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Assessment of Clinical Examination Validity in Oral Cancer Risk Patients

SUMMARY

***Background/Aim**: Oral cancer is one of the ten most common cancers in the world, recently positioned as a sixth one, unfortunately with poor prognosis after treatment because of the late diagnostics in advanced stages of the disease. Aim of this study was to present the basic criteria in assessment the accuracy/efficacy, specificity and sensitivity, the positive and negative predicted values of the conventional oral examination (COE) as the easiest and most acceptable procedure in detection of the early changes of the suspicious oral tissue changes compared to the diagnostic gold standard – tissue biopsy in two different groups of examinees. **Material and Methods**: Sixty patients divided into two study groups (one with potentially malignant oral lesions and a second consisted of clinically suspicious oral cancer lesions) were examined with COE and subjected to histopathological confirmation - tissue biopsy. All examined patients underwent the diagnostic protocol by the American Joint Commission on Cancer, selected under certain inclusion and exclusion criteria. **Results:** Sensitivity of COE in the group of examinees with oral potentially malignant lesions is 83.33%, its specificity is 20.83%, the positive predictive value is 20.83% and the negative predictive value is 83.33%. The accuracy of the COE method is 33.33%. The sensitivity, in the group of patients with oral cancer is 96.43%, specificity is 0%, the positive predictive value is 93.10% and the negative predictive value is 0%. The accuracy of this method is 90%.*

***Conclusions**: The accuracy reaches a value over 90% for the group with lesions with highly suspected malignant potential – oral cancer, and sets the thesis that COE as screening method for oral cancer or premalignant tissue changes is more valuable for the patients with advanced oral epithelial changes, but is recommended to be combined with some other type of screening procedure in order to gain relevant results applicable in the everyday clinical practice.*

Key words: Oral Examination, Potentially Malignant Lesions, Oral Cancer, Diagnostics

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Introduction

In the oral cavity and oropharynx, important vital functions take place, primarily mastication, as an initial function of the gastrointestinal system, ingestion, respiration and speech. All of these vital biological functions in humans can be endangered, or even impeded, by the occurrence of neoplasms in that anatomical space. In the facial region, neoplasms can originate from various tissues, such as the mucous membrane of the oral cavity, jaw bones, salivary glands and even tumors of odontogenic origin. However, the most common cancer in the oral cavity is the oral squamous cell carcinoma (OSCC) that originates from oral mucosa[1,2].

In 2016, oral cancer has been diagnosed in more than 600,000 cases worldwide, making it the sixth most common malignant disease in the world[3,4]. The low survival rate of patients with oral cancer can be attributed to the advanced stage of the disease at the time of diagnosis. So,

the greatest success of every clinician is the early detection of oral dysplasia or the on time diagnosis of premalignant and malignant lesions. Screening programs that identify suspicious lesions in asymptomatic patients and applying specific diagnostic procedures that include precise diagnostic tools for identification of dysplastic changes and early-diagnosed oral carcinoma in asymptomatic patients are usually used for this purpose worldwide.

Based on the SEER program of the National Cancer Institute[5], which relies on data for oral cancer, confirms that little or no change is observed in these patients in the early stages. Such abnormalities of the oral mucosa have been difficult to be recognized by patients, often physicians have not detected them in a timely manner, hence an increase in the incidence of oral cancer happen. Therefore, in most patients, the disease is diagnosed in an advanced stage, when the prognosis is quite serious and questionable.

The most common oral malignant lesions are: leukoplakia, erythroplakia, dysplastic leukoplakia, dysplastic lichenoid lesions, oral submucous fibrosis and lichen planus. They all have different malignant potentials. The highest rate of transformation is observed in lesions with clinically irregular or heterogeneous erythroplastic or dysplastic changes[6]. A special aspect in determining the malignancy relates to the ultra structural changes of the lesion. These include phenotypic alteration (presence and severity of dysplasia), DNA instability, and allelic loss (especially chromosome arms at 3p, 9p and 17p and some other molecular markers)[7-10]. All of them have the potential to influence the risk of occurrence and development of OSCC[11,12].

Opportunistic oral screening for malignancies is recommended by the Canadian Dental Association (CDA) and the American Dental Association (ADA). These organizations emphasize that early detection enables treatment in earlier stages of the disease[13,14]. The moment of diagnosis is crucial but usually the right moment, i.e. early detection of cancer is lacking in everyday practice. This is due to the insufficient number of information among the population, poor health culture and education, irregular visits to the dentist and physician but sometimes the fear of facing a bad or life-threatening diagnosis.

The aim of this study is to evaluate the accuracy/ efficacy of the easiest and most available non invasive oral cancer screening method - conventional oral examination (COE), as well as its specificity and sensitivity, the positive and negative predicted values according to the diagnostic gold standard – tissue biopsy in two different groups of examinees with suspicious oral tissue changes.

Material and Methods

The study group was consisted of 60 patients divided into two groups. The first group was formed by 30 patients with potentially malignant oral lesions (PML). Another 30 patients with working diagnosis - oral cancer (OC) were included in the second group of examinees.

All selected patients were followed by the American Joint Commission on Cancer Diagnosis Protocol, with diagnostics, pre-operative preparation, surgical excision, and postoperative clinical follow-up. The selection of patients in the study was made according to certain inclusion and exclusion criteria.

Inclusion criteria:

- Have not received antibiotic therapy for the last two months,
- Have not undergone periodontal treatment for the last two months,
- Have not been / or have not undergone radiotherapy or chemotherapy for the last three months.

Exclusion criteria:

- Inability and unwillingness to participate in the study protocol
- Gravity.

All participants who agreed to take part in the study signed a consent form for voluntary participation in the study. Selection of participants in study group was conducted at the University Clinic for Maxillofacial Surgery at the University "Ss. Cyril and Methodius", the Clinic for Oral pathology and Periodontology at the University Dental Clinical Center "St. Pantelejmon" in Skopje and at the PHO Center for Dental Health - ETERNAdent in Skopje, North Macedonia. The histopathological analysis of the specimens of the examined group was performed at the Institute of Pathological Anatomy at the Faculty of Medicine, University "Ss. Cyril and Methodius" in Skopje, North Macedonia.

Clinical examination

Clinical examination included anamnestic data, clinical examination and analysis of digital orthopantomographic X-rays. Clinical evaluation of the condition of the oral epithelium was conducted through standardized procedures (conventional oral examinations - extra oral and intraoral examination with inspection and palpation). Using inspection, we recorded the size, shape and color of the lesion, the depth of the lesion, as well as epithelial desquamation, the presence of erosions, ulcers or rashes. During the clinical examination, additional signs such as bleeding, loss of sensitivity and burning of the oral mucosa were noted. We also determined the following characteristics of the changes using palpation: lesion hardness, induction of surrounding structures and tissues, and lesion fixation for the underlying tissues.

The oral examination in all patients was double performed (by two independent examiners) and in most of the cases, they both presented same interpretation of the oral screening. In those where they reported similar or fully different findings, eminent specialists for oral medicine or maxillofacial surgeons were engaged for

confirmation. Examiners were supported by a histological reports and on the basis of the clinical examination a working diagnosis was made.

A complete blood tests in all participants in the study were done and an incisional or excisional biopsy was performed for histopathological verification of the biopsy specimens, as the current gold standard of the research procedure.

The histopathological finding, defined as a negative specimen, means that no pathological changes were found outside the edges of the biopsy material. A positive sample indicates the presence of pathological change (epithelial dysplasia, Ca in situ and oral carcinoma) and requires treatment.

Conventional oral examination (COE)

COE using normal (incandescent) light has been a standard method for screening the oral epithelium for a long time. Conventional projections of potential tissue changes at some anatomical sites can be very successful. For example, visual inspection of skin lesions can be an effective screening method for melanoma, with sensitivity and specificity up to 98 percent[15,16]. By decades, it is traditionally positioned as a first step in the oral cancer screening, but nowadays its efficacy become questionable. Many authors present low values for its sensitivity and specificity, but there are many in the literature that shows values over 70 percent[17-19]. Probably the most important thing while evaluating this short, cheap, easy to perform and totally non-invasive screening method is to take into consideration the ability of the performer and his expertise in noticing and differentiating the changes of the oral mucosa.

Statistical analysis

The statistical series, according to the defined variables of interest, are tabulated and graphically presented. Distribution of numerical statistical series (correct / incorrect) is tested with Kolmogorov Smirnov test, Lilliefors test and Shapiro-Wilk's W test. The numerical/quantitative series structure is analyzed with central tendency measures (averages) and dispersion measures (standard deviation). The structure of attribute/ qualitative series is analyzed by means of relationships and proportions.

Testing the significance of the difference between the both arithmetic environments in the independent samples, with correct distribution being performed by One-way ANOVA, and testing the significance of the difference between the two arithmetic median value with the Tukey honest significant difference Test. The accuracy/diagnostic value of the test methods is determined by the Sensitivity and Specificity Test. Significance level for $p < 0.05$ at CI = 95% is taken as statistically significant.

The database is analyzed with the statistical programs STATISTICA 7.1 and SPSS for Windows ver. 20.

Results

In the first group, consisted of patients with potentially malignant lesions, the result of the histopathological finding (biopsy) was positive in six patients and negative in 24 patients. During COE, 24 patients were classified as positive (noted changes of the oral mucosa not specified for a certain disease or disorder), five of which were true positive, 19 were false positive, one patient was defined as false negative and five were classified as true negative after biopsy. Sensitivity of COE is 83,33%, its specificity is 20,83%, positive predictive value is 20,83% and negative predictive value is 83,33%. The accuracy, i.e., the general probability that the patient will be correctly classified by the method of COE is 33.33%. (Table 1 and 2, Figures 1 and 2).

Table 2. shows the values of sensitivity, specificity, positive predictive value, negative predictive value and method accuracy, together with the lower and upper limit of the confidence interval of 95% (CI= 95%), and Figure 2. shows the ROC curve.

Table 1. Crosstabulation of the results in examinees with potentially malignant lesions (PML) by COE and pathological results

		Pathological results		Total
		Positive	Negative	
COE	Positive	5	19	24
	Negative	1	5	6
	Total	6	24	30

Table 2. Sensitivity and specificity of COE within potentially malignant lesions (PML)

COE	Value	CI = 95%
Sensitivity (Se)	83,33%	35,88% to 99,58%
Specificity (Sp)	20,83 %	7,13% to 42,15%
Positive predictive value (PPV)	20,83%	14,84% to 28,45%
Negative predictive value (NPV)	83,33 %	41,52% to 97,24%
Accuracy	33,33%	17,29% to 52,81%

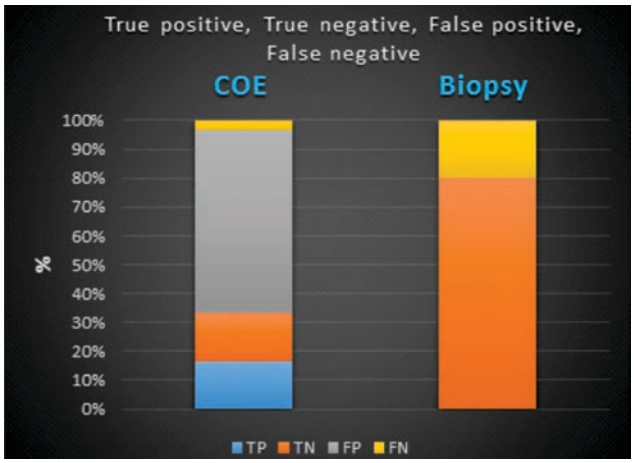

Figure 1. Distribution of examinees with potentially malignant lesions (PML) by histopathological finding and COE

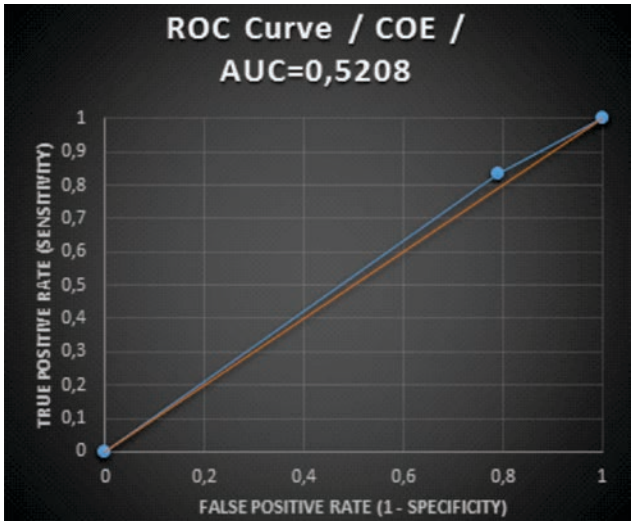

Figure 2. ROC curve - Sensitivity and specificity of COE in potentially malignant lesions (PML)

In second group with lesions with a working diagnosis- oral cancer (OC), the result of the biopsy was positive in 28 patients and negative in two patients. By COE, 29 patients were classified as positive, 27 of them were true positive, two were false positive and one case came out false negative. We measured sensitivity value for the COE method of 96,43%, specificity is 0%, positive predictive value is 93,10% and negative predictive value is 0%. The accuracy of this method that the patient will be correctly classified by clinical examination inspection is 90%. (Tables 3 and Table 4, Figure 3 and 4).

Table 3. Crosstabulation of the results in examinees with working diagnosis - oral cancer (OC) by COE and pathological results

		Pathological results		Total
		Positive	Negative	
COE	Positive	27	2	29
	Negative	1	0	1
	Total	28	2	30

Table 4. Sensitivity and specificity of COE within lesions with working diagnosis - oral cancer (OC)

COE	Value	CI = 95%
Sensitivity (Se)	96.43%	81.65% to 99.91%
Specificity (Sp)	0.00 %	0.00% to 84.19%
Positive predictive value (PPV)	93.10%	92.63% to 93.55%
Negative predictive value (NPV)	0.0%	
Accuracy	90.00%	73.47% to 97.89%

Table 4. presents the values of sensitivity, specificity, positive predictive value, negative predictive value and accuracy of COE, together with the lower and upper limit of the confidence interval of 95% (CI= 95%), and Figure 4. shows the ROC curve. Figure 5. presents the ROC curves- sensitivity and specificity of the method of COE in both study groups; the first with the potentially malignant lesions- precancerous lesions (PML) and the second study group with examinees with working diagnosis- oral cancer (OC).

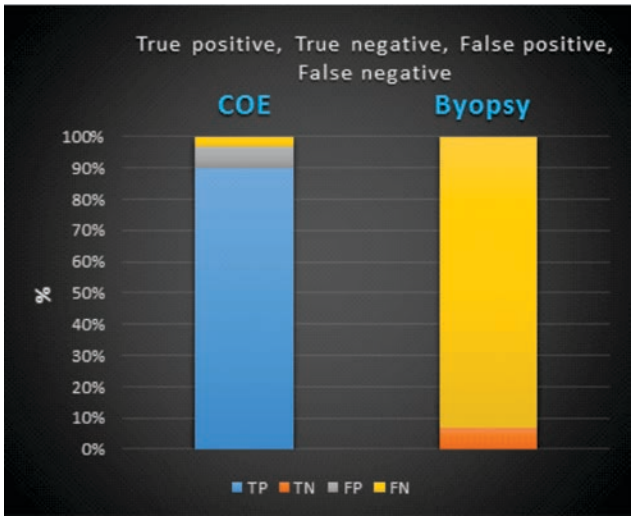

Figure 3. Distribution of examinees working diagnosis - oral cancer (OC) by histopathological finding and COE

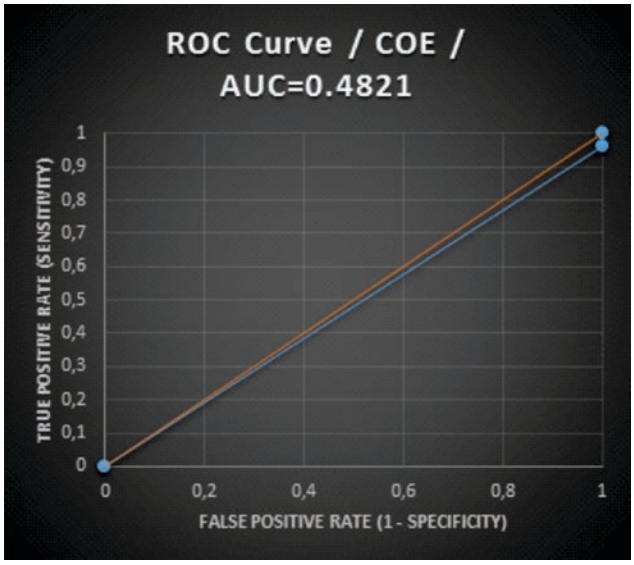

Figure 4. ROC curve - Sensitivity and specificity of COE in lesions with working diagnosis - oral cancer (OC)

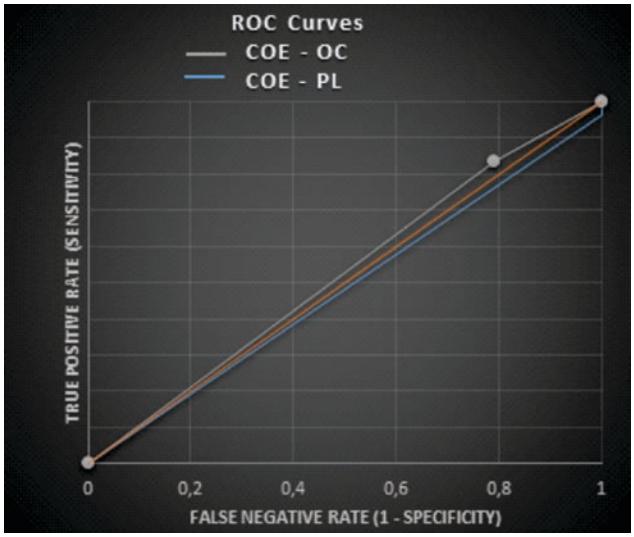

Figure 5. ROC curve - Sensitivity and specificity of COE in both study groups – PML group and OC group

Discussion

The presence of epithelial dysplasia is generally accepted as one of the most important predictors for malignant alteration of premalignant oral lesions. However, epithelial dysplasia not always develops into cancer, and some may even recur[19]. There is a positive correlation between higher grades of dysplasia and increased risk of cancer, but less so with lower grades[20].

The possibility of clinical verification with the visual detection of premature oral lesions at an early stage still remains controversial, since early changes in oral cancer and premalignant disorders are often subtle and rarely show clinical features seen in advanced stages. In addition to their clinical subtlety, premalignant lesions are highly heterogeneous in their presentation and may mimic different commonly benign or reactive conditions.

COE can detect a large number of clinical lesions and a small percentage of them may prove histologic features of premalignancy, recent data suggest that some precancerous lesions may be present in the oral mucosa that looks clinically normal under COE only[21,22]. This concept is supported by the findings of Thomson, who found that 9 out of 26 consecutive patients (36%) with newly diagnosed head and neck squamous cell carcinoma (HNSCC) had histologic evidence of dysplasia or microinvasive cancer from clinically normal mucosa in a biopsy from the contralateral anatomic site[23].

In the systematic review for determination of the performance of visual examination in detection of the oral cancer, Downer MC *et al*.[24], present that only five studies identified the sensitivity and specificity of oral examinations[23-27]. The sensitivity values ranged from 60 to 97%, and specificity ranged from 75 to 99% [24].

In these studies, the lowest specificity was 0,75, but all other studies had values above 0,94. Sensitivity ranged from 0,60 to 0,97. The meta-analysis of these data showed a general sensitivity of 0,85 (95% CI) and specificity of 0,97 (95% CI), indicating satisfactory test efficacy.

A population simulation screening model for premalignant lesions and oral cancer has shown that approximately 18000 patients need to be screened to save one life [28]. Our values for the sensitivity of the COE vary from 83,33% in the first group of patients with potentially malignant lesions (PML) to 96,43% in the examinees of the second study group with lesions with highly suspicious lesions for oral cancer (OC). They strongly correlate with the findings of Chutima Kumdee *et al*.[29].

We gained significantly lower values for the specificity of the method varying from 0% in the second group (OC) to 20.83% in the first group (PL), comparing to the Walsh *et al*.[30] and Macey *et al.*[31], presenting values from 22% to 51%.

The positive predicted value of 20,83% found for the first group (PML) from a clinical point of view could be considered as low values, but acceptable as pointed by Giovannacci *et al.*[32]. It went up to 93,10% for the second study group (OC).

The negative predictive values for the COE vary from 0% for the second study group (OC) to high 83,33% for the first group (PL), similar to other research in which the screening was carried out by community agents[33,34] and higher in comparison to that found by Ikeda *et al*.[35] using dentists as screeners.

The most possible low value of 0% for specificity measured at the second group of examinees, we can only attribute to the late visit at the dentist, with mean response time of more than three months after noticing the oral tissue changes and setting diagnosis for the noted oral lesions in advanced stage of the disease. That is the reason for the sharp contrast of our results with the recent literature data[36-38].

The percentage of people aged over 65 years will grow substantially between 2010 and 2030, so the predicted annual growth rate of oral tissue changes is expected to be 2,8% (EURON, 2004). Healthcare is expected to become increasingly inadequate over the coming years. If we rely on existing conventional diagnostic technologies, which are subjective and depend on examiner experience, provision of sufficient quality and quantity of these would place further demands on the availability of healthcare[39].

Conclusions

The accuracy of the COE method ranged from 33,33% for the first group of patients with potentially malignant lesions (PML) to 90% for the second study

group with lesions with working diagnosis - oral cancer (OC), sets the thesis that COE as screening method for oral cancer or premalignant tissue changes is more valuable for the patients with advanced epithelial changes and is necessary to be combined or accompanied with some other type of non-invasive screening procedure in order to perform a safe but sustainable less invasive procedures applicable in the everyday clinical practice.

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