

УДК: 616.31-006.04+616-097+616-08-039.75

ASSESSMENT OF THE PROGNOSIS OF RECURRENCE OF CANCER OF THE ORAL MUCOSA BY THE DEGREE OF HISTOLOGICAL DIFFERENTIATION

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Abstract. Oral mucosa cancer (OMC) is a moderate oncological disease of the head and neck, characterized by a steadily increasing incidence and potentially disabling features. Summarizing the analysis of the effectiveness of comparing the recurrence prognosis based on the degree of histological differentiation and the actual development of relapses in oral mucosal cancer, it was shown that the degree of histological differentiation, despite its importance for the morphological characteristics of the tumor, cannot be considered an independent and reliable predictor of recurrence. As clinical examples demonstrate, in both G1 and G3 cases, results may be observed that contradict those expected based on morphological criteria.

Keywords: oral mucosal cancer, oncology, treatment, relapse, outcome.

ОЦЕНКА ПРОГНОЗИРОВАНИЯ РЕЦИДИВА РАКА СЛИЗИСТОЙ ОБОЛОЧКИ ПОЛОСТИ РТА ПО СТЕПЕНИ ГИСТОЛОГИЧЕСКОЙ ДИФФЕРЕНЦИРОВКИ

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Аннотация. Рак слизистой оболочки полости рта (РСОПР) является умеренным онкологическим заболеванием головы и шеи, характеризующимся постоянным повышением заболеваемости и потенциально инвалидизирующими особенностями. Подводя итог анализу эффективности сопоставления прогноза рецидива по степени гистологической дифференцировки и фактического развития рецидивов РСОПР, показала, что степень гистологической дифференцировки, несмотря на свое значение для морфологической характеристики опухоли, не может рассматриваться как самостоятельный и надежный предиктор рецидива. Как показывают клинические примеры, в

случаях как G1, так и G3 могут наблюдаться результаты, противоречащие ожидаемым по морфологическим критериям.

Ключевые слова: рак слизистой оболочки полости рта, онкология, лечение, рецидив, исход.

ГИСТОЛОГИК ТАБАҚАЛАНИШ БЎЙИЧА ОҒИЗ БЎШЛИҒИ
ШИЛЛИҚ ҚАВАТИ САРАТОНИ ҚАЙТАЛАНИШИНИ
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Аннотация. Оғиз бўшлиғи шиллиқ қавати саратоми - бош ва бўйиннинг ўртача даражадаги онкологик касаллиги бўлиб, у доимий равишда ўсиб бораётган касаллик ва потенциал ногиронлик хусусиятлари билан тавсифланади. Оғиз бўшлиғи шиллиқ қавати саратонида рецидивларнинг гистологик дифференциация даражаси ва ҳақиқий ривожланишига асосланган рецидивланиш прогнозини таққослаш самарадорлигини таҳлил қилишни жамлаб, гистологик дифференциация даражасини, ўсимтанинг морфологик хусусиятлари учун муҳимлигига қарамай, рецидивланишнинг мустақил ва ишончли прогнози сифатида кўриб чиқилиши мумкин эмаслиги кўрсатилган. Клиник мисоллар шуни кўрсатадики, G1 ва G3 ҳолатларида ҳам морфологик мезонларга кўра кутилган натижаларга зид бўлган натижалар кузатилиши мумкин.

Калит сўзлар: оғиз бўшлиғи шиллиқ қавати саратоми, онкология, даволаш, релапс, натижа.

Relevance. Oral mucosal cancer (OMC) includes malignant neoplasms of the lips, tongue, floor of the mouth, buccal, gingival, retromolar, and palatal areas, as well as the soft and hard palates. According to GLOBOCAN, more than 377,000 new cases of oral cancer are registered annually worldwide, with more than 177,000 patients dying from this disease [7]. Oral cancers are not only associated with a high risk of mortality but also cause a significant decrease in quality of life, long-term disability, and severe economic consequences for the patient, family, and the healthcare system. Current approaches to the treatment of OMC involve the mandatory use of multi-stage regimens, including surgery, radiation therapy, and chemotherapy in various combinations. In most cases of localized tumors, surgical resection followed by radiation therapy is used, while locally advanced forms require neoadjuvant

chemoradiotherapy followed by radical surgery [6]. Combined treatment, including surgery, radiation, and chemotherapy, remains the preferred method. However, the risk of local recurrence and metastasis, even after multi-stage treatment, remains high, highlighting the need for more accurate predictors of adverse outcomes in the early stages. Predicting treatment outcomes in RCMP is traditionally based on clinical and morphological classifications, of which the TNM system proposed by the UICC and AJCC remains the leading one. TNM criteria take into account the size of the primary tumor (T), regional lymph node involvement (N), and the presence of distant metastases (M). In clinical practice, the disease stage determined by TNM directly influences the choice of treatment strategy and assessment of the long-term prognosis. Higher stages (III-IV) are associated with worse survival rates and a higher recurrence rate [1].

Along with topographic staging, morphological characteristics of the tumor play an important role. Among these, the degree of histological differentiation of the tumor (G) is particularly important. Well-differentiated tumors generally exhibit a more favorable course, while poorly differentiated forms (G3-G4) are prone to aggressive growth, early metastasis, and treatment resistance. However, the degree of differentiation remains a qualitative and, to a certain extent, subjective criterion, subject to interobserver variations [2].

The patient's overall functional status is assessed using the ECOG (Eastern Cooperative Oncology Group) scale, which reflects the degree of preservation of physical activity. These parameters are very important when planning and choosing the scope of treatment. This prognostic method can correlate with prognosis. For example, it is known that patients with ECOG scores of 0-1 generally tolerate intensive treatment programs better and have a higher chance of a favorable outcome. Meanwhile, as many clinicians point out, ECOG is a non-specific indicator reflecting the general somatic condition, and not the properties of the tumor itself [5]. In clinical practice, assessment of treatment response based on the results of visual and instrumental monitoring (RECIST, PET-CT, endoscopy, etc.) is also used. A complete or partial response after therapy is often interpreted as a favorable prognostic sign. However, even with visual tumor regression, viable cells may persist in the intervention area or lymph nodes, leading to recurrence. All this indicates that the clinical response to treatment does not always reflect the true biological activity of the tumor [3].

Despite their widespread use, the sensitivity and specificity of traditional prognostic methods, such as TNM staging, the degree of differentiation, and clinical response assessment, remain limited. According to meta-analyses, the disease stage according to the TNM classification demonstrates a moderate sensitivity (60-75%) and specificity (70-80%) in predicting overall outcomes and the risk of recurrence [4].

The aim of this study is to improve the prediction of outcomes of complex

treatment for RCMP by developing pathogenetically based methods based on regular changes in immune system parameters.

Materials and Methods. The study included 124 patients with oncological lesions of the oral mucosa, who were examined and treated 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. 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 inclusion of patients in the study were: morphologically verified diagnosis of malignant neoplasm of the oral mucosa (RSOPR, lateral surface of the tongue, cheeks, etc.), corresponding to ICD-10 (C01-C06); primary referral for specialized oncological care, without previous treatment (including chemotherapy, radiotherapy and immunotherapy); the age of patients from 18 to 75 years; Comprehensive treatment, including surgery, radiation therapy, and/or chemotherapy, administered within the framework of oncology care standards; the possibility of a 3-year follow-up after completion of the primary course of treatment (to assess prognosis and outcome); and adequately obtained informed consent to participate in the study, including immunological testing and subsequent data processing.

Study Results. An analysis of the correspondence between the recurrence prognosis formed based on the degree of histological differentiation of the tumor and the actual clinical outcomes in patients in the control group revealed both general patterns and significant discrepancies in a number of clinical situations (Table 1). For example, in the subgroup of patients who underwent surgical treatment without additional interventions, the recurrence prognosis formed based on the G-criterion was 22.7%, while in fact, relapse was recorded in only 13.6%.

We observed a similar discrepancy in prognostic values in patients who received comprehensive treatment, that is, patients who underwent surgery followed by a course of radiation and chemotherapy. The prognosis for patients in this subgroup was 33.3%, while relapse was actually observed in only 11.1%. In fact, overprediction was three times higher. This was observed in two subgroups: while in the first subgroup it was twice as high, in the second subgroup it was three times higher.

This discrepancy was particularly pronounced in patients who received chemotherapy alone. In these patients, we predicted a recurrence rate of 75%, but in reality, it occurred in only 37.5% of patients, a rate exactly half that of chemotherapy alone. In most of these cases, chemotherapy was used as the only possible treatment option when radiation therapy was contraindicated or surgery was refused. Meanwhile, with radiation (without surgery), the prognosis was 58.3%, but in reality, it occurred in 41.7% of patients. This means the discrepancy was less pronounced, but still significant

(by 16.6 percentage points).

Table 1

Comparative prognostic assessment of recurrence of RCMP based on the degree of histological differentiation and its actual progression

PARAMETERS	RECURRENCE AFTER TREATMENT	
	FORECAST	FACT
Surgeries, n (%)	10 (22,7 %)	6 (13,6 %)
Radiation therapy, n (%)	14 (58,3 %)	10 (41,7 %)
Chemotherapy, n (%)	12 (75,0 %)	6 (37,5 %)
Combination therapy, n (%)	18 (33,3 %)	6 (11,1 %)
Tumor location in the tongue, n (%)	12 (26,1 %)	14 (30,4 %)
Tumor location in the cheek, n (%)	16 (44,4 %)	12 (33,3 %)
Tumor location in the floor of the mouth, n (%)	12 (54,5 %)	16 (72,7 %)

Additional differences were found when analyzing tumor location. For example, for lesions in the floor of the mouth, the actual risk of recurrence exceeded the predicted risk by 18.2 percentage points, while for lesions on the tongue and cheek, the predicted and actual values were comparable.

For illustration purposes, two clinical examples are provided, demonstrating, on the one hand, the weak predictive power of the differentiation grade with favorable morphology, and, on the other, a comparative clinical case demonstrating the paradoxical absence of recurrence with an unfavorable G-score.

Example 1. Patient A.M., 59, was admitted with complaints of a long-term non-healing ulcer on the inner surface of his right cheek. Based on the histological report, a diagnosis of squamous cell carcinoma G1 was established. The disease stage was determined as T2N0M0, stage II, ECOG – 0. The patient underwent surgical treatment, including local excision of the buccal mucosa tumor with the creation of a local mucosal flap. The excision was performed within clinically healthy tissue, formally achieving an R0 resection. The postoperative period was uneventful. Due to the favorable stage, high degree of differentiation, and the radical nature of the surgery, no additional therapy was considered. The patient was followed as an outpatient. However, an 8-month follow-up examination revealed dense mucosal thickening along the scar margin. A biopsy confirmed tumor recurrence with G2 features and no lymph node involvement. A repeat surgery and a course of external beam radiation therapy were performed.

As demonstrated in this clinical case, despite a favorable morphological profile (G1) and radical surgery with negative wound margins, a relapse developed within the first year, calling into question the prognostic reliability of the differentiation grade in isolation. Moreover, when analyzing the disease progression, we noted clinical cases in which the prognosis was based solely on the degree of differentiation, which

repeatedly overestimated the risk of recurrence of oral mucosal cancer. To support this assertion, we provide a description of another typical clinical case.

Example 2. Patient Sh.D., 67, presented to the Bukhara Regional Branch of the Oncology Center complaining of pain in the sublingual region and difficulty speaking and swallowing. Examination and CT data revealed the diagnosis: "cancer of the oral mucosa, T3N1M0, stage III, squamous cell carcinoma, nonkeratinizing, differentiation grade G3."

On admission, her ECOG score was 1. Given the location, size of the tumor, and the presence of an enlarged regional lymph node, the patient underwent combined treatment. The first procedure was a radical surgical procedure involving a floor of mouth resection with partial resection of the hyoid muscle and unilateral cervical lymph node dissection (levels I-III). Postoperative histological examination revealed stage III tumor without extracapsular invasion. After complete wound healing, the patient underwent external beam radiation therapy (64 Gy to the tumor bed and regional lymph nodes). Following this comprehensive treatment program, no complications were observed in the postoperative period, and the patient returned to her original functional state. Follow-up examinations at 3, 6, 12, and 24 months revealed no signs of recurrence.

This case demonstrates that despite the morphologically unfavorable presentation (G3) and stage III disease, comprehensive treatment ensured sustained remission for more than 2 years. This course of the disease demonstrates that prognosis based solely on the degree of differentiation may overestimate oncological risks, especially in cases where radical treatment has been achieved and the full potential of combination therapy has been realized.

Conclusion. Summarizing the effectiveness of comparing the recurrence prognosis based on the degree of histological differentiation with the actual development of relapses in RCMP, we found that the degree of histological differentiation, despite its importance for the morphological characteristics of the tumor, cannot be considered an independent and reliable predictor of relapse. As clinical examples demonstrate, in both G1 and G3 cases, results may be observed that contradict those expected based on morphological criteria. These clinical examples and statistical data analysis highlight the need for a more multidimensional approach to prognosis, incorporating, in addition to morphology, clinical course and treatment data, on the one hand, and the need to analyze immunological markers, on the other.

List of references:

1. Романов И. С., Гельфанд И. М., Удинцов Д. Б. Тактика лечения ранних стадий рака слизистой оболочки полости рта // Head and Neck / Голова и шея. Российское издание. – 2016. – № 3. – С. 44

2. Кочурова Е. В., Муханов А. А. Местные осложнения при лучевом и химиотерапевтическом лечении пациентов с плоскоклеточным раком слизистой оболочки полости рта // Вопросы онкологии. – 2018. – Т. 64, № 2. – С. 166–170.
3. Кубанов А. А., Свищенко С. И., Донцова Е. В., Михина В. А. Плоскоклеточный рак у пациентки с эрозивно-язвенной формой красного плоского лишая слизистой оболочки полости рта // Вестник дерматологии и венерологии. – 2022. – Т. 98, № 4. – С. 76–84.
4. Михайлова Г. Ф., Цепенко В. В., Мурзаева А. В., Шинкаркина А. П. Исследование молекулярно-цитогенетических нарушений у больных раком слизистой оболочки полости рта до и после курса радиотерапии // Молекулярная диагностика: сб. трудов XI Междунар. науч.-практ. конф., Москва, 14–16 нояб. 2023 г. – Москва: АО «Сайенс Медиа Проджектс», 2023. – С. 38–39.
5. Романов И. С., Гельфанд И. М., Удинцов Д. Б. Тактика лечения ранних стадий рака слизистой оболочки полости рта // Head and Neck / Голова и шея. Российское издание. – 2016. – № 3. – С. 44
6. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Head and Neck Cancers. – Version 2.2024. – 185 p.
7. Sung H., Ferlay J., Siegel R. et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries // CA: A Cancer Journal for Clinicians. – 2021. – Vol. 71, No. 3. – P. 209–249.