chemical-based diagnostic techniques.

**Nanodiagnosis**

Nanotechnology has the potential to offer solutions to these obstacles surfacing in oral cancer diagnosis and therapeutics. Nanodiagnostics, defined as the use of nanotechnology for clinical diagnostic purposes, was developed to meet the demands of clinical diagnostics for increased sensitivity and earlier detection of disease. The use of nanotechnologies for diagnostic applications shows great promise to meet the rigorous demands of the clinical laboratory for sensitivity and cost-effectiveness. New nanodiagnostic tools include quantum dots (QDs), carbon nanotubes, paramagnetic nanoparticles, gold nanoparticles, and cantilevers. These nanoparticles can be used for drug screening to drug delivery to diagnosis/monitoring.

Nanotechnology refers to the area of science devoted to the manipulation of atoms and molecules leading to the production of structures in the nanometer scale size range (often 100nm or smaller) which retain unique properties. Nanotechnology deals with structures that range from 1 to
Nano sized semiconductor quantum dots can emit light and are applied particularly in cancer imaging studies. They have enough surface area to combine therapeutic agents and tumour specific modalities for the combined results of drug delivery, imaging and tissue engineering. Recently their use has also been implicated in near infrared imaging (700-1000nm) as imaging probes.

Carbon nanotubes scan down DNA and look for single nucleotide polymorphism which make possible to detect whether an individual has a high risk or low risk configuration for developing the processes that lead to cancer. This technique can serve as an alternative to PCR and identify multiple nucleotide polymorphic sites in large strands on nonamplified DNA at relatively high throughput and low cost.

Nanowires having the unique properties of selectivity and specificity can be designed to sense molecular markers of malignant cells. These are laid down across a microfluidic channel and cells or particles are allowed to flow through it. These nanowires can be coated with a probe such as antibody which can recognize particular antigens. Proteins that bind to the antibody will alter the nanowires electrical conductance which can be measured by a detector. Thus proteins produced by cancer cells can be diagnosed and detected early. Labeled and nonlabelled nanoparticle contrast agents are being tested as imaging agents in diagnostic procedures such as nuclear magnetic resonance imaging.

Quantum Dots, which are the most promising nanostructures for diagnostic applications, are semiconductor nanocrystals characterized by high photostability, single-wavelength excitation, and size-tunable emission. QDs and magnetic nanoparticles can be used for barcoding of specific analytes. Gold and magnetic nanoparticles are key components of the bio-barcode assay, which has been proposed as a future alternative to polymerase chain reaction (PCR). The potential diagnostic uses of QDs are numerous, with the most promising applications being in the areas of tumor detection, tissue imaging, intracellular imaging, immunohistochemistry, infectious agent detection, multiplexed diagnostics, and fluoroimmunoassays.

Gold nanoparticles also possess other favourable physicochemical properties for use as optical probes for early detection of oral cancer. They can provide an optical contrast to discriminate between cancerous and normal cells. Their conjugation with antibodies or peptides through electrostatic interaction or coordinate bonding to probe for specific cellular biomarkers (epidermal growth factor receptor [EGFR] is overexpressed in vast majority of epithelial cancer but not in normal cells. Such molecular imaging assists clinicians in diagnosis of precancers.

Nanodiagnostics promise increased sensitivity, multiplexing capabilities, and reduced cost for many diagnostic applications as well as intracellular imaging and may have a profound impact on detection and management of oral cancer in the years to come. These technologies can replace the conventional detection and therapeutic modalities thereby reducing the mortality and morbidity caused due to head and neck cancer. However cost of nanotreatment and biocompatibility are the major hindrances to the use of nanoparticles.

Conclusion

The role of oral health professionals is pivotal in early detection of oral cancer. Despite tremendous advances in the field of diagnosis of oral cancer, many challenges still remain. Keeping ourselves abreast with the emerging diagnostic trends is the need of the hour. Utilization of these diagnostic aids with well-designed clinical studies in low risk populations is warranted to assess the efficacy of these evolving diagnostic aids for oral precancer and cancer.

REFERENCES


