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IMMUNOHISTOCHEMICAL MARKERS IN PREDICTING THE CLINICAL COURSE OF CERVICAL CANCER ACCORDING TO DATA FROM THE SAMARKAND REGIONAL BRANCH OF THE REPUBLICAN SPECIALIZED SCIENTIFIC AND PRACTICAL MEDICAL CENTER OF ONCOLOGY AND RADIOLOGY

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Abstract

Cervical cancer is one of the most common tumors of the female reproductive system. Among women in the Samarkand region, cervical cancer ranks third among reproductive system diseases, after breast cancer and ovarian cancer.

In recent years, immunohistochemical methods have become increasingly important in assessing the biological characteristics of cervical cancer (CC), prognosing the disease's course, and stratifying the risk of recurrence. Traditional clinical and morphological parameters, including FIGO stage, tumor size, depth of invasion, and lymph node status, do not always allow for an objective assessment of the tumor's biological aggressiveness and the likelihood of an unfavorable outcome. In this regard, special attention is being paid to the study of immunohistochemical markers of cell proliferation, apoptosis, angiogenesis, immune response, and HPV-induced transformation. The most studied of these markers are Ki-67, p53, Bcl-2, VEGF, p16INK4a, and PD-L1. Their expression reflects the intensity of tumor growth, cell cycle disruptions, resistance to apoptosis, and the potential for tumor progression. In modern gynecological

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oncology, immunohistochemical markers are considered a promising tool for personalized recurrence risk prediction and treatment selection.

Most studies demonstrate a link between high tumor proliferative activity and an unfavorable clinical course. High Ki-67 values are associated with an increased rate of locoregional recurrence, reduced relapse-free and overall survival, and the likelihood of resistance to chemoradiation therapy. The combination of a high Ki-67 index with lymphovascular invasion, low tumor differentiation, and lymph node involvement is considered particularly unfavorable; some authors consider Ki-67 as an additional risk stratification criterion in patients with the same FIGO stage.

However, discrepancies persist in the literature due to differences in immunohistochemical assessment methods and Ki-67 index thresholds. Therefore, it is currently recommended to evaluate this marker in conjunction with other clinical, morphological, and molecular parameters.

The p53 protein is a key tumor suppressor that regulates the cell cycle, DNA repair, and apoptosis. In cervical cancer, its inactivation occurs primarily through the HPV oncoprotein E6, which induces p53 degradation via the ubiquitin-proteasome pathway, which disrupts apoptosis and DNA repair and leads to genomic instability.

Immunohistochemical overexpression of p53 is considered a sign of cell cycle dysregulation; in some studies, it has been associated with poor differentiation, treatment resistance, and poor prognosis. However, the prognostic significance of p53 remains controversial due to differences in assessment methods, HPV status, and molecular heterogeneity of tumors.

The combination of high Ki-67 expression, p53 overexpression, impaired apoptosis, and increased angiogenesis has been shown to be associated with early recurrence and decreased survival; the combination with LVSI and lymph node involvement is particularly unfavorable. Current research emphasizes that the isolated use of a single IHC marker has limited prognostic value; the most promising approach is to develop integrated models combining indicators of proliferation, apoptosis, angiogenesis, and the immune microenvironment.

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The most promising approach is the integration of immunohistochemical parameters with clinical, morphological, and molecular genetic factors to develop personalized models for predicting the risk of recurrence.

Study objective: to study the prognostic value of immunohistochemical markers in cervical cancer.

Study materials and methods: A comprehensive immunohistochemical study of surgical and biopsy specimens from patients treated at the Samarkand branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology was conducted.

The study included 40 patients with T1b-3aNxM0 squamous cell cervical cancer, including 20 patients in the study group with no signs of recurrence and 20 patients in the observation group with recurrence after treatment.

Immunohistochemical analysis was performed in the Pathology Department of the Russian Scientific and Practical Medical Center of Oncology and Radiology using a Bond Leica automated immunohistoprocessor (Leica Biosystems, Australia). Monoclonal antibodies to the Ki67, VEGFR, and CD34 markers were used.

Immunohistochemical expression was assessed on serial paraffin sections obtained from archived biopsy and surgical specimens. Immunohistochemical reactions were visualized using DAB chromogen. Marker expression was assessed semiquantitatively using a modified ALLRED scale. The analysis took into account the tumor cell staining intensity and the percentage of positively stained cells. The results were interpreted as follows: weakly positive (up to 30% positive cells), moderately positive (30–60%), and highly positive (more than 60% marker expression).

When studying the proliferative activity of Ki67 in patients with squamous cell carcinoma of the cervix, a dependence of the marker expression level on the degree of tumor differentiation was established (see Fig. 1).

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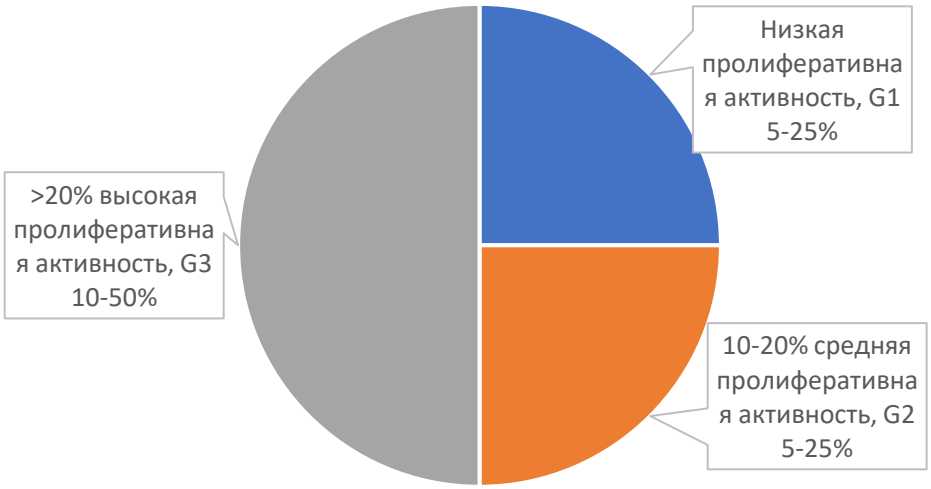

Fig. 1. Ki67 expression levels depending on the G-grading of squamous cell cervical cancer.

According to the results obtained, patients with G1 squamous cell cervical cancer predominantly had low Ki67 proliferative activity, while those with G2 tumors showed moderate expression of the marker. The highest level of Ki67 expression was observed in patients with G3 tumors, accompanied by an increased number of abnormal mitoses, pronounced cellular polymorphism, and high proliferative activity of tumor cells.

To assess tumor angiogenic activity, VEGFR expression was studied in patients with squamous cell carcinoma of the cervix (see Table 1).

Table 1 VEGFR expression levels in squamous cell carcinoma of the cervix

G Tumor grading	G1	G2	G3
Activity level	<30% low proliferative activity – 2 (10%)	30-60% moderate proliferative activity – 7 (35%)	>60% high proliferative activity – 11 (55%)

Two (10%) patients showed weakly positive VEGFR expression, seven (35%) had moderately positive VEGFR expression, and 11 (55%) had high marker expression. Morphologically, high VEGFR expression was accompanied by pronounced vascular proliferation, increased microvessel density, and intense staining of tumor endothelial structures.

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The microscopic pattern of VEGFR expression is shown in Figures 4.5–4.7. Immunohistochemical examination revealed atypical tumor cells with pronounced polymorphism, multiple abnormal mitoses, and areas of neoangiogenesis of varying severity (see Figures 4.5–4.7).

The results showed that high VEGFR expression was more often detected in patients with poorly differentiated tumors and was associated with increased angiogenic activity. Patients with low VEGFR expression tended to have slower disease progression and a lower incidence of metastatic disease.

To study neoangiogenesis processes, we examined the expression of CD34, a marker of microvascular endothelial cells. Microscopic examination revealed atypical squamous cell carcinoma cells with pronounced cellular polymorphism, multiple abnormal mitoses, and varying degrees of vascular proliferation. Microvessel density was assessed by the number of positively stained vascular structures in a single field of view at ×400 magnification. Microscopic characteristics of CD34 expression are shown in Figures 4.1.8–4.1.10. Patients with G1 tumors had low microvessel density, while those with G2–G3 tumors showed increased vascularity and angiogenesis.

To assess the prognostic significance of immunohistochemical markers, a comparative analysis of Ki67, VEGFR, and CD34 expression was conducted in patients from the study group and the group of patients with recurrent cervical cancer.

The analysis took into account the degree of tumor differentiation, the clinical course of the disease, the presence of relapse, and the characteristics of tumor progression.

The results of the immunohistochemical study of patients in the study group are presented in Table 2.

Table 2 Results of the immunohistochemical study in patients in the study group

	Ki67	**VEGFR**	**CD34**
G1	5 (25%)	2 (10%)	5 (25%)
G2	5 (25%)	7 (35%)	5 (25%)
G3	10 (50%)	11 (55%)	10 (50%)

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According to the data obtained, G1 squamous cell cervical cancer predominantly had low expression of Ki67, VEGFR, and CD34. Patients with G2 tumors had moderate expression of the studied markers, while G3 tumors had the highest expression of Ki67, VEGFR, and CD34. Increased expression of immunohistochemical markers was associated with increased tumor proliferative activity, enhanced angiogenesis, and a tendency toward a more aggressive course of the disease.

Coexpression analysis of the studied markers revealed that synchronous increases in the expression of Ki67, VEGFR, and CD34 were more frequently observed in patients with poorly differentiated forms of squamous cell cervical cancer. This category of patients tended to have a higher rate of local recurrence and a shorter recurrence-free follow-up period.

The results of the immunohistochemical study of patients in the control group with recurrent disease are presented in Table 3.

Table 3 Results of the immunohistochemical study in patients with recurrent cervical cancer

	Ki67	**VEGFR**	**CD34**
G1	2(10%)	2(10%)	3(15%)
G2	6(30%)	9 (45%)	8(40%)
G3	12(60%)	9(45%)	9(45%)

In the control group, the highest expression levels of Ki67, VEGFR, and CD34 were found in patients with G3 tumors. High expression of these markers was associated with increased tumor proliferative activity, pronounced neoangiogenesis, and signs of tumor progression. Patients with recurrent disease were more likely to have moderate to high levels of coexpression of these immunohistochemical markers.

A comparative analysis of the study and control groups revealed that increased Ki67 expression was associated with increased tumor cell proliferative activity, while high VEGFR and CD34 expression reflected enhanced angiogenesis and

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increased tumor microvascular density. The most unfavorable clinical and morphological features were observed in patients with a combined increase in the expression of all three markers.

The obtained results indicate that the immunohistochemical markers Ki67, VEGFR, and CD34 can be considered as additional prognostic criteria for assessing the biological activity of squamous cell carcinoma of the cervix. Increased expression of the studied markers was associated with a low degree of tumor differentiation, a tendency toward disease recurrence, and a more aggressive clinical course of the pathological process.

CONCLUSION

The immunohistochemical study demonstrated that the expression of Ki67, VEGFR, and CD34 markers reflects the proliferative activity, angiogenesis, and biological behavior of squamous cell cervical carcinoma. Increased Ki67 expression was associated with increased tumor anaplasia and higher cell proliferative activity. High VEGFR and CD34 expression was associated with increased neoangiogenesis, increased microvessel density, and a tendency toward a more aggressive disease course.

A comparative analysis of the study group and patients with relapse revealed that synchronous coexpression of Ki67, VEGFR, and CD34 was more frequently detected in poorly differentiated forms of cervical cancer and was associated with an increased risk of recurrence. These results demonstrate the prognostic significance of the immunohistochemical markers studied and support the feasibility of their combined use to assess tumor biological activity, predict the clinical course of the disease, and individualize treatment strategies in patients with cervical cancer.