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Review Article

Oral Cancer Diagnosis: From Biopsy to Metabolomics

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Abstract

Although significant efforts are being made in early detection, the five-year survival rates and the prognosis of OSCC have not improved due to delayed diagnosis. Early detection of oral squamous cell carcinoma (OSCC) and treatment at earliest stages are essential in therapeutic techniques and interventions, good prognosis, and survival rate. This paper reviews current potential methodologies used in OSCC detection and examination, such as vital staining, brush biopsy, and photodynamic. There is a desperate need for new non-invasive diagnostic tools in oral mucosal screenings and early detection that could be easily performed within a clinical setting. We discuss essential function of whole salivary fluids in early diagnosis of OSCC. The saliva based molecular biomarkers and metabolomics analysis offer a non-invasive and cost-effective diagnostic methodologies that evaluates body's physiological conditions and provides information on pathologies at their earliest stages.

Keywords: *Oral Cancer; Biopsy; Metabolomics*

Introduction

Oral cancer is one of the most common types of head and neck cancer, and the sixth (6th) most frequent among all cancers. It affects the lips and oral cavity, including the gums, mucosa, hard palate, tongue, and the floor of the mouth [1].

The process of cancer diagnosis begins when the patient or professional identifies the presence of an intra or extra-oral lesion that may be accompanied by pain or discomfort. It is part of the professional's responsibility to investigate changes in the characteristics observed through clinical examination [2].

More than ninety percent (90%) of oral cancers are oral squamous cell carcinoma (OSCC), that arise from the epithelial lining of the oral cavity. Over the past three (3) decades, the five (5) years survival rates of oral cancer have improved, but remain in the range of 50 - 60%, which is one of the lowest of all major cancer types. In the past twenty (20) years, there has been little or no change in the early detection of oral cancer [3].

The screening for oral cancer should be divided into:

1. Visual Examination; and
2. Photodynamics.

Visual Examination

Oral cancer demonstrates a wide range of clinically detectable changes that may appear as a small early change in the surface texture, color, or elasticity. As the lesion progresses, additional signs became visible. These signs may be ulceration, induration, boney invasion, pain, tooth mobility, dry mouth, and/or ill-fitting dentures [4,5].

Additional tools to enhance visual examination include:

1. Vital Staining [6]; and
2. Brush Biopsy [7].

Photodynamics

Lesions missed during visual examination may be seen with incandescent overhead and halogen dental illumination [8]. This technique requires a 1% acetic acid rinse (I minute), followed by examination under chemiluminescent/white light (wavelength of 490 - 510 mm) [9]. Vizilite Plus has received FDA clearance as an adjunct aid for oral tissue examination of patients at high risk for oral cancer [10].

Exfoliative cytology is a reliable tool for assessing malignant changes in various organs, and has been applied to the diagnosis of oral lesions [11-13].

A key challenge to reduce the morbidity and mortality of Oral Squamous Cell carcinoma is to develop strategies to identify and detect the cancer at its earliest stage, which enables effective intervention. While detection of Oral Squamous Cell Carcinoma is currently based upon clinical examination and histological analysis; specific biomarkers may be helpful in early detection in high risk patients [14]. Salivary screening can be an important choice for high-risk cases of Oral Squamous Cell Carcinoma. The collection procedure is low-risk and non-invasive [15].

Salivary Biomarkers

The oral cavity is composed of multiple tissue types that are colonized by different strains of bacteria and are incorporated in salivary fluids. Saliva is considered as one of the very first digestive system components that initiates the breakdown of starch and lipids [16]. In addition to its important function in taste, mastication, swallowing, digestion, and maintenance of teeth, salivary secretions could be used in detecting pathologies at their earliest stages [16]. Research has shown that salivary flow contains multiple kinds of molecular and microbial analytes and biomarkers [17]. Salivary glands are highly permeable and are surrounded by capillaries that allow for exchange pf molecules from blood into acinus cells [17]. This ultimately suggests that in the presence of a pathology, circulating biomarkers of the disease could be exchanged and find their way into salivary glands and secrete into salivary fluid. Most of the studies in OSCC detection considered using whole saliva for sample collection. Whole saliva is mainly composed of exocrine fluid collected from minor and major salivary glands as well as non-exocrine components, such as fluids from periodontal tissue, mucosal tissue, and epithelial cells [18]. Research has shown that collecting whole saliva is potentially an inexpensive and non-invasive tool that could assist in early detection of pre-cancer and oral-cancer. Biomarkers related to oral related diseases could be seen through changes in DNA that cause up or down-regulation in enzymatic levels [18]. For instance, identification is MMP-8 and MMP-9 are diagnostic biomarkers for detection of periodontal disease [19]; biomarkers such as interleukin 1b (IL-1B), interleukin 8 (IL-8), M2BP, and mRNA biomarkers, such as IL-8, S100P, SAT1, and IL1B are associated with detection of oral squamous cell carcinoma (OSCC) [20]. In addition, co-expression of various proteins such as P53 and p-glycoprotein, P53 and epidermal growth factor (EGFR), c-erbB-2,3 and c-erbB-2,4, P16 and cyclic D1, and P21 and RAR could also provide information on OSCC tissue [20]. It is important to note that there are few complications associated with salivary fluid collection that might decrease the accuracy of diagnosis. These include: lack of standardization of saliva sample, processing, and temperature storage [18].

Saliva Metabolomics

Metabolomics is a relatively new form of “omics” research. Living cells contain many metabolites, which are derived from various metabolic activities. These metabolites are the final products of cellular biochemical processes, including gene transcription, mRNA translation, protein synthesis, and metabolic enzymatic reactions. The comprehensive identification and quantification of these metabolites is called “metabolomics”. Metabolomics is essential to clarify cellular function.

Metabonomics analysis could be conducted both *in vitro* and *in vivo* through collected samples from fluids, tissues, or cells. Metabolomics enable researchers to assess cellular state of a sampled environment by analyzing genetic regulation, and changes in kinetic activity through study of small molecular weight substances [21]. Recent studies have shown the use of metabonomic analysis technique known as ultrahigh performance liquid chromatography-mass spectrometry (UPLC-MS) could be used to detect and diagnose not only oral cancer [22], but also diabetes [23], colorectal cancer [24] and hepatocellular carcinoma [25]. According to a study conducted by Wang., *et al.* five salivary biomarkers showed significant sensitivity in diagnosis of early stages of OSCC (stages I and II) including, propionylcholine, acetylphenylalanine, sphinganine, phytosphingosine, and S-carboxymethyl-L-cysteine [26].

Metobolomic research into the oral biofilm, oral cancer, and saliva is in its early stages; but, several findings have been found, including some physiological functions. In oral cancer research, the metabolomics approach has offered various novel insights into cancer metabolism (e.g. various cancer-specific metabolic pathways).

Conclusion

Early disease detection using non-invasive procedures is crucial for good prognosis. Screening for oral cancer should include thorough examination and palpation of head, neck, thyroid and pharyngeal regions as well as intraoral regions of the mouth such as, tongue (dorsal and ventral surfaces, posterior lateral, and anterior two thirds), floor of the mouth, buccal mucosa, oropharyngeal, and salivary glands.

Currently, the most definitive method for oral cancer diagnosis and screening is scalpel biopsy. It is time-consuming, invasive, and requires extensive experience. CAT Scan technology and Magnetic Resonance Imaging (MRI) have developed rapidly, but can only detect the presence of a mass-and only biopsy can verify if the mass is malignant. Therefore, novel diagnostic technologies are urgently needed to diagnose oral squamous cell carcinoma at its early stage. Saliva, as a diagnostic medium for molecular-based biomarkers offers an easy, inexpensive, non-invasive, and safe approach [27].

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