CLINICAL, MORPHOLOGICAL AND MOLECULAR MARKERS IN THE FORMATION OF PROGNOSIS IN PATIENTS WITH CERVICAL CANCER

LITERATURE REVIEW

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INTRODUCTION

Cervical cancer (CC) ranks fourth among the causes of cancer mortality in women globally. In 2022, there were approximately 662,301 new cases of CC and 341,831 deaths from CC were registered worldwide. At the same time, mortality rates were significantly higher in developing countries compared to economically developed countries [1]. The main etiological factor in the development of CC is considered to be persistent infection with high-risk human papillomavirus (HPV), which, according to available data, causes more than 90% of CC [2].

Thanks to the development of modern methods of cervical screening and the widespread use of HPV vaccination, the incidence and mortality of CC have decreased significantly in countries with a high level of economic development. At the same time, in low- and middle-income countries, this disease still remains the second most common type of cancer among women and is one of the leading causes of mortality and morbidity among young and middle-aged women (20–39 years) worldwide [1, 2].

Early asymptomatic course provokes the influence of risk factors associated with the development of CC: smoking, early onset of sexual activity, sexually transmitted infections, number of sexual partners, oral contraceptive use, and immunosuppression.

Currently, the staging of CC is based on the International Federation of Gynecology and Obstetrics (FIGO) criteria, which mainly take into account tumor size, paravaginal infiltration, and lymph node involvement [3].

The most common histological type of CC is squamous cell carcinoma, while adenocarcinoma is less common and accounts for approximately 10–25% of CC cases [4].

The main methods of treatment for CC are surgical, radiological, and radiological and chemotherapeutic. In recent years, immunotherapy and targeted drugs have been actively introduced. Treatment of early stages of CC (IA–IIA) includes several surgical methods or a combination of radiotherapy with brachytherapy and chemotherapy [5]. The combination of cisplatin based chemotherapy with combined radiotherapy is the main therapeutic strategy for locally advanced CC (stages IIB–IV) [6].

Known clinical and morphological, tumor-associated factors of CC vill atypism oglandular prognosis: staging, depth of stromal invasion, presence or absence of lymphovascular invasion, lymph node involvement and the presence of distant metastases. Tumor size, stromal invasion, lymphovascular invasion, pathologically confirmed lymph node metastases, parametrial extension, or positive resection margins are considered to predict the risk of recurrence after primary surgical treatment [7]. Based on these characteristics, the Sedlis and Peters criteria were developed to decide whether adjuvant therapy for CC should be used to reduce the risk of recurrence [8, 9]. According to these criteria, prognostic factors are divided into low-, intermediate-, and high-risk factors. The criteria for defining the intermediate risk of CC recurrence remain the most controversial and insufficiently studied.

Despite known prognostic factors and advances in treatment, the prognosis for CC remains poor, with survival rates not improving significantly over the past two decades. The development of resistance to radiation and chemotherapy is a major obstacle to successful treatment of CC [10]. The course of the disease, the response to chemo- and radiotherapy, the progression of the process, the long-term results of treatment of patients with CC with identical stage and histological type of tumors are not the same. This can be explained by the diversity of biological features of tumor cells. Therefore, the attention of researchers is directed to the identification of additional molecular-biological prognostic markers that allow clarifying the reasons for the different behavior of tumors at the same clinical stage and degree of differentiation, to make the right choice in personalized treatment, to increase the relapse-free and overall survival of patients [11–13].

Objective of the review: analysis of the prognostic informativeness of traditional clinical, morphological, novel potentially significant molecular prognostic factors and factors of tumor microenvironment in CC, which will allow

improving the accuracy of predicting disease course in both primary and recurrent CC.

MATERIALS AND METHODS

Analysis of scientific publications over the last 10 years devoted to prognostic pathological factors of CC was conducted, with an emphasis on those indicators that are not yet standardized in modern histopathological protocols in the databases PubMed, Embase, Cochrane Library (Central), Web of Science and Google Scholar using the keywords: "cervical cancer", "prognostic factors", "molecular markers" and "tumor-associated factors".

TUMOR-ASSOCIATED PROGNOSTIC PARAMETERS

Histological type and HPV status

The cause of more than 90% of CC is infection with oncogenic HPV types. More than 200 genotypes have been described, of which about 40 infect epithelial cells of the anogenital tract, 13 of which are classified as high-risk genotypes due to their high oncogenic potential [14, 15], of which HPV types 16 and 18 are the most common genotypes of squamous cell carcinomas and adenocarcinomas [16, 17]. The pathogenesis of CC is based on the integration of the HPV genome into the host cell chromosome, which is accompanied by inactivation of the viral regions E1 and E2 and increased expression of the oncogenes E6 and E7, which triggers the mechanisms of malignant transformation of cells. In particular, the E6 oncoprotein causes degradation of the p53 protein, suppressing apoptosis, while the E7 protein stimulates cell proliferation, suppressing the action of the tumor suppressor protein retinoblastoma (RB1) [18]. Despite the fact that the vast majority of cervical epithelial tumors are associated with HPV infection, it has been proven that some of these tumors, mainly adenocarcinomas, are not associated with HPV infection and are characterized by a more aggressive clinical course than HPV-associated tumors. In this context, in 2020, the WHO introduced an updated classification system for cervical epithelial tumors, based on the presence or absence of HPV infection. Currently, squamous cell carcinomas and adenocarcinomas of the cervix are classified as HPV-dependent (villoglandular, mucinous, mucinous intestinal, adenosquamous, mucoepidermoid, basal adenoid, etc.) and HPV-independent (these include rare but aggressive histological types - gastric, clear cell, mesonephric, endometrioid carcinomas). HPV-independent squamous cell carcinomas are extremely rare, but are characterized by a higher frequency of lymph node metastasis and worse survival rates than HPV-associated forms [19, 20].

Degree of differentiation of HPV-associated CC

Squamous cell carcinomas

Tumors of moderate and low degree of differentiation (G2–G3) are significantly associated with a higher stage of the disease, the presence of lymphovascular invasion, perineural spread and metastasis to lymph nodes [21].

Adenocarcinomas

Several studies have proposed a grading system for HPV-associated adenocarcinomas of the cervix that is based on a combination of architectural and nuclear features and is similar to the FIGO classification system used for endometrioid carcinomas of the uterine corpus. The most effective grading system is one that takes into account the architectural features of the tumor and the morphology of the cells' nuclei.

According to the proportion of solid architectural components of the tumor tissue, glandular CC are classified as follows

- ≤ 10% – grade 1 (highly differentiated);
- 11–50% – grade 2 (moderately differentiated);
- > 50% – grade 3 (lowly differentiated).

This classification has demonstrated good prognostic value and is recommended for practical use [22]. The Silva Pattern Classification (SPC), proposed in 2013, is a modern morphological system designed to assess the types of invasive growth in HPV-associated cervical adenocarcinoma. Recent studies have shown that the SPC classification is closely related to the likelihood of lymphogenous metastasis and patient survival. It is used only for HPV-associated cervical adenocarcinoma and divides tumors into three morphological patterns (A, B, C), which are determined by the degree of destructive growth in the stroma, the presence of lymphovascular invasion and the level of cellular atypia [19–23]. The SPC classification has important prognostic value, as it helps to determine the risk of lymphovascular invasion, lymph node metastasis and overall prognosis of the disease:

- Type A tumors consist of well-formed glands without signs of invasion, atypia or lymphovascular invasion. They do not metastasize to lymph nodes and have a minimal risk of recurrence; therefore they are suitable for conservative treatment without lymph node dissection.
- Type B is characterized by limited destructive invasion of small groups of cells (up to 5 mm). The risk of metastases is very low, but in the presence of lymphovascular invasion, it is advisable to determine sentinel lymph nodes.
- Type C has diffuse destructive invasion with desmoplasia, is accompanied by a high risk of metastases and recurrence, and therefore requires radical surgery with lymph node dissection [23].

Clinical studies have convincingly proven that adenocarcinoma of the cervix is characterized by a significantly less favorable prognosis than squamous cell histotype [24].

Lymphovascular invasion

Evaluation of lymphovascular invasion is a mandatory component of the histopathological report in CC, as this parameter is associated with the risk of regional and distant metastases and indicates the need for adjuvant therapy. Diffuse lymphovascular invasion is associated with an increased risk of lymph node metastasis, parametrial involvement, and positive surgical margins [25].

Perineural invasion

Perineural invasion is the pathological process of invasion and spread of malignant cells along peripheral nerves. In recent years, this type of invasion has been increasingly recognized as a fourth route of tumor metastasis and invasion, along with hematogenous, lymphogenous, and implantation routes. Perineural invasion is diagnosed when tumor cells invade the

endoneurium, perineurium, epineurium, or if invasion involves ≥ 33% of the circumference of the nerve sheath [26]. Perineural invasion is often associated with other risk factors, such as lymphovascular invasion, depth of invasion, large tumor size, positive surgical margins, parametrial involvement, and pelvic lymph node metastasis. However, the prognostic value of perineural invasion as an independent predictor of disease-free and overall survival remains controversial. One reason is that the choice of postoperative radiation or chemoradiation for patients with perineural invasion is often determined by comorbidities, making it difficult to isolate the independent impact of this type of invasion on prognosis. Thus, further studies are needed to clearly determine whether perineural invasion can be considered an independent prognostic factor or a risk factor. However, this indicator can already be considered as a new intermediate risk factor, which should be considered when planning postoperative adjuvant therapy [27, 28].

Depth of stromal invasion

According to the Sedlis criteria, the depth of tumor invasion is defined as the involvement of the inner, middle, or outer third of the thickness of the cervical wall. Several studies have demonstrated that the depth of tumor invasion is an independent prognostic factor for both overall survival and recurrence-free survival, and is also closely related to the risk of local recurrence. According to the results of current studies, the depth of tumor invasion can serve as a reliable criterion for assessing the pathological response of the tumor in CC after neoadjuvant therapy [29].

Parametrial extension

Closely related to the depth of invasion, parametrial involvement is another key histological feature of importance for the pathological staging of CC.

Tumor extension to the parametrial area is an independent prognostic factor associated with an increased risk of recurrence and decreased recurrence-free survival in both squamous cell carcinomas and adenocarcinomas [29].

Tumor-free distance

Tumor-free distance is defined as the minimum thickness of intact cervical stroma between the tumor margin and the pericervical stromal ring. A distance ≤ 3 mm is significantly correlated with an increased risk of recurrence and worse recurrence-free and overall survival. This indicator has demonstrated a higher prognostic value than traditional morphological factors – depth of invasion and lymphovascular invasion. A smaller distance from the tumor is also associated with a positive lymph node status. Accordingly, if these findings are confirmed in further studies, this indicator may be considered as a new independent prognostic marker useful for preoperative assessment of risk factors and justification of the choice of adjuvant treatment in patients with CC [30, 31].

PARAMETERS OF REGIONAL METASTASIS

The size of the metastases in the pelvic lymph nodes is crucial for determining the N category according to the TNM staging system.

Specifically: macrometastases are metastatic foci larger than 2 mm, which are classified as pN1. Micrometastases are between 0.2 mm and 2 mm in size and are designated as pN1(mi). Isolated tumor cells (ITCs) are single neoplastic cells or small clusters of them, not larger than 0.2 mm; they do not change the tumor stage and are classified as pN0(i+). Macro- and micrometastases have a negative impact on disease-free and overall survival, while the prognostic value of ITCs remains uncertain, and there is currently no evidence that isolated tumor cells can transform into true lymph node metastases [32].

MOLECULAR PROGNOSTIC PARAMETERS AND FACTORS OF THE TUMOR MICROENVIRONMENT

A number of molecular parameters reflect physiological or pathological changes in the body in patients with CC and allow for the assessment of response to treatment or the selection of a personalized therapeutic approach. Prognostic biomarkers determine the risk of disease recurrence or progression regardless of therapy, while predictive biomarkers reflect the likelihood of an effective response to a particular treatment. The presence of such a marker indicates a potentially better clinical outcome compared with patients who do not have it. Proteins are considered the most informative biological indicators. The prognostic value of protein biomarkers is mainly due to overexpression or aberrant expression resulting from mutations in the genes encoding them [33].

Markers resulting from the incorporation of HPV DNA into the cellular genome

Diagnostic and prognostic biomarkers in most cervical tumors are based on molecular phenomena resulting from the integration of HPV into the genome of tumor cells. These include HPV detection by polymerase chain reaction, assessment of viral load, detection of overexpression E6/E7, p16, Ki-67, p53, Rb, as well as other cellular biomarkers of proliferation and apoptosis by immunohistochemistry [34].

The p16 protein is involved in the regulation of the cell cycle, and its concentration is normally extremely low. Abnormal expression of the p16 gene leads to excessive cell proliferation and loss of control over the cell cycle, which leads to the accelerated development of pathological changes. Studies have shown that the p16 gene is not expressed in normal epithelium or benign lesions, while its overexpression is observed in cervical dysplasia cells [34]. Hyperexpression of p16 is a marker of HPV infection and indicates active expression of the HPV E7 viral oncogene and inactivation of the retinoblastoma gene by the viral E7 protein. This is observed in neoplasms caused by oncogenic HPV types. WHO recommends the use of p16 immunohistochemical staining in combination with HPV testing to distinguish HPV-associated from HPV-nonassociated CC. The results of a meta-analysis of 23 studies showed that high expression of the p16 protein is a risk factor for the development of lymph node metastases, low-grade differentiation of the tumor, older age at diagnosis, late FIGO stage, and for the occurrence of vascular invasion in patients with CC [35].

The marker Ki-67 (nuclear antigen associated with cell proliferation) according to numerous publications can be used to

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differentiate the diagnosis, stage of progression of cervical neoplasia; it is determined immunohistochemically, often in combination with other antigens. In a review study based on the analysis of 28 publications on the immunohistochemical study of the expression of Ki-67, p16 and p53 in precancer and cancer of the cervix, high expression, especially p16 and Ki-67, was found in more widespread processes, while in normal cervical epithelium its level was minimal or absent [36].

The p53 protein influences the expression of proteins involved in the induction of apoptosis, cell cycle regulation, growth inhibition, and angiogenesis. Normally, p53 is rapidly inactivated, whereas in many tumor cells, p53 expression increases, which is a marker of the development of the neoplastic process. Increased expression or aberrant expression of p53 gene products is observed in many malignant neoplasms, including CC, endometrial cancer, and serous ovarian cancer [37]. The prognostic value of viral load has been described in many studies. In locally advanced CC, low viral load is associated with rapid metastasis and worse survival, whereas the combination of high viral load and tumor size is associated with a better prognosis [38, 39]. Studies have shown that the activation and recruitment of immune components such as Langerhans cells, dendritic cells, tumor-associated macrophages, CD4+ and CD8+ lymphocytes leads to the stimulation of the immunosuppressive tumor microenvironment by HPV. High viral load affects the tumor microenvironment, causing greater immunosuppression and greater tumor infiltration by T lymphocytes, which has a positive effect on overall survivalї [40, 41].

Hypoxia-associated proteins

Hypoxia is a critical factor in the progression of solid tumors and resistance to treatment. Hypoxia-inducible factor 1α (HIF-1α) acts differently depending on the presence or absence of oxygen. In an oxygen environment, HIF-1α is destroyed, and vice versa, in anoxic environment it enters the cell nucleus and upregulates genes involved in tumor progression, which leads to the maintenance of cancer progression through angiogenesis, proliferation, invasion and metastasis, induction of genetic instability and resistance to treatment [42].

Vascular endothelial growth factor (VEGF) is a stimulator of angiogenesis (the process of formation of new blood vessels necessary for life, tumor growth and the development of metastases). According to a meta-analysis by Chinese researchers, VEGF overexpression is associated with the formation of new capillaries during carcinogenesis and metastasis, and is associated with worse survival of patients with CC [46]. The prognostic value of HIF-1 α and VEGF is mainly associated with overexpression in CC and poor response to chemoradiotherapy [43,44].

Hematological parameters

Multiple hematological parameters have been described to predict response to treatment. Low oxygenation of solid tumors increases the risk of invasion, metastasis, and treatment failure. Hematological parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and hemoglobin levels reflect the dynamic interaction between tumor-induced inflammation and the host immune response. The systemic inflammation in cancer patients is associated with reduced overall and disease-free survival. Studies have shown that hematological parameters such as NLR, PLR, and elevated C-reactive protein may serve as potential markers of systemic inflammation associated with cancer progression [45].

Anemia is a negative prognostic factor for CC, as a decrease in hemoglobin levels below 100 g/L impairs oxygen transport in tissues, which may reduce the effectiveness of radiotherapy. In addition, it has been established that anemia can serve as a marker of tumor progression and complications associated with the course of the disease. The results of the study showed a significant correlation between increased NLR and low hemoglobin levels with a higher risk of local recurrence and distant metastases. Hematological parameters provide a new vision of the relationship between inflammatory reactions and the immune response in CC, acting as simple and accessible indicators of the prognosis of the course of the disease. Chronic inflammation is an important factor in carcinogenesis, and the inflammatory microenvironment of the tumor promotes its growth and metastasis. Immune cells (neutrophils, lymphocytes and platelets) cause DNA damage and genetic instability through the formation of reactive oxygen species, which stimulates the development of cancer [46, 47].

In recent years, the relationship between inflammatory processes and cancer development has been actively studied, which has allowed to obtain knowledge to improve approaches to cancer treatment. Systemic inflammation is associated with poor outcomes in patients with malignant diseases. Neutrophilia, thrombocytosis, and relative lymphocytopenia, which occur as part of the immune antitumor response, are often observed as signs of systemic inflammation. Clinical observations have shown that prolonged (chronic) inflammation can cause proliferation of malignant cells, contributing to tumor formation and negatively affecting the prognosis of patients [48]. There is increasing evidence that certain specific immune-inflammatory biomarkers, such as levels of neutrophils, lymphocytes, and monocytes, reflect the state of equilibrium of the immune-inflammatory environment of the body. These markers are important for predicting the course of cancer and are associated with carcinogenesis and tumor progression [49]. Many studies have confirmed that indicators such as NLR, PLR, lymphocyte-to-monocyte ratio (LMR) and systemic inflammatory index have high prognostic significance in various forms of cancer. They are especially informative in malignant neoplasms resistant to chemotherapy. A meta-analysis confirmed that increased NLR value is an independent predictor of overall and relapse-free survival, regardless of stage and primary treatment [50].

The pan-immune inflammatory value (PIV) is an integral indicator, first described in 2020, which is calculated based on four key components of peripheral blood: platelets, neutrophils, monocytes and lymphocytes. This index reflects the overall state of immune-inflammatory activity of the body and has potential prognostic value in oncological diseases [51]. The results obtained indicate that high PIV is associated with a negative clinical course in patients with locally advanced CC. PIV may act as an independent prognostic marker of overall and disease-free survival. The use of this indicator in clinical

practice can increase the accuracy of predicting the effectiveness of treatment and life expectancy after therapy in patients with CC [52].

Tumor-expressed proteins

Squamous cell carcinoma antigen (SCC Ag) is a serum antigen obtained from squamous cell carcinoma cells and is important in cancer treatment because the serum is readily available and inexpensive [53]. It is detected at elevated levels in approximately 20-60% of patients with early-stage CC. In particular, elevated SCC Ag levels are detected in 64% of women with squamous cell carcinomas and in 25% of patients with adenocarcinoma. Elevated concentration of this antigen is mainly associated with treatment failure, and is also correlated with larger tumor size, lymph node invasion, lymphovascular invasion, and deep stromal invasion. Xu D. et al. reported that a preoperative SCC Ag level greater than 2.35 ng/mL can be used as a predictor of regional lymph node metastasis, and in combination with computed tomography with a sensitivity of 82.9% [54]. The results of this study confirm the potential of using this prognostic marker for planning radiotherapy in patients even with early CC. After treatment, the SCC Ag level serves as an indicator of response to treatment, and an increase in its level indicates tumor recurrence. The sensitivity and specificity of this marker for CC recurrence range from 56% to 86% and from 83% to 100%, respectively, making it a valuable tool for both diagnosis and monitoring disease progression [55].

SCC Ag levels should be evaluated in combination with other markers, including tumor characteristics such as size, tumor parameters, and lymph node enlargement. Cytokeratin 19 fragment antigen (CYFRA 21-1) may be an effective prognostic marker for CC in addition to SCC Ag. The sensitivity of CYFRA 21-1 is comparable to that of SCC Ag, the most commonly used tumor marker for CC. Elevated CYFRA 21-1 levels are associated with tumor stage, and elevated levels after treatment indicate the presence of residual tumor tissue, which may indicate disease recurrence and may be useful in patients with no SCC Ag detected in serum. However, some studies suggest that CYFRA 21-1 has limitations in terms of response to treatment: a decrease in its level does not always indicate that the patient is disease-free [56,57].

Epidermal growth factor receptor (EGFR) expression correlates with poor clinical outcomes and poorer sensitivity to chemoradiotherapy in the treatment of CC. In a meta-analysis of 22 studies, EGFR overexpression was correlated with a higher incidence of lymph node metastasis and tumor size, which was associated with lower overall and disease-free survival [58].

Tumor microenvironment factors

The tumor microenvironment (TME) is a complex and highly organized system that includes components of the extracellular matrix, blood vessels, and a variety of cellular elements, including immune, stromal, and tumor cells. Angiogenesis (the process of new blood vessel formation) is a key element of the tumor microenvironment, which contributes to the formation of an immunosuppressive environment and facilitates tumor immune escape. This dynamic microenvironment not only ensures the survival of tumor cells, but also actively influences their growth, metastasis, and the development of therapeutic resistance. Immunological parameters of the tumor microenvironment are considered important prognostic factors in CC [59].

Tumor-infiltrating lymphocytes (TILs)

Assessment of TILs levels, their quantification, and immunophenotyping can provide valuable information on the mechanisms of tumor progression and help in the development of optimal therapeutic strategies [60]. To date, only a limited number of clinical studies have been conducted on the prognostic and predictive role of TILs in CC. In particular, stromal TILs have been found to have a higher prognostic value than intraepithelial TILs, especially in squamous cell carcinomas. Different populations of TILs have been described, including CD4+ and CD8+ T cells, Th17, γδ T cells, NK cells, Treg, B cells, and macrophages. Increased numbers of CD4+ and CD8+ TILs correlate with better prognosis, highlighting the importance of accurate assessment and phenotyping of these cells in clinical practice. In addition, TILs are considered a promising direction for adoptive cell therapy for a number of malignancies, including CC. The main goal of TIL-based therapy is to restore antitumor immunity by in vitro selection of tumor-specific CD4+ and CD8+ T cells [61, 62].

Tumor-associated macrophages (TAMs)

Tumor-associated macrophages (TAMs) are large macrophage cells that constitute the most numerous populations of immune cells and one of the key components of the TME, performing regulatory functions in both the immune response and the tumor process. TAMs are considered prognostic markers and promising targets for immunotherapy. They are an integral part of the macrophage population, which performs key functions in the immune system. TAMs constitute a significant part of the TME (in some solid tumors their number can reach 50%), play a crucial role in the regulation of tumor growth, cancer progression and cell response to anticancer drugs; promote cancer cell proliferation and metastasis formation [63].

Macrophages are believed to play a dual role in cancer development. Today, TAMs are usually divided into two main groups: classically activated macrophages (type M1) and alternatively activated macrophages (type M2). This division reflects their functional properties and role in the TME.

M1 macrophages are characterized by pro-inflammatory and antitumor activity, while M2 macrophages, on the contrary, exhibit anti-inflammatory properties and support tumor growth [64]. M1 macrophages have been shown to predominate in the early stages of cancer development, where they enhance the immune response and exert antitumor effects. M1 macrophages counteract bacterial infections, angiogenesis, and tumor cells, and produce proinflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF). M2 macrophages are activated by the anti-inflammatory cytokines IL-4, IL-10, and IL-13, as well as transforming growth factor-β (TGF-β). M2 macrophages typically suppress T helper cell activity and play a key role in promoting tumor progression and neoangiogenesis.

TAMs also play an important role in distant cancer metastasis. They promote tumor cell migration by altering cell-cell contacts and disrupting the basement membrane. In general, high numbers of macrophages in tumor tissue are clearly associated with poor prognosis for CC [64, 65].

Expression of the PD-L1 protein on tumor cells in the CC microenvironment has been shown to be an important prognostic marker, leading to apoptosis and functional inactivation of T cells by specifically binding to the programmed death receptor PD-1 protein on the surface of tumor-infiltrating T cells. PD-L1 is a transmembrane protein predominantly expressed on the surface of activated T cells, B cells, and macrophages. It is an immune checkpoint molecule that enables tumor cells to evade immunologically mediated elimination. Expression of PD-L1 by tumor cells enables them to evade elimination by CD8+ T cells. In CC, PD-L1 expression on tumor cells is closely correlated with TAM density and is an important factor in tumor progression and poor prognosis. High PD-L1 expression is associated with poor prognosis in various malignancies, including CC [66, 67]. High PD-L1 expression is rarely detected in normal cervical tissues, but it is significantly elevated in T cells and tumor cells in 35–96% of cervical adenocarcinomas. In the TME, PD-1 may contribute to the formation of immune resistance. PD-L1 expression is an independent prognostic factor for adverse disease outcome, regardless of known clinicopathological characteristics, including stage, tumor size, depth of invasion, lymphovascular invasion, and lymph node involvement [68]. Blocking the PD-1/PD-L1 interaction is able to restore the cytotoxic properties of T cells and induce tumor regression, which, in turn, contributes to improving clinical outcomes. The introduction of immune checkpoint inhibitors in anticancer therapy has significantly improved clinical outcomes.

Cancer-associated fibroblasts (CAFs)

CAF, which are involved in cancer progression and metastasis, are associated with an unfavorable prognosis and are considered new promising targets for anticancer therapy, mediate the development of resistance by secreting cytokines and chemokines, which, in turn, provide protection to tumor cells through adhesion-mediated resistance resulting from the interaction of tumor cells with stromal components of the acellular matrix [69, 70].

MicroRNAs

MicroRNAs (miRNAs) are new biological markers associated with the development of many malignant neoplasms, including CC. They are non-coding RNA molecules of 18 to 25 nucleotides in length that regulate about a third of all human genes. Approximately half of all miRNAs are localized in such sensitive areas or in regions associated with oncological diseases. It is now known that miRNAs can function as oncogenes or tumor suppressors, but the study of the mechanisms of their action in the development of CC has begun relatively recently [71]. Under physiological conditions, miRNAs play an important role in many vital processes, such as proliferation, differentiation, apoptosis, regulation of the immune response, etc. In cancer, posttranscriptional regulation of gene expression is a key element in carcinogenesis and tumor angiogenesis. This occurs through changes in the levels of specific miRNAs, which can promote or inhibit tumor growth, acting as oncogenes (tumor promoters) or tumor suppressors. Thus, they affect the ability of tumors to progress and metastasize [72, 73]. Due to their tissue specificity and stability in biological fluids such as blood, lymph, and urine, miRNAs can serve as a reliable tool for early detection of malignant neoplasms and tumor staging. In particular, microRNAs such as miR-21, miR-27a, miR-34a, miR-146a, miR-155, miR-196a, miR-203, miR-221, miR-126, miR-143, and miR-133b, and their role in CC carcinogenesis, are being actively investigated [74].

Surgical techniques for CC as a prognostic factor

In addition to analyzing clinicopathological and molecular factors, we also examined the impact of treatment methods, including surgical approach and postoperative adjuvant therapy, on the prognosis of patients with CC. The LACC (Laparoscopic Assisted Radical Hysterectomy for Cervical Cancer) multicenter randomized clinical trial (2018) found that patients with early-stage CC who underwent minimally invasive surgery had significantly worse survival rates than those who underwent laparotomy [75, 76]. Since then, the surgical field has undergone rapid development and constant updating of approaches to the treatment of patients with early CC. Since then, numerous scientific papers have been published that both support and refute this hypothesis, but the scientific debate on this issue remains open. In 2024, the final analysis of the LACC trial was conducted, showing the results of the disease-free survival rate after 4.5 years: 86% with minimally invasive surgery and 96.5% with open surgery. Local recurrence was three times more common in the minimally invasive group, and the recurrence rate as carcinomatosis was 9% with open surgery compared with 23% with minimally invasive [76].

Similar results to those obtained in the LACC study were found in the European observational cohort study SUCCOR (Surgery in Cervical Cancer, Observational, Retrospective), published in 2020 [77]. This study showed that in patients with stage IB1 of CC who underwent radical hysterectomy, the use of a minimally invasive approach was associated with an increased risk of recurrence and death compared with open surgery. This result remained unchanged even when the use of a uterine manipulator was abandoned and preventive measures were taken to minimize the potential for tumor spread during colpotomy [77].

Recent data from the SHAPE (Simple Hysterectomy and Pelvic Node Assessment) trial suggest that simple hysterectomy is as effective as radical hysterectomy in early-stage CC in terms of patient survival and recurrence rates [78].

The results of the LACC and SHAPE trials have prompted a need for rapid revision of national and international clinical guidelines.

Effective control of cervical cancer cannot rely solely on the refinement of therapeutic approaches, as treatment addresses only the terminal stage of the disease pathway. Priority should instead be placed on strengthening primary prevention, primarily through the widespread implementation of human papillomavirus (HPV) vaccination. Particular emphasis must be placed on addressing the persistently low level of public awareness regarding the importance and evidence-based effectiveness of vaccination [79]. Equally crucial is secondary preven-

tion, namely organized, accessible, and high-quality cervical cancer screening aimed at the timely detection of precancerous lesions and early-stage disease. The integration of robust vaccination programs with systematic screening represents the most effective strategy for reducing both incidence and mortality [80]. In this context, the treatment of clinically manifest cervical cancer should be regarded as the final, rather than the principal, component of a comprehensive national strategy to confront this global public health challenge.

CONCLUSIONS

CC remains a significant global health problem, and traditional clinicopathological prognostic criteria do not always accurately predict the course of the disease. One of the most important tasks of modern gynecological oncology is to find tumor features and properties that can be used to predict the course of the disease and to prescribe adequate therapy. Analysis of current literature data shows that a comprehensive assessment of additional biomarkers – virological (HPV status, p16, viral load), molecular (p53, Ki-67), markers of hypoxia and angiogenesis (HIF-1α, VEGF), serum antigens (SCC Ag, CYFRA 21-1), inflammation parameters (NLR, PLR, PIV) and components of the tumor microenvironment (TILs, TAMs, PD-L1, CAF) significantly increases the accuracy of prediction.

Of particular importance are the characteristics of the TME, which affect tumor aggressiveness and response to immunotherapy. Determination of these markers can contribute to the personalization of treatment and increase the effectiveness of modern therapeutic strategies.

Thus, the integration of morphological, virological, immune and molecular indicators is a promising way to optimize the prognosis and improve the treatment outcomes of patients with CC.

Conflict of Interest

The authors declare that they have no competing interests. There is no conflict of interest between the authors.

ЛІТЕРАТУРА/REFERENCES

1. Bray F, Laversanne M, yuna Sung H, et al."Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024 May-Jun;74(3):229–63. DOI: 10.3322/caac.21834.
2. Cancer Genome Atlas Research Network, Albert Einstein College of Medicine; Analytical Biological Services, et al. Integrated genomic and molecular characterization of cervical cancer. Nature. 2017 Mar 16;543(7645):378-384. DOI: 10.1038/nature21386
3.Wright JD, Matsuo K, Huang Y, et al. Prognostic Performance of the 2018 International Federation of Gynecology and Obstetrics Cervical Cancer Staging Guidelines. Obstet Gynecol. 2019 Jul;134(1):49-57. DOI: 10.1097/AOG.0000000000003311
4. Board WC. o.T.E., WHO classification of tumours: female genital tumours[M]. Lyon (France): IARC Publications, 2020: 1–632.
5.Guimarães YM, Godoy LR, Longatto-Filho A, Reis RD. Management of Early-Stage Cervical Cancer: A Literature Review. Cancers (Basel). 2022 Jan 24;14(3):575 DOI: 10.3390/cancers14030575
6. Gennigens C, Cuypere MD, Hermesse J, et al. Optimal treatment in locally advanced cervical cancer. Expert Rev Anticancer Ther. 2021 Jun;21(6):657-671. DOI: 10.1080/14737140.2021.1879646
7.Ma GF, Lin G-L, Wanget S-T, et al. Prediction of recurrence-related factors for patients with early-stage cervical cancer following radical hysterectomy and adjuvant radiotherapy. BMC Womens Health. 2024 Jan 31;24(1):81 DOI: 10.1186/s12905-023-02853-8
8.Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. Gynecol Oncol. 1999 May;73(2):177-83 DOI: 10.1006/gyno.1999.5387
9.Peters WA 3rd, Liu PY, Barrett RJ 2rd, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol. 2000 Apr;18(8):1606-13. DOI:10.1200/JCO.2000.18.8.1606
10.George IA, Chauhan R, Dhawale RE, et al. Insights into therapy resistance in cervical cancer. Advances in Cancer Biology-Metastasis. 2022;6:100074. DOI: 10.1016/j.adcanc.2022.100074
11.Chen H-H, Meng W-Y, Li R-Z, et al. Potential prognostic factors in progression-free survival for patients with cervical cancer. BMC Cancer. 2021 May 10;21(1):531. DOI: 10.1186/s12885-021-08243-3
12. Pinto PJJ, Chen MJ, Santos Neto E, et al. Prognostic factors in locally advanced cervical cancer with pelvic lymph node metastasis. Int J Gynecol Cancer. 2022 Mar;32(3):239-245. DOI: 10.1136/ijgc-2021-003140
13.Santoro A, Inzani F, Angelico G, et al. Recent Advances in Cervical Cancer Management: A Review on Novel Prognostic Factors in Primary and Recurrent Tumors. Cancers (Basel). 2023 Feb 10;15(4):1137. DOI:10.3390/cancers15041137
14.Fontecha N, Basaras M, Hernáez Set al. Assessment of human papillomavirus E6/E7 oncogene expression as cervical disease biomarker. BMC Cancer. 2016 Nov 5;16(1):852. DOI:10.1186/s12885-016-2885-x
15.Sammarco ML, Tamburro M, Pulliero A, et al. Human Papillomavirus Infections, Cervical Cancer and MicroRNAs: An Overview and Implications for Public Health. Microrna. 2020;9(3):174-186. DOI: 10.2174/2211536608666191026115045
16.Tommasino M. The human papillomavirus family and its role in carcinogenesis. Semin Cancer Biol. 2014 Jun:26:13-21. DOI: 10.1016/j.semcancer.2013.11.002
17. Hammer A, Rositch A, Qeadan F, et al. Age-specific prevalence of HPV16/18 genotypes in cervical cancer: A systematic review and meta-analysis. Int J Cancer. 2016 Jun 15;138(12):2795-803. DOI: 10.1002/ijc.29959
18.Kusakabe M, Taguchi A, Sone K, et al. Carcinogenesis and management of human papillomavirus-associated cervical cancer. Int J Clin Oncol. 2023 Aug;28(8):965-974. DOI: 10.1007/s10147-023-02337-7
19.Park KJ, Selinger CI, Alvarado-Cabrero I, Duggan MA. Dataset for the Reporting of Carcinoma of the Cervix: Recommendations From the International Collaboration on Cancer Reporting (ICCR). Int J Gynecol Pathol. 2022; 41(1):S64-S89. DOI: 10.1097/PGP.0000000000000909
20.Höhn AK, Brambs CE, Hiller GGR, et al. 2020 WHO Classification of Female Genital Tumors. Geburtshilfe Frauenheilkd. 2021 Oct;81(10):1145–53. DOI: 10.1055/a-1545-4279
21.Kang S, Wu J, Li J, et al. Prognostic Significance of Clinicopathological Factors Influencing Overall Survival and Event-Free Survival of Patients with Cervical Cancer: A Systematic Review and Meta-Analysis. Med Sci Monit. 2022 Mar 9;28:e934588. DOI: 10.12659/MSM.934588
22.Silverberg SG, Ioffe OB. Pathology of cervical cancer. Cancer J. 2003 Sep-Oct;9(5):335-47. DOI: 10.1097/00130404-200309000-00003.
23.Silva DC, Gonçalves AK, Cobucci RN, et al. Immunohistochemical expression of p16, Ki-67 and p53 in cervical lesions - A systematic review. Pathol Res Pract. 2017 Jul;213(7):723-729. DOI: 10.1016/j.prp.2017.03.003
24.Meng Y, Chu T, Lin S, et al. Clinicopathological characteristics and prognosis of cervical cancer with different histological types: A population-based cohort study. Gynecol Oncol. 2021 Dec;163(3):545-551 DOI: 10.1016/j.ygyno.2021.10.007
25.Ronsini C, Anchora LP, Restaino S, et al. The role of semiquantitative evaluation of lympho-vascular space invasion in early stage cervical cancer patients. Gynecol Oncol. 2021 Aug;162(2):299-307 DOI: 10.1016/j.ygyno.2021.06.002
26.Liebig C, Ayala G, Wilks JA, et al. Perineural invasion in cancer: a review of the literature. Cancer. 2009 Aug 1;115(15):3379-91. DOI: 10.1002/cncr.24396
27. Wan T, Tu H, Liu L, et al. Perineural Invasion Should Be Regarded as an Intermediate-Risk Factor for Recurrence in Surgically Treated Cervical Cancer: A Propensity Score Matching Study. Dis Markers. 2021 Aug 3;2021:1375123 DOI: 10.1155/2021/1375123
28.Chen X, Duan H, Zhao H, et al. Perineural invasion in cervical cancer: A multicenter retrospective study. Eur J Surg Oncol. 2024 Jun;50(6):108313. DOI: 10.1016/j.ejso.2024.108313
29.Zannoni GF, Travaglino A, Raffone A, et al. Depth of Stromal Invasion as the Most Prognostically Relevant Regression System in Locally Advanced Cervical Cancer after Neoadjuvant Treatment: A Systematic Review and Meta-Analysis Grading. Diagnostics (Basel). 2021 Sep 26;11(10):1772. DOI: 10.3390/diagnostics11101772
30.Cibula D, Slama J, Dostálek L, et al. Tumour-free distance: a novel prognostic marker in patients with early-stage cervical cancer treated by primary surgery. Br J Cancer. 2021 Mar;124(6):1121-1129. DOI: 10.1038/s41416-020-01204-w

31.Bizzarri N, Pedone Anchora L, Zannoni GF, et al. Validation of tumour-free distance as novel prognostic marker in early-stage cervical cancer: a retrospective, single-centre, cohort study. Br J Cancer. 2021 Aug;125(4):561-568
DOI: 10.1038/s41416-021-01384-z
32.Guani B, Mahiou K, Crestani A, et al. Clinical impact of low-volume lymph node metastases in early-stage cervical cancer: A comprehensive meta-analysis. Gynecol Oncol. 2022 Feb;164(2):446-454.
DOI: 10.1016/j.ygyno.2021.12.015
33.Hishinuma E, Shimada M, Matsukawa N, et al. Identification of predictive biomarkers for diagnosis and radiation sensitivity of uterine cervical cancer using wide-targeted metabolomics. J Obstet Gynaecol Res. 2023 Aug;49(8):2109-2117.
DOI: 10.1111/jog.15709
34. Ansari SA, Anshu. Utility of p16INK4a Staining on Cell Blocks Prepared from Residual Liquid-Based Cervicovaginal Material. Acta Cytol. 2025;69(3):248-258.
DOI: 10.1159/000544071
35. Chong L, Zou Z, Xia L, et al. p16 expression and its correlation with the clinical pathological characteristics of patients with cervical cancer: a systematic review and meta-analysis. BMJ Open. 2025 Sep 11;15(9):e102602.
DOI: 10.1136/bmjopen-2025-102602
36.Van Zummeren M, Leeman A, Kremer WW, et al. Three-tiered score for Ki-67 and p16ink4a improves accuracy and reproducibility of grading CIN lesions. J Clin Pathol. 2018 Nov;71(11):981-988.
DOI: 10.1136/jclinpath-2018-205271
37.Zhao L, Sanyal S. p53 Isoforms as Cancer Biomarkers and Therapeutic Targets. Cancers (Basel). 2022 Jun 27;14(13):3145. DOI: 10.3390/cancers14133145
38. Huang Y, He Q, Xu K, et al. A new marker based on risk stratification of human papillomavirus DNA and tumor size to predict survival of locally advanced cervical cancer. Int J Gynecol Cancer. 2019 Mar;29(3):459-465.
DOI:10.1136/ijgc-2018-000095).
39.Zuo J, Huang Y, An J, et al. Nomograms based on HPV load for predicting survival in cervical squamous cell carcinoma: An observational study with a long-term follow-up. Chin J Cancer Res. 2019 Apr;31(2):389-399.
DOI: 10.21147/j.issn.1000-9604.2019.02.13
40.Cao M, Wang Y, Wang D, et al. Increased High-Risk Human Papillomavirus Viral Load Is Associated With Immunosuppressed Microenvironment and Predicts a Worse Long-Term Survival in Cervical Cancer Patients. Am J Clin Pathol. 2020 Mar 9;153(4):502-512.
DOI: 10.1093/ajcp/aqz186
41.Zhou C, Tuong ZK, Frazer IH.. Papillomavirus Immune Evasion Strategies Target the Infected Cell and the Local Immune System. Front Oncol. 2019 Aug 2;9:682.
DOI: 10.3389/fonc.2019.00682
42. Rashid M, Zadeh LR, Baradaran B, et al. Up-down regulation of HIF-1α in cancer progression. Gene. 2021 Sep 25;798:145796. DOI: 10.1016/j.gene.2021.145796
43.Apte RS, Chen DS, Ferrara N. VEGF in Signaling and Disease: Beyond Discovery and Development. Cell. 2019 Mar 7;176(6):1248-1264.
DOI: 10.1016/j.cell.2019.01.021
44.Zhu P, Ou Y, Dong Y, et al. Expression of VEGF and HIF-1α in locally advanced cervical cancer: potential biomarkers for predicting preoperative radiochemotherapy sensitivity and prognosis. Onco Targets Ther. 2016 May 23;9:3031-7.
DOI: 10.2147/OTT.S104142
45.Holub K, Biete A. Impact of systemic inflammation biomarkers on the survival outcomes of cervical cancer patients. Clin Transl Oncol. 2019 Jul;21(7):836–44.
DOI: 10.1007/s12094-018-1991-4
46.Elmali A, Guler OC, Demirhan B, et al. Long-term analysis of hematological parameters as predictors of recurrence patterns and treatment outcomes in cervical cancer patients undergoing definitive chemoradiotherapy. Strahlenther Onkol. 2024 Nov;200(11):949–7. .
DOI: 10.1007/s00066-024-02278-8
47.Lizano M, Carrillo-García A, De La Cruz-Hernández E, et al. Promising predictive molecular biomarkers for cervical cancer (Review). Int J Mol Med. 2024 Jun;53(6):50. DOI: 10.3892/ijmm.2024.5374
48.Singh N, Baby D, Rajguru JP, et al. Inflammation and cancer. Ann Afr Med. 2019 Jul-Sep;18(3):121–6
DOI: 10.4103/aam.aam_56_18
49.Gao Y, Guo W, Cai S, et al. Systemic immune-inflammation index (SII) is useful to predict survival outcomes in patients with surgically resected esophageal squamous cell carcinoma. J Cancer. 2019 Jun 2;10(14):3188–96. DOI: 10.7150/jca.30281
50.Zou P, Yang E, Li Z. Neutrophil-to-lymphocyte ratio is an independent predictor for survival outcomes in cervical cancer: a systematic review and meta-analysis. Sci Rep. 2020 Dec 14;10(1):21917. DOI: 10.1038/s41598-020-79071-x
51. Guven DC, Sahin TK, Erul E, et al. The association between the pan-immune-inflammation value and cancer prognosis: A systematic review and meta-analysis. Cancers (Basel). 2022 May 27;14(11):2675 DOI: 10.3390/cancers14112675
52.Yan S, Gong X, Liu R, Jia X. Prognostic significance of systemic pan-immune-inflammation value in locally advanced cervical cancer. Front Oncol. 2024 Oct 28;14:1492251. DOI: 10.3389/fonc.2024.1492251
53. Hong R, Luo L, Xu X, et al. The treatment response evaluation through the combination of contrast-enhanced ultrasound and squamous cell carcinoma antigen in cervical cancer Quant Imaging Med Surg. 2024 Oct 1;14(10):7587–99 DOI: 10.21037/qims-24-132
54.Xu D, Wang D, Wang S, et al. Correlation Between Squamous Cell Carcinoma Antigen Level and the Clinicopathological Features of Early-Stage Cervical Squamous Cell Carcinoma and the Predictive Value of Squamous Cell Carcinoma Antigen Combined With Computed Tomography Scan for Lymph Node Metastasis. Int J Gynecol Cancer. 2017 Nov;27(9):1935-1942.
DOI: 10.1097/IGC.0000000000001112
55. Tony V, Sathyamurthy A, Ramireddy JK, et al. Role of squamous cell carcinoma antigen in prognostication, monitoring of treatment response, and surveillance of locally advanced cervical carcinoma. J Cancer Res Ther. 2023 Jul-Sep;19(5):1236–1240.
DOI: 10.4103/jcrt.jcrt_335_21
56.Lin C, Xiao N, Chen Q, et al. Prognostic implications of tumor volume reduction during radiotherapy in locally advanced cervical cancer: a risk-stratified analysis. Radiat Oncol. 2025 Mar 31;20(1):47.
DOI: 10.1186/s13014-025-02623-w
57.Piao X, Kong TW, Chang SJ, et al. Pretreatment serum CYFRA 21-1 level correlates significantly with survival of cervical cancer patients: a multivariate analysis of 506 cases. Gynecol Oncol. 2015 Jul;138(1):89–93.
DOI: 10.1016/j.ygyno.2015.04.012
58.Muthusami S, Sabanayagam R, Periyasamy L, et al. A review on the role of epidermal growth factor signaling in the development, progression and treatment of cervical cancer. Int J Biol Macromol. 2022 Jan 1;194:179-187.
DOI: 10.1016/j.ijbiomac.2021.11.117
59.Binnewies M, Roberts EW, Kersten K, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat Med. 2018 May;24(5):541–50. DOI: 10.1038/s41591-018-0014-x
60.Lin B, Du L, Li H, et al. Tumor-infiltrating lymphocytes: Warriors fight against tumors powerfully. Biomed Pharmacother. 2020 Dec;132:110873.
DOI: 10.1016/j.biopha.2020.110873
61.Gultekin M, Beduk Esen CS, Ates Ozdemir D, et al. Stromal or intraepithelial tumor-infiltrating lymphocytes: which one has more prognostic significance in cervical cancer? Arch Gynecol Obstet. 2023 Mar;307(3):969-980.
DOI: 10.1007/s00404-022-06687-x
62.Ohno A, Iwata T, Katoh Y, et al. Tumor-infiltrating lymphocytes predict survival outcomes in patients with cervical cancer treated with concurrent chemoradiotherapy. Gynecol Oncol. 2020 Nov;159(2):329-334. DOI: 10.1016/j.ygyno.2020.07.106
63.Choi Y, Lee D, Kim NY, et al. Role of Tumor-Associated Macrophages in Cervical Cancer: Integrating Classical Perspectives with Recent Technological Advances. Life (Basel). 2024 Mar 27;14(4):443.
DOI: 10.3390/life14040443
64.Liang W, Huang X, Carlos CJJ, Lu X. Research progress of tumor microenvironment and tumor-associated macrophages. Clin Transl Oncol. 2020 Dec;22(12):2141–52.
DOI: 10.1007/s12094-020-02367-x
65.Guo F, Feng YC, Zhao G, et al. Tumor-Associated CD163+ M2 Macrophage Infiltration is Highly Associated with PD-L1 Expression in Cervical Cancer. Cancer Manag Res. 2020 Jul 15;12:5831–43.
DOI: 10.2147/CMAR.S257692
66.Solorzano-Ibarra F, Alejandre-Gonzalez AG, Ortiz-Lazareno PC, et al. Immune checkpoint expression on peripheral cytotoxic lymphocytes in cervical cancer patients: moving beyond the PD-1/PD-L1 axis Clin Exp Immunol. 2021 Apr;204(1):78–95.
DOI: 10.1111/cei.13561
67.Wendel Naumann R, Leath CA 3rd. Advances in immunotherapy for cervical cancer. Curr Opin Oncol. 2020 Sep;32(5):481-487. DOI: 10.1097/CCO.0000000000000663
68.Galicia-Carmona T, Arango-Bravo EA, Coronel-Martínez JA, et al. Advanced, recurrent, and persistent cervical cancer management: in the era of immunotherapy Front Oncol. 2024 Aug 5;14:1392639.
DOI: 10.3389/fonc.2024.1392639.
69.Wang Y, Xu M, Yao Y, et al. Extracellular cancer-associated fibroblasts: A novel subgroup in the cervical cancer microenvironment that exhibits tumor-promoting roles and prognosis biomarker functions. Oncol Lett. 2024 Feb 22;27(4):167.
DOI: 10.3892/ol.2024.14300
70.Lv B, Wang Y, Ma D, et al. Immunotherapy: Reshape the Tumor Immune Microenvironment. Front Immunol. 2022 Jul 6;13:844142. DOI: 10.3389/fimmu.2022.844142
71. do Nascimento Medeiros JA, Sarmento ACA, Bernardes-Oliveira E, et al. Evaluation of Exosomal miRNA as Potential Biomarkers in Cervical Cancer. Epigenomes. 2023 Aug 1;7(3):16 DOI: 10.3390/epigenomes7030016

72. Tornesello ML, Faraonio R, Buonaguro L, et al. The Role of microRNAs, Long Non-coding RNAs, and Circular RNAs in Cervical Cancer. Front Oncol. 2020 Feb 20;10:150. DOI: 10.3389/fonc.2020.00150
73. Miao J, Regenstein JM, Xu D, et al. The roles of microRNA in human cervical cancer. Arch Biochem Biophys. 2020 Sep 15;690:108480. DOI: 10.1016/j.abb.2020.108480
74. Pulliero A, Cassatella G, Astuni P,et al. The Role of microRNA Expression and DNA Methylation in HPV-Related Cervical Cancer: A Systematic Review. Int J Mol Sci. 2024 Nov 26;25(23):12714. DOI: 10.3390/ijms252312714
75.Ramirez PT, Frumovitz M, Pareja R, et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. N Engl J Med. 2018 Nov 15;379(20):1895–1904. DOI: 10.1056/NEJMoa1806395
76.Ramirez, Robledo KP, Frumovitz M, et al. LACC Trial: Final Analysis on Overall Survival Comparing Open Versus Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer. J Clin Oncol. 2024 Aug 10;42(23):2741–46. DOI: 10.1200/JCO.23.02335
77.Chiva L, Zanagnolo V, Querleu D, et al. SUCCOR study: an international European cohort observational study comparing minimally invasive surgery versus open abdominal radical hysterectomy in patients with stage IB1 cervical cancer. Int J Gynecol Cancer. 2020 Sep;30(9):1269 DOI: 10.1136/ijgc-2020-001506
78.Plante M, Kwon JS, Ferguson S, et al. Simple versus Radical Hysterectomy in Women with Low-Risk Cervical Cancer. N Engl J Med. 2024 Feb 29;390(9):819–29 DOI: 10.1056/NEJMoa2308900
79. Tatarchuk T, Kalugina L, Antipkin Y, et al. Exploring awareness, attitudes and clinical practices of Ukrainian health professionals regarding human papillomavirus and vaccination: a qualitative study. BMJ 2025, 15(11), e089968. DOI: 10.1136/bmjopen-2024-0899680
80. Volodko N, Chopyak V, Mazur Y. Barriers to implementing cervical cancer screening in Ukraine: the path forward. Proc Shevchenko Sci Soc Med Sci. 2025 Jun.20;77(1). DOI: HYPERLINK «https://doi.org/10.25040/ntsh2025.01.01» 10.25040/ntsh2025.01.01

КЛІНІЧНІ, МОРФОЛОГІЧНІ ТА МОЛЕКУЛЯРНІ МАРКЕРИ У ФОРМУВАННІ ПРОГНОЗУ У ХВОРИХ НА РАК ШИЙКИ МАТКИ
Огляд літератури

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Рак шийки матки (РШМ) залишається однією з провідних причин онкологічної смертності серед жінок у світі, попри значний прогрес у профілактиці, скринінгу та лікуванні. Внаслідок дії факторів ризику, асоційованих із розвитком РШМ (куріння, ранній початок статевого життя, інфекції, що передаються статевим шляхом, кількість статевих партнерів, прийом оральних контрацептивів, імуносупресії), для цього захворювання характерний ранній безсимптомний перебіг. Незважаючи на актуальні методи лікування РШМ (хірургічний, радіологічний, хіміотерапевтичний, а також впровадження протягом останніх років імунотерапії та таргетних препаратів) прогноз за РШМ залишається несприятливим. Вибір правильної схеми лікування залежно від прогностичних та предиктивних факторів перебігу РШМ є найважливішим етапом. Класичні клініко-патологічні прогностичні чинники недостатньо пояснюють варіабельність перебігу захворювання в пацієнток із подібними характеристиками пухлини, особливо за проміжного ризику.
У цьому огляді проаналізовані як відомі фактори прогнозу РШМ (стадія захворювання, глибина стромальної інвазії, лімфоваскулярна інвазія, ураження лімфатичних вузлів, поширення на параметрій), так і нові маркери, роль яких активно досліджується: периневральна інвазія, вільна від пухлини відстань. Узагальнено сучасні дані щодо відомих та перспективних прогностичних біомаркерів: наявність вірусу папіломи людини, вірусне навантаження, протеїни p16, p53, Ki-67, маркери гіпоксії та ангіогенезу HIF-1α, VEGF, сироваткові антигени SCC Ag, CYFRA 21-1, гематологічні індекси системного запалення (NLR, PLR, PIV) та компоненти пухлинного мікрооточення, а саме: пухлино-інфільтруючі лімфоцити (TILs), пухлиноасоційовані макрофаги (TAMs), асоційовані з пухлиною фібробласти (CAF), ліганд запрограмованої смерті 1 (PD-L1). Показана роль мікроРНК – нових біологічних маркерів, асоційованих із розвитком багатьох злоякісних новоутворень, зокрема РШМ.
Інтеграція цих маркерів у клінічну практику значно підвищує точність прогнозування перебігу РШМ, дає змогу краще оцінити ризик рецидиву та потенційну відповідь на терапію, а також сприяє індивідуалізації лікувальної тактики. Представлений огляд підкреслює необхідність подальших багатоцентрових досліджень для стандартизації та впровадження нових прогностичних маркерів у клінічну практику.

Ключові слова: рак шийки матки, фактори прогнозу раку, маркери раку.

CLINICAL, MORPHOLOGICAL AND MOLECULAR MARKERS IN THE FORMATION OF PROGNOSIS IN PATIENTS WITH CERVICAL CANCER
Literature review

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Cervical cancer (CC) remains one of the leading causes of cancer mortality among women in the world, despite significant progress in prevention, screening and treatment. Due to risk factors associated with the development of CC (smoking, early onset of sexual activity, sexually transmitted infections, number of sexual partners, oral contraceptive use, and immunosuppression), this disease is characterized by an early asymptomatic course. Despite the current methods of treatment of CC (surgical, radiological, chemotherapeutic, as well as the introduction of immunotherapy and targeted drugs in recent years), the prognosis for CC remains unfavorable. The choice of the correct treatment regimen depending on the prognostic and predictive factors of the course of CC is the most important stage. Classical clinicopathological prognostic factors do not sufficiently explain the variability of the course of the disease in patients with similar tumor characteristics, especially at intermediate risk.
This review analyzes both known factors of prognosis of CC (stage of the disease, depth of stromal invasion, lymphovascular invasion, lymph node involvement, spread to the parametrium), and new markers, the role of which is actively studied: perineural invasion, tumor-free distance. Current data on known and promising prognostic biomarkers are summarized: the presence of human papillomavirus, viral load, proteins p16, p53, Ki-67, markers of hypoxia and angiogenesis HIF-1α, VEGF, serum antigens SCC Ag, CYFRA 21-1, hematological indices of systemic inflammation (NLR, PLR, PIV) and components of the tumor microenvironment, such as tumor-infiltrating lymphocytes (TILs), tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAF), programmed death ligand 1 (PD-L1). The role of the new biological markers microRNAs is associated with the development of many malignant neoplasms, in particular CC.
The integration of these markers into clinical practice significantly increases the accuracy of predicting the course of CC, allows for a better assessment of the risk of recurrence and potential response to therapy, and also contributes to the individualization of treatment tactics. The presented review emphasizes the need for further multicenter studies to standardize and implement new prognostic markers into clinical practice.

Keywords: cervical cancer, cancer prognosis factors, cancer markers.