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REVIEW ARTICLE

ROLE OF AUTOFLUORESCENCE SPECTROSCOPY IN THE DETECTION OF POTENTIALLY MALIGNANT DISORDERS AND ORAL CANCER AT AN EARLY STAGE. A SYSTEMATIC REVIEW

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Abstract

Aim this review is to highlight the autofluorescence spectroscopy features encountered in oral cancer and to outline the role of autofluorescence spectroscopy for diagnosis this cancer.

Material and Methods: The systematic review included articles from Google Scholar, Medline, Scopus, Web Of Sciences, PubMed was conducted.

For Search the following keywords: oral mucosa and fluorophores, VELscope; autofluorescence; oral potentially malignant disorders; oral epithelial dysplasia, oral cancer, tissue autofluorescence, diagnosing and/or treatment of oral cancer in humans.

Results: Conducted a preliminary search and reviewed 132 titles and abstracts in this review and 52 full-text articles were selected of high methodological quality.

Delayed diagnosis is a major contributor to the dismal oral cancer survival rate over five years.

Early recognition and diagnosis can improve patient survival and reduce morbidity.

The current systematic review demonstrated, based on the observed features, this method allows for differential diagnosis of malignant and benign, as well as diagnosis of tumors at the earliest stage of their development.

Conclusion: The introduction of autofluorescence spectroscopy into dental practice as an additional method of visualizing pathological changes in the oral cavity is not only relevant, but also necessary for conducting oncological screening and showing oncological alertness.

Key-words: *VELscope; autofluorescence; oral potentially malignant disorders (OPMDs); oral epithelial dysplasia (OED); oral cancer*

Introduction

The problem of oncological diseases is one of the main problems in modern society.

Oral cancer is a major public health problem worldwide and the prevention of oral cancer and its associated morbidity and mortality depends on early detection.[1]

According to the World Health Organization, oral cancer has one of the highest mortality rates at stage III and IV among all malignancies and timely detection and early treatment of cancer of the oral cavity are very importan.t[2]

Despite the fact that oral cancer is a so-called visual, i.e. accessible for examination, localization, the number of patients diagnosed with it at late stages does not decrease.

The World Health Organization (WHO) based on the inspection of the ocular inspection and conventional oral examination proposed screening of cancer of the oral.[3]

The American Joint Committee on Cancer 2020 published a new TNM classification for oral cavity and oropharyngeal cancers.[4]

When examining the ocular inspection and conventional oral examination, it is difficult to differentiate oral cancer at an early stage (T1-20M0) in situ (CIS).[5]

The high percentage of detection of malignant neoplasms in the oral cavity at stages III and IV (i.e., T3/T4) (advanced) is associated with late patient referral, difficulty in diagnosis.[5]

Risk factors malignant neoplasms in the oral cavity: - smoking - alcohol abuse, especially strong alcohol - harmful working conditions (in the presence and excess of maximum permissible concentrations of harmful chemicals in the air of the working area) - long-term trauma to the tongue, cheeks with sharp edges of teeth, dentures - allergic reactions - diseases of the oral mucosa: leukoplakia, erythroplakia, lichen planus - infection with the human papillomavirus - poor nutrition - lack of oral sanitation, poor hygiene - the presence of hereditary syndromes and genetic mutations - exposure to ionizing and ultraviolet radiation.[6,7]

Symptoms in the initial stages of the disease are not specific - patients often do not pay attention to them.

Changes in the oral mucosa can only be seen by a doctor during an examination. Symptoms that require you to see a doctor: - the presence of long-term non-healing ulcers, painless nodules, cracks, white and red spots in the oral cavity; - prolonged pain in the oral cavity, including radiating to the head, ear, and temporal region; - sore throat; - injury to the oral mucosa by dentures, tooth fragments; - discomfort when chewing and swallowing; - difficulty moving the tongue or lower jaw; - numbness of the tongue, part of the oral cavity; - unpleasant putrid odor from the mouth; - increased salivation; - weight loss.

When cancer is localized on the lip, early symptoms are revealed: - long-term non-healing wounds and erosions, long-term rashes similar to simple herpes; - chronic cracks; - papillomas. These symptoms can also be observed in other diseases. However, if they last more than two weeks, then you should immediately consult a doctor. The success of treatment depends primarily on the timely detection of early forms of the disease.

To improve the treatment of patients with oral cancer, early detection of precancerous and malignant lesions of the oral cavity is very important.

Diagnostics malignant diseases are difficult to diagnose using a routine clinical examination, so for diagnostics, a microscopic examination of the affected cells is first performed and tissues in this area.[8]

Currently, various screening methods have been actively used for the purpose of active early detection of asymptomatic oral cancer. Forms of oral cancer screening include cytology,[9] vital staining,[10] and fluorescence visualization (FV).[11]

The diagnosis of oncological diseases of the oral cavity is established by an oncologist based on a histological conclusion after a biopsy and a number of additional examination methods.

The current standard of care for diagnosis and detection is based on clinical evaluation, the histological study of biopsy material, and genetic methods.[12-15]

For the diagnosis of oral cancer, biopsy is the gold standard, however erroneous diagnoses established for patients with neoplasms after a biopsy are most often associated with an inaccurate conclusion by a morphologist.[16-19]

Histological examination of samples of oral mucosal lesions obtained by incisional or excisional biopsy allows a diagnosis to be made based on the examination of a tissue section

However, biopsy may be a technical limitation

because it is necessary to select the most representative areas since different locations have different histopathological characteristics that can lead to error in diagnosis.[20,21]

Biopsy can have negative psychological effects on patients, making many of them reluctant to undergo the examination due to fear of the procedure, which hinders the early detection of oral squamous cell carcinoma.[22]

Alternative diagnostic methods used for the diagnosis of oral cancer cytology immunohistochemical and polymerase chain reaction (PCR) methods.[23]

It should be noted that the methods for diagnosing neoplasms of the oral mucosa should be simple, accessible and effective.

The presence of various methods for diagnosing neoplasms of the oral mucosa indicates the absence of a clear algorithm for their application, an objective assessment of the significance and sequence of each stage of diagnostics.[24]

Based on the above, the most promising direction is the improvement of non-invasive and simple accessible diagnostic methods at dental and oncological appointments to reduce both false-positive and false-negative results, which affect the diagnosis and subsequent treatment. Thus, the high significance of identifying neoplasms of the oral mucosa confirms the need for new approaches to early diagnostics of early forms of neoplasms of the oral cavity.

Many non-invasive light-based diagnostic methods have been developed for the early detection of oral cancer. Among them, diagnostic methods based on autofluorescence are becoming one of the most promising tools for the early diagnosis of oral cancer.[25]

This is a systematic review that aimed to answer the following does autofluorescence spectroscopy have diagnostic value for early diagnosis of oral cancer.

Autofluorescence spectroscopy may be a handy noninvasive diagnostic tool for oral cancers by analyzing cellular changes in structure and chemistry.[26,27]

Autofluorescence spectroscopy is based on the autofluorescence of cells because when cells interact with light of a certain wavelength, they become excited and re-emit light of different wavelengths (colors).[28]

In cancerous conditions of the oral mucosa, the spectral properties of the tissue are altered, which can be used as a diagnostic tool for potentially malignant disease.

In malignant diseases of the oral cavity, structural and biochemical changes in the mucous membrane at the molecular level occur before clinical signs appear.

In normal mucosa, fluorescence in the ultraviolet (UV) and visible regions of the spectrum is due to collagen, the reduced form of nicotinamide, adenine dinucleotide (NADH), flavin, adenine dinucleotide (FAD), porphyrins, elastin and keratin present in connective tissue. Normal mucosa emits green autofluorescence due to the presence of natural fluorophores in the mucosa.[29]

Flurophores of the molecule, which are responsible for the phenomenon of fluorescence and can absorb and reemit the specific lengths of the waves of light and, therefore, malignant changes can lead to changes in the FP, potentially useful for diagnostic purposes.[30]

Normal oral mucosa and submucosa when excited by a light source of appropriate wavelength (400–460 nm) natural Endogenous autofluorescent substances (NADH, collagen, etc.) in the mucosa. emit light green autofluorescence.[31,32]

Cell and tissues within dysplastic and malignant lesions display modifications of the amount and distribution and chemical–physical properties of the endogenous fluorophores.

Molecular, cellular, and tissue changes lead to loss of fluorescence in these lesions.

In neoplastic changes of the mucous membrane, it appears dark due to changes in the quantity and quality of fluorophores in the mucous membrane.[33,34]

In neoplasia, there is a loss of stromal collagen, which leads to a loss of autofluorescence.

These changes in the optical properties of the mucous membrane can help in the early diagnosis of oral cancer (figure 1).

Epithelial carcinoma has a bright red fluorescence or a non-uniform pink glow with foci of red fluorescence.

Mucosal cancer is visualized as a dark spot with clear boundaries against the background of green normal oral mucosa (figures 2, 3).[35]

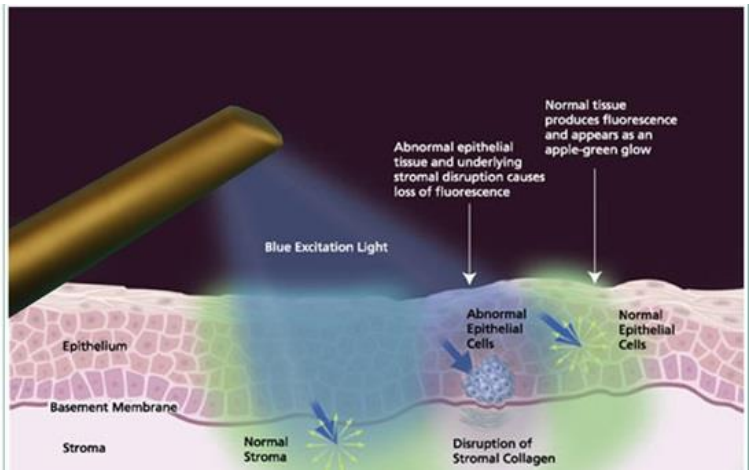

Figure 1. *Fluorescence optical properties of the normal and abnormal epithelial mucous membrane*

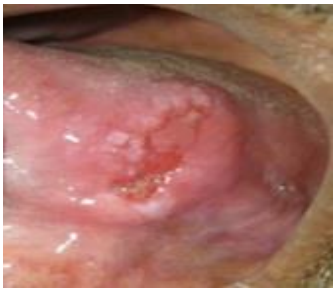

Figure 2. *Clinical picture of tongue cancer*

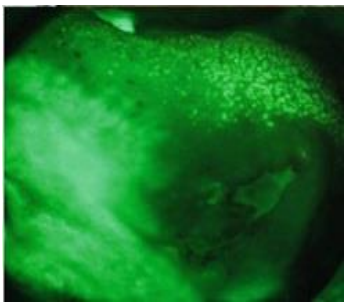

Figure 3. *Fluorescence picture of tongue cancer*

With the VELscope applied, the loss of green fluorescence in oral cancer tissues was confirmed based on the change in fluorescence signal between normal and neoplastic lesions, and this enables physicians to determine the tumor boundaries.[36] VELscope was approved by Food and Drug Administration (FDA).

Farah et al. 2019 demonstrated in their study that optical fluorescence imaging is a useful tool in combination with traditional oral examination (COE) to identify high-risk oral lesions. This method helps dentists identify patients with possible oral cancer in primary care.[37]

Simonato et al. 2019 also demonstrated in their study that the inclusion of FV in the oral examination screening program improved the detection of oral potentially malignant disorders when used by general dentists in a study to diagnose these lesions.[38]

Maryam Amirchaghmaghiк et all 2018analyzed the results of FV for the detection of oral lesions and concluded that this method is not capable of distinguishing benign lesions from malignant and dysplastic ones due to its low specificity.[39]

Ganga RS et al. 2017 demonstrated in their study that the VELscope examination alone cannot provide a definitive diagnosis as to the presence of dysplastic tissue change. In spite of having a reasonable sensitivity, the high number of false-positive results limits its effectiveness as an adjunct.[40]

Oral cavity cancer (OCC) is considered one of the most aggressive and difficult to treat and is a special problem in oncostomatology due to diagnostic errors in incurable forms of OC cancer. At the same time, modern achievements of science and technology make it possible to use new optical technologies for visualization of pathologically altered epithelium of the OC.

This review of the scientific literature showed that the use of fluorescence visualization (FV) has the potential to improve early detection of OSCC and OPMD and may be applicable in clinical practice for general dentists, although further studies in population screening are still needed.

Autofluorescence spectroscopy can classify normal from precancerous and malignant lesions with good accuracy, however the inability to delineate the area of lesions due to small sample size makes scanning the entire oral cavity laborious.

The advantage of the autofluorescence method is that it is a non-invasive procedure and can be

performed in patients with medical problems for whom biopsies are contraindicated, and can also be used as a tool in mass screening procedures.[41-44]

With the VELscope applied, the loss of green fluorescence in oral cancer tissues was confirmed based on the change in fluorescence signal between normal and neoplastic lesions, and this enables physicians to determine the tumor boundaries.[45-47]

Autofluorescence spectroscopy helps to highlight oral lesions and can act as an adjunctive test in the diagnosis of oral cancer.[48]

However, FV should not be considered as a diagnostic method, but as an aid for the clinician with little or no experience in detecting and diagnosing oral diseases.

Early detection of early neoplastic lesions of the oral cavity may be the most effective means to improve the survival and quality of life of patients with oral cancer.

As the technology and protocol standardization of autofluorescence spectroscopy advances, this method may gradually reduce the need for conventional biopsy methods and may become a powerful diagnostic tool for the diagnosis of oral cancer.[49,50]

For the evaluation of any suspicious lesions of the oral mucosa, a comprehensive and systematic conventional oral examination), surgical biopsy and histopathological evaluation are the current gold standards.

Primary care dentists working in outpatient clinics play a key role in oncological alertness and early diagnostics of precancerous diseases of the oral mucosa.

The red border of the lips and oral organs are accessible for visual examination, so precancerous and cancerous changes can be detected in a timely manner. However, ignorance of the principles of oncological alertness, insufficient use of modern methods of visualization of altered epithelium lead to late or erroneous diagnosis of oncological diseases, an increase in the number of patients requiring complex traumatic treatment, and a low survival threshold among patients with oncological diseases of the oral mucosa.

In the future, as digital technology advances, a method capable of performing optical biopsy for non-invasive pathological diagnosis of cancer may prove to be a powerful diagnostic method in clinical oncology.[51]

The current situation is due to the extremely insufficient use of modern methods of oncological screening, insufficient oncological alertness of primary care physicians, and low efficiency of preventive examinations.

At the same time, modern achievements of science and technology make it possible to use new optical technologies for visualization of pathologically altered epithelium of the patients with oncological diseases of the oral mucosa.

Declarations

Conflicts of interest and financial disclosures

The author declares that he has no conflict percent and there was no external source of funding for the research in question.

Ethical approval

The study was approved by the University ethics committee and was conducted in accordance with the Declaration of the World Medical Association.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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