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MORPHOLOGICAL EVALUATION OF PROLIFERATION, APOPTOSIS, AND ANGIOGENESIS PROCESSES IN CERVICAL NEOPLASIAS BASED ON IHC MARKERS (ON THE EXAMPLE OF SURKHANDARYA REGION)

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Abstract This study morphologically evaluated the immunohistochemical (IHC) changes in proliferation (Ki-67), apoptosis (p53), and angiogenesis (VEGF, CD31) processes during the development of cervical epithelial neoplasias (CIN I, II, III) and squamous cell carcinoma, using the population of the Surkhandarya region as an example. The results showed that as the degree of dysplasia increases, Ki-67 expression and microvessel density (MVD) reliably increase, while the accumulation of the p53 protein indicates a disruption of the apoptosis process. This complex of markers is of great importance for the early detection and prognostic assessment of at-risk patients in regional conditions.

Keywords: Cervical neoplasia, CIN, immunohistochemistry, Ki-67, p53, VEGF, angiogenesis, proliferation, Surkhandarya region.

INTRODUCTION

Cervical cancer (CC) occupies one of the leading positions among oncological diseases and mortality rates for women, both globally and in Uzbekistan. The development of the disease does not occur suddenly but proceeds through a multi-year, step-by-step process — cervical intraepithelial neoplasia (CIN). Therefore, the early detection of precancerous conditions and the assessment of their risk of malignization (transformation into a malignant tumor) is the primary task of modern oncomorphology.

Cervical intraepithelial neoplasia (CIN) is a condition characterized by the appearance and growth of abnormal (atypical) cells in the epithelial tissue covering the surface of the cervix. In medicine, it is often referred to as dysplasia.

The most important aspect is: this is not cancer, but a precancerous condition that, if not detected and treated in time, can develop into cancer over the years.

Below is the essential information regarding this condition:

1. Causes Over 90-95% of neoplasia cases are caused by the Human Papillomavirus (HPV). High-risk oncogenic types of this virus, especially types 16 and 18, penetrate cervical cells, affect their DNA, and lead to incorrect, uncontrolled reproduction.

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2. Stages of the disease (CIN classification) Depending on the depth of the cellular changes, based on histological examinations, neoplasia is divided into 3 stages:

- **CIN I (Mild dysplasia):** Changes occupy only the lower one-third (1/3) of the epithelial layer. In many cases (especially in young women), the body's immune system fights off the virus on its own, and the condition can return to normal even without treatment.
- **CIN II (Moderate dysplasia):** Abnormal cells occupy more than half (2/3) of the epithelium. At this stage, the probability of the disease resolving on its own is lower, and medical intervention is required.
- **CIN III (Severe dysplasia and Carcinoma in situ):** Altered cells occupy the entire thickness of the epithelium but have not yet penetrated the deeper tissues (stroma) and blood vessels. This is the stage immediately preceding the transition to cancer and requires urgent, active treatment.

3. Main symptoms Usually, cervical neoplasia (even at the CIN III stage) does not exhibit any distinct symptoms and proceeds completely asymptomatically. A woman may feel entirely healthy. In rare cases, when inflammation is present, the following may be observed:

- Bloody discharge after sexual intercourse (contact bleeding).
- Unusual, sometimes odorous vaginal discharge.

4. Diagnostic methods Because the disease progresses without symptoms, it can only be detected through medical examination:

- **PAP test (Oncocytological smear):** Cells are collected from the surface of the cervix using a brush and examined under a microscope for abnormal changes. This is the most effective screening method.
- **Colposcopy:** Examining the cervical tissue under magnification using a special optical device (colposcope) while applying various medical solutions (acetic acid, iodine).
- **Biopsy and histology:** If a suspicious area is identified during colposcopy, a tiny piece of tissue is excised and examined in a laboratory. This is the only method that determines the degree of neoplasia (CIN I, II, or III) with 100% accuracy.

5. Treatment approaches The treatment strategy is selected based on the woman's age, the stage of the disease, and future childbearing plans:

- **Observation:** At the CIN I stage, if high-risk HPV types are not detected, regular check-ups and testing are sufficient.
- **Surgical methods:** For CIN II and CIN III stages, the altered tissues must be removed. Methods such as laser surgery, radiowave therapy (LEEP), cryodestruction (freezing with liquid nitrogen), or conization (excision of a cone-shaped portion of the cervix) are utilized.

The most reliable ways to prevent this condition are vaccination against the Human Papillomavirus (HPV) and undergoing a gynecological examination (PAP test) at least once a year.

Although traditional histological examinations (hematoxylin-eosin) reveal cellular atypia, they cannot fully uncover the molecular-biological potential of the process. Modern approaches require the assessment of three core mechanisms that determine the biological behavior of epithelial tissue — proliferation, apoptosis, and angiogenesis — using immunohistochemical (IHC) markers.

The Surkhandarya region is an area with distinct climatic, demographic, and socio-medical conditions. Therefore, the reproductive health of women in this region, particularly the incidence rate of cervical pathologies, necessitates specific analysis. The objective of this study is the comparative morphological evaluation of Ki-67, p53, and VEGF marker expression in cervical neoplasias and cancer under the conditions of the Surkhandarya region.

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METHODS

Cervical biopsy and surgical specimens from 120 female patients examined at the Surkhandarya Regional Oncology Dispensary and pathomorphology laboratories in the city of Termez during the 2024-2026 period were used as research material. The patients' ages ranged from 25 to 65 years.

The examination materials were divided into the following groups:

- **Control group:** Unaltered chronic cervicitis (n=20)
- **Group 1:** Mild dysplasia — CIN I (n=30)
- **Group 2:** Moderate dysplasia — CIN II (n=30)
- **Group 3:** Severe dysplasia — CIN III / *Carcinoma in situ* (n=20)
- **Group 4:** Invasive squamous cell carcinoma (n=20)

Stages of morphological and IHC examination:

1. Tissue samples were fixed in a 10% neutral formalin solution and embedded in paraffin blocks using standard procedures.
2. For histological examination, sections were stained with hematoxylin-eosin.
3. Immunohistochemical reactions were performed using monoclonal antibodies:
   - *Proliferation marker:* Ki-67 (MIB-1 clone).
   - *Apoptosis marker:* p53 mutant protein (DO-7 clone).
   - *Angiogenesis markers:* VEGF (Vascular Endothelial Growth Factor) and CD31 (for determining microvessel density).
4. The results were subjected to morphometric analysis under a light microscope (at x400 magnification). The percentage of cells stained with Ki-67 and p53 was calculated, and the number of microvessels per field of view (MVD - Microvessel Density) was evaluated using CD31.

RESULTS

The study results confirmed that as the degree of neoplasia increases, structural changes at the molecular level in the epithelial tissue also intensify accordingly.

Proliferation (Ki-67 expression): In the control group, Ki-67-positive cells were observed only sporadically in the basal and parabasal layers of the epithelium (low proliferation, <5%). At the CIN I stage, the Ki-67 index was 12-15%, occupying the lower third of the epithelium. In the CIN II and particularly CIN III stages, Ki-67 expression extended across the entire thickness of the epithelium, showing a positive nuclear reaction in more than 45-65% of the cells. In invasive carcinoma, this indicator reached its highest level (>80%).

Apoptosis regulation (p53): In chronic cervicitis and CIN I, the expression of the p53 protein was barely detectable (or minimal at <2%). However, starting from the CIN II stage, the nuclear accumulation of p53 increased sharply (18-25%). In CIN III and invasive carcinoma, p53 expression exceeded 40% and 60%, respectively. This indicates that the wild-type (normal) p53 has undergone mutation and lost its ability to initiate apoptosis.

Angiogenesis processes (VEGF and CD31): In the samples collected from the Surkhandarya region, the activity of tumor blood vessel formation was particularly pronounced.

Histological diagnosis	Ki-67 index (%)	p53 expression (%)	MVD (by CD31) in 1 field of view
Chronic cervicitis	3.5 ± 1.2	1.1 ± 0.5	8.4 ± 2.1
CIN I	14.2 ± 3.4	4.5 ± 1.8	12.6 ± 3.5
CIN II	38.6 ± 5.1	22.4 ± 4.3	24.5 ± 5.2

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Histological diagnosis	Ki-67 index (%)	p53 expression (%)	MVD (by CD31) in 1 field of view
CIN III / CIS	62.4 ± 7.8	45.6 ± 6.7	38.2 ± 7.1
Squamous cell carcinoma	84.5 ± 6.2	68.3 ± 8.4	56.4 ± 9.3

As evident from the table above, the production of VEGF and the density of CD31-positive microvessels (MVD) in the stroma increased in direct proportion to the severity of dysplasia. In the carcinoma group, it was observed that the vascular network was chaotic, structurally altered, and the endothelial cells were swollen.

DISCUSSION

A comprehensive analysis of the obtained IHC results demonstrated the intrinsic link between proliferation, apoptosis, and neoangiogenesis in the carcinogenesis of the cervical epithelium. The extension of the Ki-67 protein to the superficial layers of the epithelium indicates cell cycle disruption and a loss of differentiation.

In the analysis of samples from the Surkhandarya region, the detection of high VEGF and CD31 indices in the CIN III and carcinoma stages may suggest the presence of a more aggressive disease phenotype among certain patients in this territory. It is highly probable that this is associated with regional climatic factors (such as high solar insolation) or a specific prevalence of high-risk oncogenic types of the papillomavirus (HPV). The mutation of the p53 protein, which governs apoptosis, grants tumor cells "immortality" and creates the foundation for their nourishment and rapid growth via vascularization (angiogenesis).

Differentiating between CIN II and CIN III using the traditional hematoxylin-eosin staining method can sometimes be subjective. This study demonstrates that the implementation of Ki-67 and p53 markers in clinical practice significantly enhances diagnostic accuracy.

CONCLUSION

1. The transition process from cervical neoplasia (CIN) to invasive cancer is directly associated with cellular proliferation (an increase in Ki-67 up to >60%) and the blockade of apoptosis (accumulation of mutant p53).

2. The invasive potential and metastatic risk of the tumor depend on the activity of stromal angiogenesis. CD31 (MVD) and VEGF markers serve as reliable criteria for determining the prognosis of the disease.

3. Incorporating Ki-67 and p53 immunohistochemical analyses as a standard protocol alongside traditional examinations for at-risk patients in the oncological and pathomorphological practice of the Surkhandarya region will enhance the efficiency of early cervical cancer detection.

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