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Optimization of Diagnostic Methods for Locally Advanced Forms of Cervical Cancer Based on Molecular Genetic Markers

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Abstract--*Objective to improve the diagnosis of locally common forms of cervical cancer based on molecular genetic markers.*

Materials and methods: *The study included 120 patients with locally advanced forms of cervical cancer (T2bN0-1M0, T3N0-1M0). In a comparative aspect, two groups of patients were studied. All patients received chemoradiotherapy: 3 courses of neo adjuvant chemotherapy were performed according to the cisplatin + 5 fluorouracil regimens, followed by a combination of radiation therapy, including remote gamma therapy, Sum. 46 Gy and intracavitary radiation therapy, ec Summary to point A 70-90 Gy, to point B 50-58 Gy. All biological materials obtained by biopsy were subjected to immunehistochemical studies. The immunohistochemical method was used to study Ki67, VEGF, p53 and the apoptosis regulator Bcl-2.*

The results of the analysis of the general three-year survival of patients with MRSHM, in which positive indicators of molecular genetic markers VEGF, Ki67, p53 were noted, according to the results of the study, it was revealed that of 21 patients who had high expression of the mutant p53 gene, after radical treatment, the overall three-year survival rate was 4.76%. The overall three-year survival of patients with positive VEGF protein figures was 13.6%, the expression of the Ki67 proliferative activity gene was 20.83%, and the overall and disease-free survival of patients with positive Bcl2 protein was statistically significant higher than the same values for cervical cancer (76.6%) ($p<0.05$). For example, with negative markers, the overall and relapse-fee three-year survival rates were high when, while maintaining a positive status, these indicators decreased ($p<0.01$).

Keywords--*VEGF, Ki67, Bcl2, p53, chemoradiotherapy, cervical cancer*

I. INTRODUCTION

Malignant tumors of the female genital organs occupy a special place in clinical oncology: they are the most common malignant neoplasms in women [11]. Every year, 12.7 million new cases of cancer are registered in the world, of which more than 1 million are female genital diseases [2].

Among the countries of Central Asia and the Russian Federation for the period 1991–2016, the increase in the absolute number of patients with cervical cancer ranged from 9% (in Belarus) to 44–92% (in the Russian Federation, Kazakhstan, and Kyrgyzstan). In 2016, the highest incidence rates were recorded in the Russian Federation, Kazakhstan and Kyrgyzstan (15.4 and 16.4 per 100 thousand female population); at the level of 10–11 per 100 thousand — in Armenia, Uzbekistan, Moldova and Tajikistan; less than 7 per 100 thousand —in the Republic of Azerbaijan [12].

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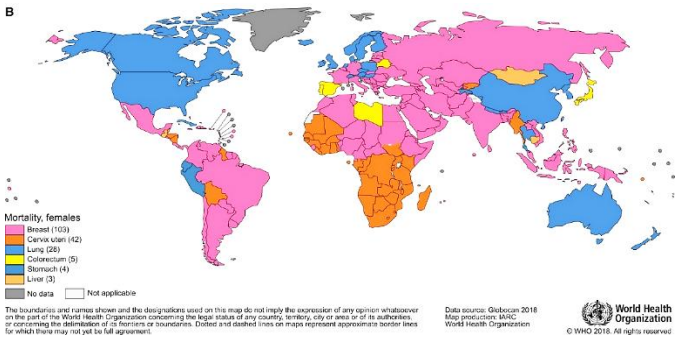
Global map representing the most common type of cancer mortality in countries in 2018 among women [1].



The long-term results of treatment of patients with cervical cancer remain unsatisfactory, relapses after special treatment more often occur after 12-20 months and are observed in 32-78.3% of cases. Up to 45% of patients die within the first 5 years of disease progression [16].

This requires improving the quality of early diagnosis and improving the treatment of locally advanced cervical cancer to predict relapse of the disease. Prognostic factors for cervical cancer are often more significant in terms of the outcome of the disease. The dependence on the stage of the disease, the volume of the primary tumor, the degree of prevalence of the tumor process has been proven and recognized for a long time. It should be noted that according to the literature, none of the listed factors can explain why, even with similar clinical and morphological signs, as well as treatment tactics, the effectiveness of treatment is different? Some patients live for 5 years or more, while others die in the early stages after treatment for disease progression. An attempt to explain this fact prompts researchers to study the molecular genetic characteristics that can influence the prognosis of the disease.

Antoneeva I.I. and co-authors believe that the morphology of the tumor is related to the degree of its clinical aggressiveness. So, the histological classification of tumors was developed taking into account the level of malignancy of their nosological forms. At the same time, the biological behavior of tumors remains sufficiently unpredictable even for patients with the same stage of the disease. In connection with these, the role of molecular genetic markers in the occurrence and course of cervical cancer requires in-depth study.

Today, one of the most promising directions in the diagnosis of malignant tumors is the determination of tumor markers, which can provide additional information about the biological characteristics of the tumor. Much attention is paid to the study of markers characterizing apoptosis, cell proliferation - these are p53, Bcl-2, Ki-67 proteins [13].

Currently, much attention is paid to the study of markers characterizing apoptosis, cell proliferation - these are VEGF, p53, Bcl-2, Ki-67 proteins, which is the main cause of the more malignant course of the disease.

One of the most studied indicators of tumor growth aggressiveness is cell proliferation, which can be assessed using the mitotic index and Ki-67 index. The Ki-67 antigen is expressed in almost all phases of the mitotic cycle, and in accordance with this reflects the proliferative pool of the tumor. The Ki-67 proliferative index is considered as an independent prognostic indicator of relapse, overall and relapse-free survival, a predictive factor for determining the sensitivity to chemotherapy and radiation therapy [9]. In the world

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literature there is no consensus on the effect of proliferative activity of tumors on their radiosensitivity. A number of authors indicate a lack of dependence of proliferative activity and response to radiation therapy in patients with cervical cancer [6]. Other authors prove the dependence of the effect of chemoradiotherapy for cervical cancer on the proliferative activity of the tumor. According to Sahebali (2003), the best treatment results were achieved in patients with maxi cervical cancer with an initially high proliferation index compared with patients with lower Ki-67 rates [7].

p53 is a transcription factor that regulates the cell cycle and acts as a suppressor of malignant tumors. One of the functions of p53 is to monitor the state of cellular DNA. In response to signals of abnormal processes and the presence of damage to the genetic apparatus, p53 is activated, which leads either to an acceleration of the repair process, or to a halt in the cell cycle and, under severe stress stimulus, to apoptosis. Thus, this protein prevents the division of potentially oncogenic cells. The functions of p53 boil down to maintaining the genetic identity of the cells of a multicellular organism, which is why it is often called the "genome keeper" [3,4,5]. According to the researchers, overexpression of p53 correlates with patient survival. In their studies, overexpression of p53 was predominantly observed in patients with more common forms and was practically absent in patients with localized forms of the disease. In the work of Yu.N. Ponomareva (2011) found that p53 oncoprotein was detected in 21.3 ± 4.2% of cases of cervical intraepithelial neoplasia (CIN) and exceeded 10.0% of stained cells; p53 was not detected in control samples of the cervix [15]. In cervical cancer, the frequency of determination of p53 was 54.2 ± 5.1% of its expression level (10-60%). Analysis of the clinical course showed that p53 overexpression was associated with an adverse course of CIN and cervical cancer. The p53 expression level, exceeding 9.9% of positive cells with CIN and 30.6% with cervical cancer, prevailed in the poor prognosis group ($p < 0.001$ and $p = 0.034$, respectively) [15]. The frequency of accumulation of p53 increases with increasing malignancy of tumors, while the accumulation of mut-p53 does not occur in benign tumors, while in malignant tumors the frequency of accumulation increases to 46% [10].

Bcl-2 and similar cytoplasmic proteins are the main regulators of apoptosis, a program of cell suicide, which is crucial for the development, homeostasis of tissues and protection from pathogenesis. The proteins closest to Bcl-2 ensure cell survival by inhibiting the adapters needed to activate the proteases that disassemble the cell. Members of the Bcl-2 protein family are essential for maintaining the order of most organ systems, and mutations that damage them play an important role in carcinogenesis. The absence of functionally active Bcl-2 genes in mice causes the death of animals at the embryo stage or in the postnatal period, respectively, due to extended programmed cell death of various organs. Similar results indicating a significant increase in the expression of the Bcl-2 gene in patients with invasive cervical cancer compared with patients with cervical dysplasia were obtained by Yu.N. Ponomareva (2004) [6].

The author believes that the minimal expression of Bcl-2 in patients with dysplastic processes indicates the possible regulation of apoptosis of atypical cells by other factors. At the same time, the progression of cervical cancer is probably due to an increase in the production of the Bcl-2 gene. Vascular Endothelial Growth Factor (VEGF), originally known as Vascular Permeability Factor (VPF) [8], is a signaling protein produced by cells that stimulate the formation of blood vessels. To be specific, VEGF is a subset of growth factors, a family of cystine node growth factors derived from platelets. They are important signaling proteins involved in both

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vasculogenesis (the formation of the denovo embryonic circulatory system) and angiogenesis (the growth of blood vessels from an existing vascular system).

II. MATERIALS AND METHODS

The study included 120 patients with locally advanced forms of cervical cancer (T2bN0-1M0, T3N0-1M0). In a comparative aspect, two groups of patients were studied. The first group consisted of 30 patients with poor prognoses, the second group consisted of 90 patients with a favorable prognosis. A retrospective and prospective analysis of case histories of patients were carried out. Before therapy, patients have examined clinically laboratory. All patients received chemoradiotherapy: 3 courses of neoadjuvant chemotherapy were performed according to the cisplatin + 5 fluorouracil regimen, followed by a combination of radiation therapy, including remote gamma therapy, single focal dose 2, total focal dose 46 Gy (TERABALT type 80 model SCS 2012 Czech Republic) and intracavitary radiation therapy (BEBIG apparatus MULTISOURSE Co60 2013 Germany) a single focal dose of 5 Gy, the equivalent total focal dose to point A 70-90 Gy, to point B 50-58 Gy.50
биологическиематериалы,полученныеприбиопсииподвергалисьиммуногистохимескомуисследованию. Иммуногистохимическим методом изучались Ki67, VEGF, p53 и регулятор апоптозаBcl-2.

There were 86 patients with stage IIb disease (71.6%), stage IIa - 17 (14.2%), stage IIIb - 17 (14.2%). It should be noted that a group of patients with stage IIIb disease. Patients with stage IIb made up 71.6% (n = 86), with stage IIIa (n = 17) 14.2% and patients with stage IIIb (n = 12) 14.2%. The greatest number of patients met at the age of 40-49 with stage IIb - 28 (68.3%), stage III- 15 (12.5%). 68% of patients were under 49 at menopausal age. According to the histological structure of the tumor, the examined groups were statistically homogeneous p> 0.05. In most cases, the tumor was represented by squamous cervical cancer in 117 patients (97.5%). Cervical adenocarcinoma was diagnosed in 3 (2.5%) patients. Analysis of morphological verification was carried out in the pathomorphology department of the Republican specialized scientific and practical center of oncology and radiology of the Republic of Uzbekistan. Histological examination was performed on a 3-4 micrometer paraffin section stained with hematoxylin-eosin and was used for panoramic microscopy followed by reclassification and refinement of the morphological features of neoplasms based on the criteria of the International Histological Classification of Cervical Tumors.

Biopsies were fixed in 10% neutral formalin on phosphate buffer. In the case of a cervical biopsy in another medical institution, glass preparations and histological examination blocks were reviewed.

A thorough analysis of clinical and morphological observations show that the most important is the data of the study: the form of tumor growth, the stages of the process, the histological structure of the tumor. The degree of tumor differentiation was determined in all patients, with G-1 detected in 6 (%) in group 1, G-2 in 11, G-3 in 10, G-4 in 3 cases.

In patients of the 2nd group G-1 - 23, G-2 - in 49, G-3 - in 18 cases. A study of the distribution of patients depending on the form of tumor growth allowed us to establish that the rarest was mixed forms - 15.83%, endophytic - 30.83% and exophytic - 53.33% of the growth form. Immunohistochemical analysis was

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performed on biopsy materials from the cervix taken from 50 patients. Of the 50 patients, 20 patients without relapse, 30 with relapses.

Immunohistochemical studies were carried out by standard methods for biopsy material embedded in paraffin using monoclonal antibodies from Dako. The tumor markers VEGF, Ki-67, bcl-2, p53 were studied.

III. CHARACTERIZATION OF THE RESULTS OF THE STUDY

Patients with locally advanced cervical cancer with a high level of VEGF expression in the G-3 and G-4 process have an unfavorable prognosis for the detection of metastases and relapses of the disease.

In the main group of 60 patients with positive VEGF, there were 22 (73.33%) patients, of which 4 (18.2%) were diagnosed with highly differentiated squamous cell carcinoma, 6 (27.3%) were moderately differentiated, and 9 (40, 9%) low-grade forms of squamous cell carcinoma, in 3 (13.6%) patients undifferentiated forms of the tumor were detected. In the control group of 20 VEGF patients, 2 (10.0%) patients were positive in which the tumors were moderately and poorly differentiated.

Depending on the degree of differentiation, Ki 67 increased in group I patients with disease progression and the risk of relapse in 24 (80.0%) of 30 patients. Of these, 4 (16.66%) had highly differentiated, 8 (33.33%) moderately differentiated forms, 9 (37.5%) low-differentiated forms, and 3 (12.5%) undifferentiated forms of tumors.In the second group of 20 Ki67 patients, only 5 (25%) patients with highly, moderately, and low-grade tumors were positive.

A study of p53 expression showed that a positive reaction was determined in 70% of cases of locally advanced cervical cancer. The p53 study showed an increase in indicators in 21 (70%) of 30 patients in group 1 with the progression of the process and the risk of recurrence.

Thus, p53 overexpression can be a prognostic factor in the event of recurrence of the process, which must be taken into account in each individual case. A positive response to the p53 tumor marker was mainly observed during G-3 differentiation (42.8%). Moreover, in patients with locally advanced cervical cancer, in which a relapse of the disease was detected in the next 3 years of observation, the level of p53 expression was as high as possible (table 8.). In the control group of 20 p53 patients, positive in 3 (15%) patients revealed moderate and low-grade forms of tumors. Assessment of Bcl-2 expression was carried out in the fields of view at an increase of (x400), based on the percentage of stained cells semi-quantitatively (objective 40), based on the prevalence and intensity of immunohistochemical reactions (lack of expression or less than 10% of cells were stained - 0 points, from 10 to 25 % - 1 point, from 26 to 50% - 2 points, from 51 to 75% - 3 points and more than 75% - 4 points. Patients subsequently showed relapses, high expression of this tumor marker was detected in 36.66% of cases. Bcl of 2 expressed patients was as follows: in 1 (9.1%) highly differentiated 4, (36.4%) moderately differentiated, 5 (45.4%) low-differentiated and 1 (9.1%) undifferentiated tumors.

It can be seen from the figure that positive expression of the mutant p53 gene was observed in 21 (70.0%) patients, Ki-67 in 17 (56.7%) patients, and the level of VEGF and Bcl-2 oncoprotein were positive in 22 (73, 3%) of patients and 11 (36.7%), respectively, but the most negative expression of Bcl-2 was 19 - (63.3%). In the second group of 20 patients, the specific gravity was shown by Ki67 and Bcl2 for 4 and 5 patients, respectively.

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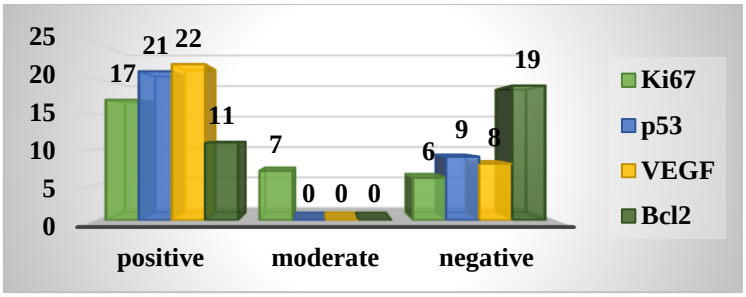

Figure 1. Indicators of expression of tumor markers in immunohistochemistry of the first group (n = 30)

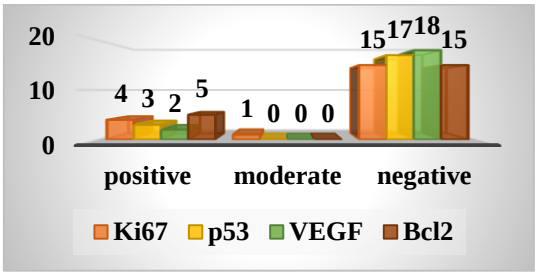

Figure 2. Indicators of expression of tumor markers in immunohistochemistry of the second group (n = 20)

When studying the expression of tumor markers with endophytic forms of p53 - 100.0%, and mixed forms of tumor growth, a positive reaction was noted at 77.8%, Ki-67 high level of expression - 100.0% with VEGF-87.5%, 77, 8% respectively. In the second group, high rates were observed in patients with exophytic forms of tumor growth.

We analyzed the overall and relapse-free survival of patients with locally advanced cervical cancer included in the study, depending on the level of VEGF, Ki67, p53 and bcl-2, as well as on the prognosis of these genes after chemoradiotherapy.

So in the first group, where molecular genetic markers were positive, the relapse of the disease was established in all patients, which amounted to 100%. In this group, relapse of the disease up to a year was detected with high expression of p53 in 17 (81.0%) patients, Ki67 in 19 (79.2%) patients, VEGF in 18 (81.8%) patients, Bcl2 in 4 (36, 4%) patients. In the second and third years of follow-up, relapses were little detected.

A characteristic feature of the development of relapse of locally advanced cervical cancer in the first group was an initial increase in the number of patients with relapse during the first year, and then a slow decrease in their number.

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Table 1. Time to relapse in patients with relapses of locally advanced cervical cancer, depending on immunohistochemical parameters (Group I)

Markers (positive numbers)		**Relapse (n=30)**			
		Intervals (months)			**Total**
		12	24	36	
P53 (21)	N	17	3	1	21
	%	81,0	14,3	4,7	100
Ki67 (24)	N	19	4	1	24
	%	79,2	16,7	4,2	100
VEGF (22)	N	18	3	1	22
	%	81,8	13,6	4,5	100
Bcl2 (11)	N	4	3	4	11
	%	36,4	27,3	36,7	100

An analysis of gene expression revealed a consistent decrease in the overall three-year survival of patients with locally advanced cervical cancer as it increases. The adverse effects of a combination of overexpression of these genes and their combined increase, and the likelihood of death from locally advanced cervical cancers were confirmed by a survival analysis. The table shows that the 1-year and 3-year survival in the first group according to the stages was as follows: stage IIb 80%, 70% and 45%, stage IIIa 80% and 60%, with stage IIIb 80% and 60%, respectively.

And the survival curve used to describe survival reflects the probability of surviving any of the times t after treatment.

A decrease in the degree of differentiation of tumor growth leads to an increase in the number of p53 positive reactions, the level of which was 90.0%, Ki-67 - 90.0%, a positive Bcl-2 reaction is most common with G-2 - 54.5%, and VEGF with low-grade - 90.0% ($p < 0.05$).

Table 2. Expression of tumor markers depending on the degree of tumor differentiation

Markers	**Expression level**	**Squamous cell carcinoma**							
		G-1 (6)		**G-2 (11)**		**G-3 (10)**		**G-4 (3)**	
		abs.	**%**	**abs.**	**%**	**abs.**	**%**	**abs.**	**%**
p53	Positive	3	50,0	6	54,5	9	90,0	3	100,0
	Negative	3	50,0	5	45,5	1	10,0	0	20,0
Ki-67	High	3	50,0	5	45,45	7	70,0	2	66,66
	Moderate	1	16,66	3	27,27	2	20,0	1	33,33
	Negative	2	33,33	3	27,27	1	10,0	0	0,0
VEGF	Positive	4	66,66	6	54,5	9	90,0	3	100,0
	Negative	2	33,33	5	45,5	1	10,0	0	0,0

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Bcl-2	Positive	0	0,0	6	54,5	5	50,0	0	0,0
	Negative	6	100,0	5	45,5	6	60,0	3	100,0

So in the first group of the IIb stage, the overall three-year survival rate was 45.0%, at the same time in the second group 93.9%. At stages IIIa and IIIb, survival rates were low in the first group and 58.3% in the second group, respectively. An analysis of the studies showed that in both groups the survival rates for the exophytic form of tumor growth were higher than for endophytic and mixed forms of tumors in 38.5% (5), 25.5% (2), 22.22% (2) with the first group and 88.2% (45), 75.9% (22), 90.0% in the second group, respectively. The frequency of occurrence of the results of the analysis of the morphological differentiation of the tumor shows that the lowest data are expressed in G3 and G4 10.0%, 0.0% in the first group and 57.9% in the second group, respectively ($p < 0.05$).

The results of the analysis of the general three-year survival of patients with locally advanced cervical cancer, in which positive indicators of the molecular genetic markers VEGF, Ki67, p53 are shown, are presented in Fig. 4.5. According to the results of the study, it was revealed that out of 21 patients who had high expression of the mutant p53 gene, after radical treatment, the overall three-year survival rate was 4.76%.

The overall three-year survival of patients with positive VEGF protein figures was 13.6%, the expression of the Ki67 proliferative activity gene was 20.83%, and the overall and disease-free survival of patients with positive Bcl2 protein was statistically significant higher than the same values for locally advanced cervical cancer (76.6%) ($p < 0.05$).

When analyzing the dependence of the overall and relapse-free survival of patients with locally advanced cervical cancer, statistically significant differences were noted between the groups where the expression of markers is positive and negative. For example, with negative markers, the overall and relapse-free three-year survival rates were high when, while maintaining a positive status, these indicators decreased ($p < 0.01$).

IV. CONCLUSION

Prognostic factors for locally advanced cervical cancer are numerous. All of them to one degree or another affect both the survival of patients and the risk of metastases and further progression of the disease.

When analyzing immunohistochemical factors, namely, an increase in the expression of VEGF protein, Ki67 proliferative protein, and mutant p53 gene, a natural decrease in the overall and disease-free survival of patients with locally advanced cervical cancer was revealed; The increased likelihood of cervical cancer mortality is also adversely affected by a combination of overexpression of the above genes, morphological differentiation of tumors and the form of tumor growth.

In the first group of stage IIb, the overall three-year survival rate was 45.0%, while at the same time, in the second group, 93.9%. In stages IIIa and IIIb, it is seen that survival rates are low at 0.0% in the first group and 58.3% in the second group, respectively. In both groups, the survival rates in the exophytic form of growth swelled higher than in endophytic and mixed 38.5% (5), 25.5% (2), 22.22% (2) in the first group and 88.2% (45), 75.9% (22), 90.0% in the second group, respectively.

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When analyzing overall and relapse-free survival in patients with locally advanced cervical cancer, statistically significant differences were observed between groups with positive and negative marker expression. For example, with negative marker expression, overall and relapse-free three-year survival was high, while maintaining a positive status, these indicators decreased. With high positive values of the mutant p53 gene in patients with locally advanced cervical cancer, the overall three-year survival rate was 4.76%, VEGF protein indicators - 13.6%, Ki67 - 20.83%, respectively ($p < 0.01$).

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