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EFFECTIVE METHODS OF EARLY DIAGNOSIS OF ORAL LEUKOPLAKIA

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✓ ***Resume***

Oral leukoplakia is rarely symptomatic, and the importance of screening and early diagnosis is derived from its frequent association with oral cavity squamous cell carcinoma [3,4]. Oral leukoplakia constitutes 85% of all potential malignant disorders occurring in the oral cavity, with a described prevalence of 2.89% to 3.6%, a higher incidence among men [5,7]. The etiology of oral leukoplakia is multifactorial [8,12] Consumption of tobacco, whether through smoking or chewing, appears to be the sole direct risk factor implicated in the induction of oral leukoplakia [13,15].

Keywords: malignancy risk, leukoplakia prevention, leukoplakia treatment, malignancy risk.

Introduction

The most commonly described locations are represented by mandibular alveolus (25%-40%), buccal mucosa (22%-46%), palate (27%), tongue (26%), and floor of the mouth (19.3%) [8,10] Negative prognostic risk factors include being of the female gender, advanced age, having a size greater than 200 mm², and having a *Candida albicans* infection. HPV, or human papillomavirus, plays a significant role in developing oral leukoplakia [8]. Particularly, high-risk strains like HPV-16 and HPV-18 are associated with an increased likelihood of developing oral leukoplakia and its progression to cancer [2]. Also, different genes involved in DNA damage response and repair pathways have been reported as candidates for cancer susceptibility.

Visual examination represents the first cost-effective approach, compromised by its inherent subjectivity and the heavy reliance on the clinician's experience. Toluidine blue staining is employed to supplement visual examination, due to selectively stain areas of dysplasia or malignancy [2,3]. However, diagnostic accuracy is sometimes compromised by potential false positives and negatives. As a more sensitive approach, brush biopsy and cytology are often utilized [4,5] While minimally invasive, their sensitivity and specificity can vary, and more severe or deeper dysplastic changes may not be captured. Although tissue biopsy remains the definitive diagnostic method with high diagnostic accuracy, the procedure can present risks and potential discomfort for the patient. In the face of emerging technologies, optical imaging techniques such as Raman spectroscopy (RS) and narrow-band imaging (NBI) are gaining attention [1,4]. These innovative, noninvasive techniques can pinpoint subtle structural and biochemical tissue changes in real time. However, their successful implementation requires specialized equipment and expertise for accurate interpretation.

Methods: The authors performed a comprehensive literature search in the following electronic databases: PubMed/Medline, Embase, Web of Science, Google Scholar, and the Cochrane Library. The search strategy included the combination of keywords and MeSH terms related to "oral leukoplakia," "oral precancerous lesions," "early diagnosis," "early detection," "neoplastic lesions," "oral cavity," "diagnostic techniques and procedures," and "biomarkers." The search was limited to English-language publications with no publication date restrictions.

Study Selection and Data Extraction

Full-text articles were obtained for those that appeared to meet the inclusion criteria or when there was uncertainty. Disagreements between reviewers were resolved through discussion or by involving a third reviewer.

Data extraction was performed using a standardized data collection form. The extracted data included study design, population characteristics, diagnostic procedures, outcomes, and follow-up.

Data Synthesis

The primary objective of this review was to evaluate the diagnostic accuracy of various methods for the early detection of oral leukoplakia. The secondary objective was to compare different diagnostic

techniques and identify potential biomarkers that could aid in the early diagnosis of oral leukoplakia. Due to the expected heterogeneity in study designs and diagnostic methods, a formal statistical analysis was not performed.

Result and discussions

Several different diagnostic methods were used across the studies. These included salivary microRNA, methylene blue staining, Rose Bengal (RB) staining, blue toluidine staining, Lugol's iodine staining, RS, elastic scattering spectroscopy (ESS), diffuse reflectance (DR) spectroscopy (DRS), autofluorescence, NBI, high-resolution microendoscopy (HRME), and photodynamic diagnosis.

The sensitivity of the diagnostic methods ranged from 64.3% to nearly 100%. The specificity of the methods ranged from around 60% to 100%. Several studies reported instances of false positives and false negatives. The diagnoses made included normal tissues, dysplasia, potentially malignant disorders (PMDs), and OSCC. Some studies reported on the ability of the diagnostic method to restrict the margins of premalignant lesions or differentiate between different types of oral lesions.

Patients who are suspected to have premalignant disease will undergo incisional biopsy for histological examination to confirm the diagnosis. However, oral leukoplakia remains a diagnostically challenging lesion that is a potential hurdle for clinicians [7]. It was reported that the 5 year survival rates have not improved despite advancements in treatment [9]. Given the aggressive nature of this condition, the high rates of malignant transformation, and its propensity for early lymphatic spread, early diagnosis is critical in limiting treatment morbidity and maximizing oncologic control.

The technique involves the collection of saliva samples from patients, which is a noninvasive, easy-to-perform, and stress-free procedure.

Several comparative studies have collectively advanced the understanding of other salivary biomarkers in the detection and monitoring of oral diseases with potential malignant transformations.

The study al reinforced the concept that saliva testing could be an effective and reliable method for the early detection of OSCC, particularly in high-risk populations such as those with diabetes. A salivary proteomic analysis was conducted to identify potential biomarkers for OSCC, utilizing Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) and Matrix-Assisted Laser Desorption/Ionization Time-of-Flight/Time-of-Flight (MALDI TOF/TOF) mass spectrometry, the researchers found elevated levels of annexin A8, peroxiredoxin-2, and tyrosine kinase in the saliva of diabetic individuals, proteins previously associated with cancer and OSCC in saliva. The research revealed that salivary IL-8 concentrations were significantly higher in OSCC patients compared to both the precancer group and healthy controls, indicating its promise as a biomarker for OSCC but not for oral precancerous conditions (OPCs), potentially informing prognostic decisions and treatment strategies. Salivary and serum alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels were also assessed among individuals with varying tobacco use and oral health statuses to explore their potential as early diagnostic markers for oral lesions.

The researchers found that both serum and salivary TSA/TP ratios and α-l-fucosidase activity were significantly higher in the patient groups compared to the controls, indicating that these biomarkers could be useful in monitoring the progression of oral cancer. The effect of antioxidant treatment on salivary biomarkers has been assessed in the literature.

Methylene blue has been utilized since 2007 as a tool to detect oral mucosal lesions. The strength of methylene blue lies in its ability to stain cells that contain large amounts of nucleic acid, indicating rapid cell division, a common characteristic of malignant or potentially malignant cells. When applied, methylene blue is absorbed by cells in the oral cavity, resulting in a more intense coloration.

Its reported specificity, which is the test's ability to identify those without the disease correctly, is around 66% to 69%. On the other hand, the sensitivity of methylene blue, or the ability to correctly identify those with the disease, is higher, ranging from 90% to 91%. However, it is important to note that while methylene blue staining is useful, it is not definitive. Areas that appear stained may still be benign, and not all areas of concern will necessarily take up the stain. Therefore, methylene blue staining is typically used as an initial screening tool, and any areas of concern are usually followed up with more definitive tests, such as a biopsy.

The iodine reacts with the glycogen stored in cells. Normal cells, which have a regular amount of glycogen, will stain brown. In contrast, potentially malignant cells, which often have enhanced glycogenesis and loss of cell differentiation, will not take up the stain and appear pale in comparison. The sensitivity and specificity of Lugol's iodine stain have been reported to range from 87.5% to 92.7%

and 60% to 84.2%, respectively [5]. While these figures suggest a high accuracy level, the method has limitations. For example, it can sometimes yield false positives and negatives and may be less effective in patients with certain conditions that affect glycogen storage. In addition, interpreting Lugol's iodine staining results can be subjective and requires experienced clinicians. When Lugol's iodine is combined with RB staining, the sensitivity and specificity in detecting leukoplakia are similar or slightly reduced. This suggests that while combination techniques can potentially enhance diagnostic accuracy, the interaction between different staining methods must be carefully considered to avoid a reduction in effectiveness. One concern is patient discomfort. Applying Lugol's iodine can cause a burning sensation ranging from mild to moderate, potentially leading to a less-than-comfortable experience for the patient during the procedure. Another issue is the potential for nonspecific staining. Lugol's iodine is designed to react with glycogen in cells, but it can also stain other substances like mucous. This nonspecific staining can complicate the interpretation of results, potentially leading to inaccuracies.

By utilizing the structural abnormalities in oral leukoplakia, healthy and cancer cells emit different wavelengths of light. There are 2 main types of light-based systems, namely chemiluminescence and photodynamic diagnosis.

The oral cavity is first rinsed with acetic acid before being examined under chemiluminescent illumination. This allows the user to differentiate between normal and hyperkeratinized epithelium. Dysplastic or hyperplastic tissue has increased nuclear content that reflects light and hence appears white when viewed at low-energy wavelengths. Conversely, the normal epithelium appears dark.

Photodynamic diagnosis involves treating cells with a photoactivated compound that accumulates more in cells with malignant potential when exposed to photoirradiation. A common compound used is 5-aminolevulinic acid (ALA), which induces the fluorescence of protoporphyrin IX in cancerous and precancerous cells. The procedure involves rinsing the oral cavity with a 0.4% ALA solution followed by exposure to a specific light wavelength of 405 nm. This technique boasts a high sensitivity, as studies have reported a range between 80% and 99% [8] However, its specificity can be compromised in patients with a history of radiotherapy, as indicated by some studies [1]. Despite this limitation, using ALA and photodynamic diagnosis can provide valuable information for the early detection and diagnosis of conditions like oral leukoplakia. It is worth noting, however, that the effectiveness of this technique can be influenced by factors such as the patient's individual characteristics and the specific location of the tissue being examined.

Discussion: The early diagnosis of premalignant lesions of the oral cavity can make use of noninvasive, easy-to-use, and effective methods [10,12]. Salivary diagnostics is a method that has spread in recent years [9]. Saliva has a very complex composition, including enzymes, antibodies, hormones, antimicrobial elements, and cytokines [4,9]. The saliva collection is easy, safe, noninvasive, and inexpensive. In recent years, interest has grown in miRNAs (found in various biological fluids, including saliva) being the latter considered as potential markers for diagnosing, prognosis, and evaluating the effectiveness of treating multiple diseases.

Tissue biopsy is an invasive, time-consuming, painful, operator-dependent method frequently not readily accepted by patients [3,8]. Despite this, oral biopsy remains the gold standard method today. Typically, nonearly detection of a premalignant lesion leads to an advanced stage at diagnosis [11,13]. However, several follow-ups have shown that the risk of malignant transformation can persist for over 10 years. For this reason, long-term follow-up with regular checkups by the oral surgeon, maxillofacial, or ENT specialist is required.

A significant limitation in diagnosing oral potentially malignant lesions, such as oral leukoplakia, is the need for more awareness and knowledge among dental and medical professionals. Despite the availability of various techniques for oral examination, the challenge persists due to a limited understanding of oral leukoplakia and its diagnostic process [2,7]. Bridging these gaps by enhancing awareness and knowledge is crucial to facilitate early detection and prevent the progression of OSCC and other potentially malignant lesions in the oral cavity.

Subjectivity in diagnosis due to visual interpretation and the variability in lesion appearance further complicate accurate identification[3,6]. In addition, sampling bias during biopsy procedures, the absence of reliable predictive biomarkers, limited accessibility to specialized care, and patient compliance with follow-up appointments all contribute to the challenges in achieving early and precise diagnoses. Overcoming these limitations requires standardized diagnostic criteria, diagnostic

techniques, biomarker research advancements, improved accessibility to specialized care, and enhanced patient education and engagement.

Conclusion

Today, surgical biopsy and histology remain the primary therapeutic choices, but the advent of salivary biomarkers presents promising new techniques. Scientific progress is continually modernizing diagnostic procedures to facilitate early detection of oral cancer and reduce diagnostic delay. Although any light-based diagnostic device could aid in diagnosing oral mucosal lesions, chemiluminescence examination can delineate oral lesions more effectively, as the edges of the lesions exhibit improved brightness and clarity. Other emerging techniques include OCT and molecular imaging, which offer high-resolution imaging capabilities.

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