Diagnostic aids for the detection of oral cancer

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Abstract

Background: Different oral mucosal conditions have a similar appearance and it is the real challenge for clinicians to properly diagnose the lesion. Survival rates for a patient with oral cancer are highly dependent on the stage at which the diagnosis is made. Early diagnosis of oral cancer is critically important for improving survival rates and quality of life for oral cancer patients worldwide. A wide range of commercial diagnostic tools is available for screening. They can be used to screen a healthy patient for cancerous and precancerous lesions as well as to assess the biological potential and risks of malignant mucosal lesions. It is essential to develop critical diagnostic tools for early detection of oral dysplasia and malignancy that are simple and practical to use, non-invasive, affordable and can be easily performed in the chairside in general dental practice.

Aim: The aim of our review was to systematically and critically examine the literature about the aids used in oral cancer screening such as toluidine blue, brush cytology, tissue reflection, and autofluorescence and assess their efficacy in the diagnosis of oral lesions.

Methods: Data was collected using the electronic search method in the following databases: PubMed/Medline, Web of Science. Terms “oral cancer”, OR “oral precancerous lesion”, AND “oral diagnosis” OR “Fluorescence visualization” were utilized. English articles published between 2000-2019, with the available summary and in humans were included.

Results: A total of 239 articles were found from different sources and finally, 14 were selected for this review. Three groups of screening and case-finding aids to the diagnosis of oral cancer and precancerous diseases were identified from the literature: Standard screening tests established diagnostic adjuncts and light-based detection systems. All methods and devices have different advantages and disadvantages and the published papers are controversial. Several studies prove the high specificity and sensitivity of these tests while others reveal no significant improvement of oral lesions detection ability and low clinical value of these methods.

Conclusions: Tools and methodologies reviewed have significant potential to improve routine oral cancer screening procedures. All methods and devices have their limitations, which hinder their wide implementation in general dental practice. There is no sufficient evidence to declare the superiority of any of these methods. Further research is needed to improve the sensitivity and specificity of these methods. (TCM-GMJ November 2020; 5(2):P57-P61)

Keywords: Oral Cancer, Diagnosis, Spectroscopy.

Introduction

Oral squamous cell carcinoma (OSCC) accounts for 90% of all oral malignancies. It is the 11th most frequent cancers worldwide (1). In 2018, 354 864 new cases were registered and ¾ of these cases are in developing countries (2). Majority of oral cancer cases develop from premalignant lesions of oral mucosa (3,4). Since the different oral mucosal conditions have the similar appearance and it is the real challenge for clinician to properly diagnose the lesion. In addition, criteria for diagnose of oral lesions are changing according to advances is oral pathology. In 2017 WHO updated WHO grading system for tumors. In this document certain important terms regarding oral cancer has been changed (3). There are two main potentially malignant lesions of oral mucosa: erythroplakia and leukoplakia. Erythroplakia has a higher malignant transformation rate compared to leukoplakia, while oral leukoplakia has higher incidence rate and is detected more commonly in the clinic (5).

There are certain measures which can decrease the risk of malignant transformation of potentially malignant oral lesions. Among them timely detection and correct diagnosis have crucial importance. Early diagnosis of potentially malignant lesions can affect positively also the diagnosis of oral invasive tumors and give the clinicians possibility to diagnose them at early stages. This can significantly improve the clinical outcomes and increase overall survival rate of oral malignancies (6).

In addition, scientist and public health professionals suggest that another powerful measure to improve early diagnosis can be the increase of public awareness about the importance of regular oral screening and case finding examination. These type of secondary prevention enables general dentist to check also asymptomatic patients and detect small lesions at very first stages which could be otherwise not detected by patient itself.

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For early and proper identification of oral lesions effective diagnostic tools and tests with high sensitivity are needed. The advances in easy and effective diagnostic technologies and their successful implementation in dental clinic can give possibility to general dentists or other dental professionals like dental hygienists more easily and rapidly examine suspicious oral lesions without invasive procedures. This can significantly improve the overall early detection rate of oral cancer.

In this article we will review the relevant recent literature and assess the efficacy of contemporary diagnostic tools which are designed to enable the early detection and diagnosis of cancerous and precancerous lesions.

Methods

Data was collected using electronic search method in following databases: PubMed/Medline, Web of Science. Terms “oral cancer”, OR “oral precancerous lesion”, AND “oral diagnosis” OR “Fluorescence visualization” were utilized. English articles published between 2000-2019, with available summary and in humans were included. Eligibility criteria included publications reporting about efficacy of various diagnostic methodologies and tools in process of oral examination, with sufficient clinical, radiological, and histological information to confirm the efficacy.

Results and discussion

Total 239 articles were found from different sources, 127 were excluded because they were repeated. Summary of remaining 112 articles were analyzed. After screening 69 further records have been removed because the title did not meet the objective of the present review. Abstracts of remaining 43 articles were further analyzed and finally 14 were selected for this review, considering in most of relevance to topic of review and excluding most of case reports. For article selection process PRISMA systematic review guidelines were adapted and flow diagram was done (Figure 1) (7).

Prior to assessing the efficacy of different diagnostic tools we have identified the contemporary definition of two main terms used in cancer diagnostics: “Screening” and “case finding”. Systematic review done by Kujan and colleagues evaluates the screening programs for oral cancer and gives definitions of these terms. In particularly, under the term “screening” is meant: “the application of a test or tests to people who are apparently free from the disease in question in order to sort out those who probably have the disease from those who probably do not” while the term “case finding” is defined as “diagnostic test or method that is applied to a patient who has abnormal signs or symptoms in order to establish a diagnosis and bring the patient to treatment” (8). Oral cancer and precancerous diseases screening and case finding methods are summarized in Table 1. According to this systematic review there are not sufficient data to suggest that only visual inspection can be successfully used as diagnostic method in oral cancer screening procedures. This finding underlines the importance of use of different tools to improve the early diagnostic of oral lesions.

The most convenient way of evaluation of oral suspicious lesion is biopsy. Conventional biopsy is associated with some disadvantages for patients as well as for dentists and is considered as invasive procedure. The easier alternative for conventional scalpel biopsy can be more recent method of morphological evaluation of oral mucosa – brush biopsy. These method was implemented in oral pathology in 1999 and was suggested to be effective oral cancer case-finding method (9). Brush biopsy is performed with special oral brush biopsy instrument, which enables rapid and painless collection of trans epithelial specimen. The sample is further applied on glass slide and fixed for morphological analysis. The great advantage of these method is its ability to be used in dental practice by general dentists without anesthesia. Several studies have evaluated the efficacy of this test. Nanayakkara and colleagues...
report the brush biopsy sensitivity 89.58% for detection of oral cancer, 96. 36% - for sever dysplastic lesions and 98.02% - for any dysplastic findings (9). Poate et al. conducted a retrospective study and reported following results: a sensitivity of 71%, specificity of 32% and a positive predictive value of 44% (10). Scheifele et al. reported higher numbers for sensitivity (92.3%) and specificity (94.3%) (11).

From the results of above mentioned studies it can be concluded that brush biopsy can be powerful tool for screening and early diagnosis of oral malignant lesions. Patients with multiple oral lesions can especially benefit from this method avoiding several invasive procedures. Also, it is more acceptable method comparing to scalpel biopsy for anxious and non-cooperative patients which may refuse referral to oncologist.

Another noninvasive diagnostic method for oral mucosal abnormalities is toluidine blue staining. Toluidine blue is a vital metachromatic dye that stains nucleic acids and abnormal tissues. It is well known and widely used staining in oral pathology. In our search we found several recent studies evaluating the efficacy of toluidine blue staining. Most of them demonstrated relatively high numbers for test sensitivity. Onofre et al reported sensitivity 74%, specificity 66% (12); Barrellier et al reported sensitivity 92%, specificity 42% (13). However, there are some limitations and disadvantages associated with this test. Main disadvantage is that staining is a multistep process requiring acetic rinse before and after. This makes procedural difficulties and also can negatively affect oral mucosa. In addition, analyzed studies report relatively high rates of false positive or false negative results. According to these results we can conclude that it is not advisable to use toluidine blue staining as stand-alone test. However, it can be very helpful to localize the exact smaller areas for further brush or scalpel biopsy procedures and allow dentist to act less invasive.

In order to reveal more complex image of structural and biochemical changes in oral mucosa, more advance methods and tools should be used. It is known that abnormal epithelial tissues after rinsing with diluted acetic acid solution appear acetowhite if seen under blue light (400-460 nm). Acetic acid has ability to make abnormally thickened keratin on the surface of oral mucosa more visible. In contrast, normal epithelium under blue light will absorb light and appear dark (14). ViziLite (Zila Pharmaceuticals, Phoenix, AZ, United States) is special device, whose diagnostic ability is based on the above described phenomenon. Several studies have assessed the effectivity of the use of tissue reflectance as an oral cancer screening method. Kerr and colleagues based on evaluation of 270 subjects report that 78.5 % of lesions detected with this device were clinically suspicious. In addition, 6.6% of lesions were not seen during visual evaluation and could be detected only with ViziLite (14). Study of Pierre and colleagues compared the detection rates between gold standard method – histology and ViziLite and revealed 98% sensitivity and 100% specificity of the test done with this device (15). In contrast to these results another studies revealed not so encouraging results and suggested that overall detection rate is not significantly increased with this technology (16,17). Similar study by Epstein and colleagues revealed only the increase of sharpness of lesions by ViziLite tool (18).

According to these result we can conclude that ViziLite can help to better visualize highly keratinized areas increase the visibility of different oral mucosal lesions (19). However, the high rate of false positive and false negative results demonstrated in studies can be considered as main disadvantage of this method. Clinicians when implementing this device into their daily practice should consider the limitations associated with its use.

Tissue florescence is important property which is used in recent oral cancer diagnostic technologies. In the normal oral mucosa there are certain substrates which have ability to produce endogenous autoflorescence. Collagen and flavin adenine dinucleotide (FAD) are two main exaplanes of such molecules. Certain type of light (blue excitation light, wavelength 400-460nm) emitted from special light source, when directed to these substances decreases the level autoflorescence energy and the letter becomes

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**Table 1. Oral cancer and precancerous diseases screening and case finding methods**

<table>
<thead>
<tr>
<th>Standard screening test</th>
<th>Established diagnostic adjuncts</th>
<th>Light-based detection systems</th>
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<tr>
<td>• Conventional oral examination</td>
<td>• Oral cytology</td>
<td>• ViziLite Plus</td>
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<tr>
<td></td>
<td>• Toluidine Blue Staining</td>
<td>• MicroLux DL</td>
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lower compared to the level of energy coming from source. This lower energy autoflorescence is seen as green light coming from healthy tissues under this type of special illumination (20). The special device which emits this type of light and is based on autoflorescence abilty of oral mucosa is VELscope (LED Medical Diagnostics, White Rock, BC, Canada). The VELscope is a portable device, which allows direct visualization of the oral cavity under special light. Device was approved by FDA and meant for commercial use in oral cancer screening. Lane et al., have studied the efficacy of VELscope in diagnostic process of oral cancers and precancers (21). Results of this study suggest that VELscope can improve the detection rate of oral mucosa lesions that cannot be seen during visual inspection under normal light. Another retrospective pilot study investigates effectiveness of VELscope system in general dental practice among low-risk population (22). Authors demonstrated that implementation of this device in dental practice increased the revealed prevalence of oral lesions from 0.83% for standard protocol to 1.3% for protocol using direct tissue fluorescence visualization and therefore can be useful in detection of oral mucosal abnormalities. Consistent to this previous results the same suggestion have Poh et al. and De Veld et al. (23,24). However, in contrast, Balevi critically analyzes several studies and suggests that more evidence is needed to make strong recommendations to implement VELscope in general dental practice as routine oral cancer screening tool. At same time he finds that this device can be more helpful for special departments or clinics in the field of oncology (25).

In conclusion, main critical issue with VELscope is the fact that the value of its use in general dental clinic is not yet finally proved. However, the technology is promising, with positive data about its efficacy and further research can aim to increase its specificity (26). Further positive results can encourage the wider implementation of VELscope in general dental practice for routine screening procedures.

Conclusion

In this review we have discussed several technologies used to enhance the early diagnosis or oral suspicious lesions. Tools and methodologies reviewed have significant potential to improve routine oral cancer screening procedures. However, sometimes published papers are controversial. All methods and devices have its limitations, which hinder their wide implementation in general dental practice. There is no sufficient evidence to declare the superiority of any of these methods or devices compared to conventional oral examination and morphologic evaluation which is still considered to be gold standard of diagnostics. Therefore, existing diagnostic devices can be used as ad-junctive tools. Further research is needed to improve the sensitivity and specificity of these methods.

References


