



INVESTIGATION OF THE ROLE OF THE ORAL MICROBIOTA IN THE OCCURRENCE OF HPV-POSITIVE OROPHARYNGEAL CANCER

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ABSTRACT

Diseases of the oral mucosa (COPD), which is associated not only with the tendency of aging of the population, general somatic diseases, the presence of bad habits, environmental degradation, but also with the spread of systemic diseases that manifest themselves on the oral mucosa. The prevalence of COPD diseases among the Russian population varies from 3% to 20%. Many diseases of COPD have a chronic course, and with inadequate diagnosis and treatment, they tend to malignancy. Malignant neoplasms (ZNO) of the SOPR are a severe pathology of the maxillofacial region, which affects the quality of life of patients [2].

Volume 6, Issue 8, May 2024

Received: 09 March 2024

Accepted: 10 April 2024

Published: 20 May 2024

[doi: 10.33472/AFJBS.6.8.2024.2257-2263](https://doi.org/10.33472/AFJBS.6.8.2024.2257-2263)

Introduction.

An oncologist based on a histological conclusion after a biopsy and a number of additional examination methods.

The established erroneous diagnoses in patients with tumors of the SOPR after a biopsy are most often associated with the lack of appropriate tools, the determination of the exact location for sampling the material and, as a result, with an inaccurate conclusion of the morphologist [4].

It is necessary to pay special attention to precancerous conditions with the incidence of ZNO SOPR, since, according to the literature, in 61-85% of cases ZNO SOPR develop from a disease [3]. A number of chronic inflammatory diseases of the COPD are precancerous, with

their long-term course, the disease may exist without change, with regression, growth or progression - the development of malignant tumors. The impact or long-term existence of adverse factors, the lack of adequate therapy at the stages of treatment and follow-up are very important in the development of PD and ZNO [3]. A special group in the practice of a dentist consists of diseases of the oral cavity, which can be converted into malignant ones. Most often, precancerous diseases are transformed into squamous cell carcinoma, which accounts for 90% of the histological type of ZNO SOPR [1]. More than 20% of the prevalence of ZNO SOPR worldwide 15 may be associated with infectious agents, including viruses, bacteria and parasites [1.3].

Precancerous diseases of the SOPR are considered as an intermediate stage of malignant tumors. Depending on the frequency of malignancy, they are divided into two main groups: facultative (with a low probability of malignancy) and obligate (degenerating into ZNO in the absence of treatment) [4.5.6]. There are several classifications of precancerous diseases of the oral cavity. According to the classification of precancerous diseases of the Committee for the Study of Head and Neck Tumors of the All-Union Scientific Medical Society of Oncologists (1976), there is a division of facultative diseases into two groups with low and high incidence of malignancy. In our country, the most famous is the classification of A.L. Mashkillyson (1977), where obligate and facultative forms of precancerous diseases of the oral mucosa are distinguished [3.7.8].

Diseases include Bowen's disease, facultative ones include: flat, verrucous and erosive leukoplakia, papilloma and papillomatosis, erosive and hyperkeratotic forms of lupus erythematosus and lichen planus, chronic ulcers of the oral mucosa, post-X-ray stomatitis [Bykovskaya T.Yu. et al., 2017; Sidorova A.S., Baroyan M.A., 2020]. The World Health Organization (WHO) has considered precancerous lesions within one group of diseases known as potentially malignant diseases. The term "potentially malignant oral diseases" (OPMD), previously defined at a WHO workshop in 2005, has been redefined as potentially precancerous lesions of the oral epithelium (PPOELs).

Common among precancerous diseases are various forms of leukoplakia (flat, verrucose, erosive), lichen planus and papillomatosis COPD. According to the WHO definition, leukoplakia is a white spot or plaque that cannot be characterized clinically or pathologically like any other disease [3.9]. If a white spot in the oral cavity is diagnosed as some other disease (for example, candidiasis, lichen planus, etc.), then this lesion should not be considered as an example of leukoplakia [3].

The dental status of patients in both groups was assessed using special indices: determination of the CPI index (h), determination of the level of oral hygiene, the condition of periodontal tissues. For an objective assessment of the condition of the teeth, the CPI index of teeth and CPI surfaces was recorded to determine the intensity of the carious process in permanent teeth and calculated using the formula (1): $CPI = K + N + Y$, (1) where K is the number of permanent teeth with caries and its complications, as well as caries in previously restored teeth; N is the number of permanent teeth with fillings that do not require restoration; Y is the number of permanent teeth removed. The hygienic condition of the oral cavity was assessed using the Green– Vermillion hygienic index (IGR-U) without the use of special dyes [3.10].

Experimental part

The hygienic condition of the oral cavity according to the indicators of plaque and tartar of the index of GAMES-Y: 0-0.6 points – low, good hygiene; 0.7–1.6 points – average, satisfactory; 1.7–2.5 points – high, unsatisfactory; 2.6 points or more – very high, poor hygiene. The condition of periodontal tissues was determined on the basis of the periodontal index PI (PI) (Russel, 1967), which makes it possible to take into account the presence of both gingivitis and other symptoms of periodontal pathology. The following estimates were used: 0 – no changes and inflammation; 1 – mild gingivitis (gingival inflammation does not cover the entire tooth); 2 – gingivitis without damage to the attached epithelium (pathological pocket is not determined); 43 6 – gingivitis (periodontitis) with the formation of a gingival pocket, there is no dysfunction,

the tooth is not mobile; 8 – pronounced destruction of all periodontal tissues, the tooth is mobile, may be displaced. The periodontal condition is assessed for each existing tooth from 0 to 8, taking into account the degree of gingival inflammation, tooth mobility and the depth of the gingival pocket. In doubtful cases, they give the highest possible rating.

An X-ray examination of the periodontium introduces a score of "4", where the leading sign is the condition of the bone tissue, manifested by the disappearance of the closing cortical plates at the tops of the alveolar ridge. This is especially important for the diagnosis of the initial stage of development of periodontal pathology. To calculate the index, the obtained estimates are added and divided by the number of available teeth according to the formula (2): The sum of the estimates for each tooth is 0 and the number of teeth is 10, (2) at the same time 0.1–1.0 is the initial and mild degree of periodontal pathology; 1.5–4.0 is the moderate degree of periodontal pathology; 4.0–8.0 – severe periodontal pathology.

Pathologically altered area of the oral mucosa in the rays of the lamp. Then, the border of the dark locus of light quenching was marked with a medical dye (methylene blue solution 1%); retreating 2 mm along the office from the border of the marking, a biopsy of 46 tumors of the SOPR was performed "cruciformly" using an otorhinolaryngological conchotome (exciter) in natural light by immersing the working part of the conchotome blades to the full depth, then in the rays of a lamp "AFS" with a green filter determined the focus of light extinguishing of the neoplasm and the site of the performed biopsy. The biopsies obtained using both techniques were placed in a container with a 40% formalin solution and sent to the pathology laboratory for histological examination. After receiving the result of the histological conclusion, the clinician decided on the need for further treatment in the conditions of SOCOD or treatment and follow-up by a dentist. In order to make an accurate diagnosis for histological verification, patients of the control group ($n = 63$) underwent traditional IB at an appointment with an oncologist, which was performed once, and if necessary – twice.

Oral cavity under local anesthesia (applicative, infiltration and / or conduction anesthesia); with the help of otorhinolaryngological conchotomes, a tissue section was taken along the edge of the tumor of the SOPR with the capture of healthy tissue by immersing the working part of the blades of the conchotome to the full depth. After 7-10 working days from the moment of the first (single) biopsy, the clinician/oncologist, based on the data of the clinical picture and histological conclusion, decided to conduct a repeat biopsy, that is, a double one. Repeated incisional biopsy was performed similarly to the primary one, tissue sampling for examination was carried out from the other edge of the neoplasm with the capture of healthy tissue by immersing the working part of the conchotome blades to the full depth. After receiving the histological conclusion, the clinician/oncologist, based on the data of the clinical picture and histology, referred the patient for consultation to the head of the specialized surgical oncology department (head and neck tumors) to determine the indications for EB.

During the main examination methods, complaints about the presence of a neoplasm were made by patients of the main group – 34.2%, the control group – 54.0%; for pain in the area of the neoplasm – the main group – 23.3%, the control group – 47.6%; for discomfort in the oral cavity – the main group – 64.4%, the control group – 81.0%; for burning in the oral cavity – the main group – 55.39.7%, the control group – 42.9%; for itching in the oral cavity – the main group – 28.8%, the control group – 39.7%; for bleeding from neoplasms – the main group – 6.8%, the control group – 22.2%.

According to the results of ultrasound of the lymph nodes of the neck in the main group, 7 patients were found to have suspected metastases to the lymph nodes of the neck, in the control group – in 9 patients. After the puncture under the supervision of ultrasound with cytological examination of the punctate in the main group, metastases to the lymph nodes of the neck were confirmed in 5 patients, in the control group – in 7. According to CT scans of the oropharynx and neck organs with contrast agent administration, 3 patients of the main group were diagnosed with a primary tumor and metastases to the lymph nodes of the neck, in patients of the control group such a picture was present in 6 cases. After CT scan of the oropharynx and neck organs

without administration of a contrast agent in the main and control groups, 2 patients were diagnosed with a primary tumor and metastases to the lymph nodes of the neck. According to ultrasound of the abdominal cavity, patients of both groups were mainly diagnosed with gallstone disease, hepatosis, and chronic pancreatitis. After fibrogastroduodenoscopy, chronic gastritis (erosive, atrophic) was mainly diagnosed in both groups. Thus, the results of the main and additional methods of examination of patients in the main and control groups made it possible to diagnose metastases to the lymph nodes of the neck and assess the prevalence of the tumor process, since the tumors of the COPD have a fairly rapid growth and metastasis.

Harmful factors such as smoking, which amounted to 69.9% versus 46.0% in the control group ($p = 0.008$), alcohol abuse, hot meals – 63.0% versus 50.8% ($p = 0.207$). The presence of factors such as smoking, alcohol abuse and hot meals confirms the fundamental risk in the development of PD and ZNO; in the developed protocol at the survey stage, they occupy leading positions, especially smoking: smoking – 0.5 points, the presence of bad habits (except smoking) – 0.25 points. The influence of harmful production factors in the groups did not differ statistically. The ROC analysis carried out in the selection of the INGV threshold value in the protocol developed by us confirms and positively characterizes the selected INGV values: up to 5 points for high and low, and 5 or more points for low and low, which indicates that the different score for each individual feature in the protocol is not random and is selected depending on from a blastomogenic factor or risk. An analysis of the state of the SOPR during an examination of the oral cavity in patients showed that the presence of plaque on the mucous membrane of the back of the tongue was detected in both groups. When examining the red lip border, no pathological changes were found in 136 patients.

Pathology of the gastrointestinal tract or candidiasis infection, which 91 is permissible to consider as a general somatic pathology associated / not associated with a neoplasm of the SOPR. When assessing the dental status, high prevalence rates of major dental diseases were revealed: dental caries and its complications, periodontal diseases. When assessing the hygienic condition of the oral cavity using the index of GAMES-Y, all the examined patients revealed a poor level of hygiene, which averaged 3.7 ± 0.63 . The Russel periodontal index (PI) was 3.87 ± 0.58 , which corresponds to a moderate degree of periodontitis. 118 patients (86.8%) of both groups had partial or complete removable prostheses, while their quality was not always satisfactory. All patients needed oral sanitation. The distribution of patients in the comparison groups according to the localization of tumors of the oral mucosa allowed us to conclude that the localization of lesions of the SOPR in the groups did not differ statistically, the mucous membrane of the tongue was most often affected (39.72% in the main and 41.28% in the control group, $p = 0.994$), followed by the mucous membrane of the cheek (30.14% and 28.57%, respectively, $p = 0.991$) and to a lesser extent other localizations. The data obtained on the localization of neoplasms on the SOPR once again confirm what is stated in the literary review [2.3].

In the main and control groups, according to the form of tumor growth of neoplasms of COPD, it should be noted that the most common neoplasms were represented by an exophytic papillary form, in the main group it was observed in 68.5%, and in the control group – in 55.5% ($p = 0.169$), but in the control group the ulcerative form was slightly more often observed – 17.5% against 12.3% in the main ($p = 0.549$) and mixed form – 22.2% in the control group and 16.5% in the main ($p = 0.524$). The data obtained confirm the fact that neoplasms of the SOPR at the beginning of their development have a papillary exophytic growth type. The results obtained using the main and additional methods of examination of patients in the main and control groups made it possible to diagnose metastases to the lymph nodes of the neck and assess the prevalence of the tumor process; thus, tumors of the COPD have a fairly rapid growth and metastasis. Despite the fact that visual examination is the main method for determining pathological changes in the SOPR, in order to identify PD or ZNO, it becomes necessary to apply a modified approach to early diagnosis, determining indications for verifying a pathological condition in order to prevent transformation into a malignant neoplasm and neglect of the malignant process.

In patients of the main group ($n = 73$) with suspected neoplasms of the COPD, an examination conducted according to the developed protocol makes it possible to determine indications for histological verification of formation on the oral mucosa according to precise criteria using a point system with minimizing errors and, as a result, inspires confidence when making an informed decision by a gynecologist about further referral of the patient to a doctor to the oncologist.

The developed method makes it possible to determine with a high degree of reliability the indications for the distribution of the flow of patients with neoplasms of the SOPR, to pre-differentiate inflammatory, benign and malignant neoplasms of the SOPR. At the same time, the specificity of the method was 73%, sensitivity – 97% and accuracy – 93%. It should be noted that the developed protocol for the early detection of PD and ZNO SOPR and filling in the data in the developed computer program to systematize the results of the examination and calculate the index of the need for histological verification allow the primary care dentist to make an informed decision on referring the patient to an oncologist for histological verification of the detected neoplasm on the mucous membrane of the cavity at the initial visit of the patient mouth to exclude or confirm the PZ and ZNO. The results of the examination recorded in the computer program can serve as accompanying documentation directly to accompany the patient to a consultation with an oncologist at GBUZ SOKOD or to another specialist on an electronic resource using the principle of telemedicine.

Biopsies for diagnosis made it possible to verify exophytic papillary neoplasms in 53.5% of cases in patients of the main group and only in 17.5% of cases in patients of the control group, respectively ($p < 0.001$). The need for a double incision biopsy was 2.5 times less in the main group than in the control group, this is 13.7% of cases compared with the control group – 34.9% of cases ($p = 0.007$). As for other forms of growth and the multiplicity of biopsies, no special differences were observed. These circumstances once again emphasize the relevance of developing a new method for determining the locus when performing a biopsy of a tumor of the SOPR, since it has a high sensitivity compared to traditional incisional biopsy of tumors with exophytic papillary growth type. Of particular interest is the fact that performing a biopsy of a tumor of the SOPR using a new method for determining the locus for collecting pathological material showed a high percentage of diagnosis verification after a single biopsy, which amounted to 74%. The effectiveness of the new method is undeniable, since it eliminates or reduces the number of repeated biopsies. It should be noted that repeated biopsies lengthen the examination time and affect ablasy. When distributing patients in comparison groups, depending on the type of biopsy performed and the established diagnosis, it was revealed that malignant neoplasms were established in patients of the main group after performing a single incision biopsy to a greater extent, which amounted to 30.10% of cases compared with the control group – 12.80% of cases ($p = 0.026$).

Precancerous diseases of the SOPR were diagnosed after a single incisional biopsy in a higher percentage of cases (35.60%) compared with the control group (7.90%) ($p < 0.001$). Especially informative were the differences in the diagnosis of inflammatory COPD diseases in the main group (1.4%) compared with the control group (17.4%) ($p = 0.003$). In this regard, it is important to note that the use of a new method for determining the locus when performing a neoplasm biopsy has reduced the number of repeated incision biopsies to verify PD and ZNO of the SOPR in the main group. This once again emphasizes that a high percentage (74%) of diagnosis verification, namely the diagnosis of PD and ZNO, significantly reduces the time of examination and eliminates the need for repeated traumatization of the lesion and surrounding tissues, which has a negative impact if ablasy is followed. When comparing patients in comparison groups according to established diagnoses after a biopsy, it was determined that precancerous diseases and malignant neoplasms of the COPD in patients of the main group were detected in 94.5% of cases against 60.3% of cases in the control group ($p < 0.001$). Inflammatory diseases in the main group were detected in only 1 patient (1.4%) versus 20 patients (31.7%) in the control group ($p < 0.001$), which indicates a high specificity of the technique, where the key

goal is to diagnose early forms of ZNO and PD (Appendix 6). Verrucous leukoplakia was the most common of facultative PD ($p = 0.120$) and papillomatosis ($p = 0.033$) in the main group, and this pathology was not observed in the control group. Inflammatory diseases of the COPD were diagnosed to a greater extent in the control group (31.7%), the most obvious representatives that were not observed in the main group were papillary hypertrophy ($p = 0.096$) and chronic recurrent aphthous stomatitis ($p = 0.023$), which once again indicates the high specificity of the technique.

Conclusions.

1. To diagnose and reduce the neglect of malignant neoplasms of the oral mucosa in patients on an outpatient basis, a protocol of sequential examination using autofluorescence stomatoscopy and INGV has been developed. The threshold value of the INGV score, corresponding to 5 points or more, based on ROC analysis is the basis for conducting a biopsy.

2. Neoplasms of the SOPR made it possible to perform a single incision biopsy with reliable accuracy and establish a diagnosis in 54 patients (74%), and with the traditional method – in 27 patients (42.8%) ($p < 0.001$), exophytic papillary neoplasms were verified in the main group in 53.5% of cases and only in 17.5% of cases – in the control group, respectively ($p < 0.001$).

3. Diagnose PD and ZNO with high accuracy (93%), specificity (73%) and sensitivity (97%) compared to the control group (50%, 3.8% and 81.6%, respectively). The frequency of early stages (0, I, II) of ZNO in the main group was 70%, and in the control group – 27% ($p = 0.015$). In turn, the advanced stages of ZNO were diagnosed in the control group in 73% versus 27% in the main group ($p = 0.015$).

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