COMPLEX TREATMENT OF ORAL MUCOSA CANCER BASED ON CHANGES IN IMMUNOLOGICAL PARAMETERS

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Abstract. *Comparative assessment of effectiveness showed that integration of immunological data significantly increases the accuracy of prognosis and compensates for the shortcomings of traditional scales. Thus, as a result of the study, we achieved the main goal of the study - improved prediction of the outcomes of complex treatment of cancer of the oral mucosa by developing a pathogenetically substantiated method based on changes in immune parameters.*

Keywords: *cancer of the oral mucosa, oncology, treatment, immunological parameters, prognosis.*

КОМПЛЕКСНОЕ ЛЕЧЕНИЕ РАКА СЛИЗИСТОЙ ОБОЛОЧКИ ПОЛОСТИ РТА ПО ДАННЫМ ИЗМЕНЕНИЯ ИММУНОЛОГИЧЕСКИХ ПОКАЗАТЕЛЕЙ

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Аннотация. *Сравнительная оценка эффективности показала, что интеграция иммунологических данных существенно повышает точность прогноза и восполняет недостатки традиционных шкал. Таким образом, в результате проведенного исследования нами была достигнута основная цель исследования - улучшено прогнозирование исходов комплексного лечения рака слизистой оболочки полости рта за счет разработки патогенетически обоснованного способа, основанного на изменениях иммунных показателей.*

Ключевые слова: *рак слизистой оболочки полости рта, онкология, лечение, иммунологические показатели, прогноз.*

IMMUNOLOGIK PARAMETRELARNING O'ZGARISHI ASOSIDA OG'IZ BO'SHLIG'I SHILLIQ QAVATI SARATONINI KOMPLEKS DAVOLASH

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Annotatsiya. *Samaradorlikni qiyosiy baholash shuni ko'rsatdiki, immunologik ma'lumotlarning integratsiyasi prognozning aniqligini sezilarli darajada oshiradi va an'anaviy o'lchovlarning kamchiliklarini qoplaydi. Shunday qilib, ushbu ilmiy tadqiqotimiz natijasida biz tadqiqotning asosiy maqsadiga erishdik - immun parametrlarining o'zgarishiga asoslangan patogenetik asoslangan usulni ishlab chiqish orqali og'iz bo'shlig'i shilliq qavati saratonini kompleks davolash natijalarini bashorat qilish yaxshilandi.*

Kalit so'zlar: *og'iz bo'shlig'i shilliq qavati saratoni, onkologiya, davolash, immunologik ko'rsatkichlar, prognoz.*

Relevance. Oral mucosal cancer is one of the most common forms of malignant neoplasms in the head and neck region, which has a high level of medical and social significance. According to international statistics GLOBOCAN, more than 370 thousand new cases of this disease are detected worldwide every year, of which about 200 thousand are fatal [1]. Such epidemiological indicators not only indicate the high prevalence of oral mucosal cancer, but also emphasize its aggressive biological behavior, often associated with late diagnosis and a high risk of relapse [2].

Modern research indicates the important role of the immune system in controlling tumor growth, developing metastases and forming a response to antitumor therapy [3]. The immune system is involved not only in recognizing and destroying malignant cells, but also in regulating the tumor microenvironment, including the processes of angiogenesis, stromal remodeling and immune tolerance.

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In this context, oral mucosal cancer represents a tumor growth model with active immunopathogenetic interaction between tumor cells and cells of innate and adaptive immunity [4].

Despite the growing number of scientific papers devoted to immunopathogenesis and immunomonitoring in malignant neoplasms, existing clinical guidelines for the treatment of oral mucosal cancer either do not consider immunological parameters at all or use them in a purely descriptive manner. This approach significantly limits the possibilities of personalized treatment and prevents early identification of patients with a high risk of relapse or therapeutic resistance.

The aim of the study is to improve the results of predicting the outcomes of complex treatment of oral mucosal cancer by developing pathogenetically substantiated methods based on regular changes in immune system parameters.

Materials and methods of the study. The study included 124 patients with oncological lesions of the oral mucosa, who underwent examination and treatment at the Bukhara regional branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Republic of Uzbekistan for the period from 2020 to 2022. Moreover, all patients were verified and classified by outcomes during a three-year follow-up (until 2025) depending on the outcome of complex treatment into comparative and main groups. The criteria for including patients in the study were: morphologically verified diagnosis of a malignant neoplasm of the oral mucosa (OMC, lateral surface of the tongue, cheeks, etc.), corresponding to ICD-10 (C01-C06); primary treatment for specialized oncology care, without previous treatment (including chemo-, radio- and immunotherapy); patient age from 18 to 75 years; complex treatment, including surgery, radiation therapy and/or chemotherapy, carried out within the framework of the standards of oncological care; the possibility of 3-year observation after completion of the main course of treatment (to assess the prognosis and outcome); reliably obtained informed consent to participate in the study, including immunological examination and subsequent data processing. Immunological examination performed before the start of treatment included an assessment of

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cellular ($CD3^+$, $CD4^+$, $CD8^+$, NK cells, $CD19^+$) and humoral (IgG, IgA, IgM, CIC) immunity, cytokine profile (IL-2, IL-6, IL-10, TNF-α, IFN-γ), as well as systemic inflammatory indices (NLR, PLR, SII, C-reactive protein). The study was conducted using flow cytometry (FACSCalibur), ELISA and immunoturbidimetry.

Research results. The study of immunological changes in patients with OMC who underwent complex treatment revealed reliable differences between groups of patients with different clinical outcomes. In the study, the immune status was assessed using a set of parameters reflecting the state of cellular and humoral immunity, levels of proinflammatory and immunoregulatory cytokines, and systemic inflammatory indices. Such a multidimensional examination made it possible to establish which immunological changes are associated with the risk of disease relapse. At the level of cellular immunity, a reliable decrease in $CD3^+$- and $CD4^+$-lymphocytes was revealed in patients with an unfavorable outcome. The $CD3^+$ level was 58.3±7% in the main group versus 63.1±6.2% in the comparative group and 66.4±5.1% in healthy individuals. Similarly, the $CD4^+$ lymphocyte count in the relapse group was 35.1±5.2%, which was significantly lower than both the control group and the group with a favorable outcome. The $CD8^+$ level remained stable, and the $CD4^+/CD8^+$ ratio significantly decreased in the main group compared to the control group by 1.3 times, indicating an imbalance between the coordinating and cytotoxic components of the immune response. NK cell activity ($CD16^+CD56^+$) was also reduced in patients with relapse compared to the comparison and control groups by 1.3 times. According to our data, a decrease in the number of T-helpers and NK cells can be interpreted as one of the pathogenetic mechanisms for reducing antitumor control in patients with relapse of OMC. In the humoral link of immunity, the most significant changes concerned the level of the CIC. In patients of the main group, the CIC level reached 92.7±18.3 optical units, which was significantly higher than in the comparative group (1.2 times) and in the control group (1.6 times). The levels of immunoglobulins A, G and M did not differ statistically significantly between the groups. The cytokine profile also showed significant shifts in relapse. The IL-6 level in patients with relapse was 15.7±4.0 pg/ml, which was significantly

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higher than in the comparison group (1.4 times) and in healthy individuals (1.9 times). The increase in IL-10 also reached statistical significance in the main group (5.2±1.4 pg/ml) compared to the control (1.5 times) and the comparative group (1.3 times). At the same time, the level of IFN-γ, on the contrary, was reduced in patients with relapse to 10.4±2.9 pg/ml versus 11.9±3.0 pg/ml in the comparative group and 12.6±2.8 pg/ml in the control. The revealed changes indicate the dominance of the immunosuppressive and proinflammatory cytokine background in an unfavorable clinical course.

Based on correlation analysis and clinical significance, nine immunological parameters were identified that were most closely associated with the risk of relapse: $CD4^+$, $CD4^+/CD8^+$, NK cells, IL-6, IL-10, IFN-γ, CIC, NLR, and SII. The obtained parameters cover both cellular elements of the antitumor response and humoral-inflammatory markers reflecting immune system dysregulation. Multivariate logistic analysis allowed us to quantitatively assess the prognostic significance of each of them. Thus, a decrease in the level of $CD4^+$ lymphocytes increased the risk of relapse by more than 1.8 times ($p=0.001$), a decrease in the $CD4^+/CD8^+$ index - by 1.5 times ($p=0.012$), and a decrease in the number of NK cells - by 1.6 times ($p=0.01$). An increase in IL-6 and IL-10 increased the risk by more than twofold ($p<0.01$), while a decrease in IFN-γ was associated with the likelihood of relapse with an OR=0.588 ($p=0.003$). Similarly, an increase in the level of CIC ($p=0.016$), NLR ($p<0.001$) and SII ($p<0.001$) statistically significantly correlated with tumor progression.

Conclusion. The immunological analysis allowed us to identify reliable markers associated with the risk of relapse, including a decrease in $CD4^+$, IFN-γ and NK cell activity, as well as an increase in the levels of IL-6, IL-10, CIC and inflammatory indices NLR and SII. Based on these indicators, a prognostic model and an automated scale "ONIX" were constructed, which demonstrated high sensitivity and specificity in stratifying patients by the risk of relapse. Comparative assessment of effectiveness showed that integration of immunological data significantly increases the accuracy of prognosis and compensates for the

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shortcomings of traditional scales. Thus, as a result of the study, we achieved the main goal of the study - improved prognosis of the outcomes of complex treatment of OMC by developing a pathogenetically substantiated method based on changes in immune parameters.

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