Piotr Wesołowski[1], Katarzyna Mańka-Malara[1], Izabela Strużycka[2], Andrzej Wojtowicz[1]

Selected methods for the early diagnostics of oral malignant lesions – a literature review

Wybrane metody wczesnej diagnostyki nowotworowej w jamie ustnej – przegląd piśmiennictwa

[1] Department of Oral Surgery Medical University of Warsaw
[2] Department of Conservative Dentistry Medical University of Warsaw

Streszczenie

Wczesna diagnostyka zmian nowotworowych odgrywa kluczową rolę w przebiegu procesu leczenia oraz dalszego rokowania pacjentów. W pracy przedstawiono wybrane techniki służące do wczesnej diagnostyki zmian patologicznych występujących na błonie śluzowej jamy ustnej, takie jak: chemiluminescencja (system ViziLite Plus), TBlue (który łączy chemiluminescencję z wybarwiania błękitem toluidyny), system oceny VELscope, OralCDx i biopsja szczoteczkowa. Zastosowanie dodatkowych technik wczesnej diagnostyki zmian w jamie ustnej może być pomocne dla każdego lekarza dentysty. Ich zastosowanie nie pozwala na jednoznaczne stwierdzenie charakteru zmiany, nie zastępuje biopsji i diagnostyki histopatologicznej, pozwala jednak z większą czujnością badać jamę ustną oraz wykrywać zmiany we wczesnym stadium zaawansowania

Słowa kluczowe: ViziLite, TB, VELscope, OralCDx, biopsja szczoteczkowa.

Abstract

Early diagnostics of oral cancerous lesions plays a crucial role in the process of treatment and evaluation of the patient's chances for recovery. The article presents new techniques of identifying and detecting abnormal lesions within oral mucosa, such as oral lumenoscopy (ViziLite), TBlue (toluidine blue marking system), VELscope screening system, OralCDx and the brush biopsy. Their application does not allow a definite diagnosis, nor does it replace biopsy or histopathologic assessment, but it permits a more accurate examination of the oral cavity, as well as oral lesion detection at the early stage of progression.

Key words: ViziLite, TBlue, VELscope, OralCDx, brush biopsy.

Early diagnostics of oral malignant lesions plays a key role in the process of treating and evaluating a patient's chances of recovery – oral lesions detected at an early stage, especially in the case of squamous cell carcinoma, markedly improve survival rates [1]. Unfortunately, two thirds of patients are diagnosed with oral cancer in the third or fourth stage of the disease's progression. The conventional visual and manual examinations, supported by biopsy and histopathologic analysis of material, remains the gold standard in identifying and detecting abnormalities in the oral cavity. Histological criteria, evaluations of dysplasia and the stage of the disease, make it possible to evaluate the risk of malignant transformations [2]. Modern diagnostic methods help to conduct ever more precise and accurate examinations.

One of the techniques applied in the diagnostics of oral mucosal lesions is their staining with substances which aid the diversification between normal and abnormal tissues. These substances include 3% Lugol's solution, which works by binding compounds of iodine with glycogen found in cytoplasm, simultaneously marking the tissue brown [3]. The cancerous cells, which are distinguished by an increased activity of glycolysis do not become stained; in contrast to the mucus membrane of healthy tissue, which changes colour [4]. Many publications extensively describe the method of toluidine blue (TB) application. It is an organic substance used for the vital staining of tissues. It binds with the DNA of the cells which are subject to intensive division (during inflammation or regeneration processes), or whose genetic material is damaged [5, 6]. The compound was originally applied in order to aid the detection of oral epithelial dysplasia, and currently it is also used in detecting areas particularly at risk of a malignant transformation, as well as indicating the best possible site in the oral cavity to obtain a tissue sample for biopsy – the tissue sample is obtained from the most stained areas. Toluidine blue is characterized by high sensitivity;

however, it seems to have low specificity – both the benign and inflammatory lesions become stained [7]. Research publications present various methods of TBlue application – in the form of a topical application or as an irrigant. Apart from single applications, in order to eliminate the false-positive results mentioned above, double staining is performed – by repeating the decolourisation procedure during the follow-up appointment which takes place approximately two weeks later [8]. Such a course of action is recommended by Mashberg [9] – before the follow-up visit it is advisable to eliminate all irritating and inflammatory factors which may lead to the false-positive results associated with staining such areas by the use of a toluidine blue solution. The sensitivity in respect of detecting the lesions through TBlue application varies, depending on the researcher, between 38–98% (on average 85%), and in the case of specificity between 22–92% (on average 67%). Onfre *et al.* consider the described method as trustworthy in oral cancer detection, whether invasive or in situ [10].

Another method used in oral cancer diagnostics is chemiluminescence – with the application of commercially available ViziLite Plus together with the TBlue marking system this combines the advantages of chemiluminescence and toluidine blue staining. The ViziLite system consists of two components: a 1% solution of acetic acid with a raspberry flavour which removes the layer of glycoprotein from the surface of the mucus membrane in order to decrease the light reflection and desiccates the cells to increase the nucleus-cytoplasm ratio; the other component being a retractor emitting light for over 10 minutes after its activation with an emission wavelength of 430–580 nm, which enables a precise examination of oral tissues. The retractor constitutes a disposable device. The blue light of ViziLite becomes absorbed by healthy cells and reflected by the cells with abnormal keratin production. Lesions detected by means of this technique then become stained by the use of TBlue system. The TBlue marking system includes three swab components – the first swab, used for initial application, is saturated with a 1% solution of acetic acid; the second one contains a 0.5% solution of toluidine blue; and the last component – a 1% acetic acid solution swab – is used after the dye application. The oral mucosal abnormalities identified during the ViziLite examination have their brightness increased, and are more distinctly demarcated compared to lesions examined using conventional dental illumination [8]. It was also demonstrated that the outlines of the examined lesions are sharper than of those detected during conventional examination [11].

Considering the advantages of applying the presented methods, one must bear in mind that they still have only an auxiliary function. The drawbacks of ViziLite examinations include the disposable retractors and hence increased costs of the method's application, as well as the impossibility of determining the character of a lesion at this stage of examination. The study conducted by Kerra *et al.* demonstrated that some of the red lesions, which are often associated with dysplasia, were not detected by a ViziLite examination [12]. By stating that the application of the VisiLite system improves the effectiveness of white lesion detection, Epstein *et al.* [13] have recognized the usefulness of chemiluminescence in the diagnostics of early malignant lesions in the oral cavity [14]. Other researchers share the view that the application of the diagnostic methods described above enables a detection of lesions that are invisible when examined under conventional dental illumination [15]. This opinion is also supported by the statement that TBlue application decreases the false-positive results by 55.26%, without increasing the percentage of false-negative results [16].

In general, from the quoted assessments made by experienced specialists, it can be concluded that the application of the ViziLite system, owing to its ability to enhance lesion brightness and sharpness, may aid general dentists in the performance of screening tests.

Another well-known system used for oral mucosal lesion detection is the VELscope screening system. Its action is based on the disturbed fluorescence of pathological tissues, which are characterized by a modified fluorophore system [17]. Tissue fluorescence depends on the structural changes which it undergoes, the metabolic activity, the presence of haemoglobin, the blood vessel condition, as well as the possible presence of inflammation. In the light emitted at a wavelength of 400–460 nm healthy tissues are illuminated in green, whereas abnormal lesions are coloured between brown and black. This technique is of great assistance in lesion detection; however, it does not make it possible to differentiate between benign and malignant lesions [18]. According to Poh *et al.*, the application of this lesion identification system may become useful in demarcating the boundaries of a malignant lesion [19]. Moreover, they emphasize the considerable costs of colour interpretation and the difficulties in its performance, which may result in diagnostic errors [20]. Balevi *et al.* recommend the use of the VELscope system only in specialized medical clinics. [21]. The sensitivity of this method is evaluated as ranging between 98–100%, whereas its specificity is estimated at 94–100% [22].

Other systems using light emission for lesion detection include the Microlux DL system. The source of light, which is powered by batteries, is reusable – it can be sterilized. According to the recommendations of the Microlux DL producer, it helps in the detection of pathological tissues and should be used together with conventional exa-

mination [22]. The patient rinses the oral cavity with acetic acid to remove the glycoprotein layer and hence to improve the light penetration. Correspondingly to the previous solutions, it is impossible to differentiate between benign and malignant lesions; however, the visibility of lesions and their visual separation become enhanced.

The Orascoptic DK constitutes a similar lesion identification system, where after the oral rinse with a mild acetic acid solution the oral mucosa is illuminated by an LED diode powered by batteries [23].

The brush biopsy makes it possible to obtain a tissue sample for biopsy with minimal tissue invasion; intrasurgical bleeding is kept to a minimum, the risk of complications is low [24], and the waiting period for results is not long. Nevertheless, the method itself has some drawbacks. Unless all epithelial layers, together with the basement membrane, are taken, there is a considerable risk of false-positive results in the order of 37% [25]. The OralCDx Brush Test helps to eliminate diagnostic errors. In order to obtain a tissue sample a special kit is used, which comprises a brush, a microscopic slide, and a bag with a fixing solution (propylene glycol), as well as an information sheet and a plastic container to ensure dry transportation. The collection of oral mucosal cells is performed with a wet brush, until bleeding spots on the mucus membrane occur [26]. The dentist spreads the obtained material on a microscopic slide, and then fixes it. After staining is performed through the use of the modified Papanicolau method, the obtained tissue sample is analysed under the microscope with the aid of a computer-assisted screening system [27, 12]. It evaluates the shape and size of the cells. This becomes the basis for describing the sample as "negative" or the lesion "benign"; "positive" – including cancerous lesions and dysplasia; as well as "atypical" – encompassing atypical epithelial lesions with an unclear diagnostic meaning or impossible to assess due to the scarcity of epithelial layers [28]. After the introductory assessment the result is interpreted by a histopathologist. A positive result requires obtaining a tissue sample in a conventional way in order to continue the diagnostics procedure. Thus, the ORalCDx Brush Test system is only applied in the case of small-sized mucosal lesions, when obtaining a typical tissue sample is not a procedural option [23]. According to research publications, the sensitivity of this method, depending on the chosen technique of sensitivity analysis, varies between 88% and 100%, and the specificity ranges between 25% and 96% [4]. In their research Acha *et al.* [29] and Driemel *et al.* [30] regard as one of the additional advantages of the Oral CDx system the possibility of an additional cytomorphometrical and molecular analysis. Sciubba *et al.* [26], Christian *et al.* [31] and Scheifele *et al.* [32] recommend the application of the Oral CDx system as a screening technique for the detection of malignant lesions in the oral cavity.

The emergence of new techniques for abnormal lesion identification and detection, indicated in the article, has expanded and enhanced the set of diagnostic methods that are available to dentists for the early detection of oral mucosal lesions. The application of these methods often does not make it possible to expressly determine a lesion's character, hence they cannot replace biopsy or histopathologic diagnostics. However, they provide invaluable help with regard to examining the oral cavity with more precision, and the possibility of detecting oral mucosal lesions at an early stage of progression.

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Adres do korespondencji:
ul. Nowogrodzka 59 Pawilon 11B
02-006 Warszawa
tel.: 22 502 12 42
e-mail: awojt@kcs.amwaw.edu.pl