DETERMINING THE EFFECTIVENESS OF COMPREHENSIVE DIAGNOSIS OF CERVICAL PRECANCER AND CANCER

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Relevance. Early diagnosis of precancer and cervical cancer should be based on the use of a combination of methods: liquid cytology, HPV testing using the PCR-HB method and ICC with double staining p16/Ki67 - this significantly increases their sensitivity and specificity.

Keywords: human papillomavirus, cervical cancer, cervical intraepithelial neoplasia.

Abstract. Cervical cancer is the most common form of oncological pathology of the female reproductive system. In terms of incidence, cervical cancer ranks 7th among all malignant tumors and 3rd among malignant tumors in women (after breast cancer and colon cancer) and accounts for 9.8% [1,9]. In 2022, 527,624 cases of cervical cancer were registered worldwide [1,11], with 265,653 deaths. Mortality from cervical cancer ranks 9th among all malignant tumors and 2nd among epithelial malignant tumors of the female reproductive system [1,12]. Cervical cancer most often affects women under 35 years of age, often with a subsequent fatal outcome [3,13]. In Uzbekistan, the incidence of cervical cancer is growing annually, which indicates the inadequacy of measures related to the primary and secondary prevention of this disease. In 2019, 14.7 thousand patients with cervical cancer were registered in Uzbekistan. The mortality rate from cervical cancer in Uzbekistan in 2019 was 5.2 per 100,000 and is currently the leading cause of death among all women with cancer aged 15 to 40 years (±19.5). After 40 years, mortality from cervical cancer moves to 2nd place (9.7%) [1,5,9,10]. The survival rate of patients with cervical cancer depends primarily on the level of the healthcare system in different regions. In less socio-economically developed countries, cervical cancer is mostly diagnosed at a late stage of the disease, therefore, low survival rates are recorded. The 5-year survival rate among women diagnosed with late-stage cervical cancer is approximately 30% lower than in more developed countries [1,10]. Clinical symptoms in patients with cervical diseases are usually caused by the presence of combined uterine pathology (endo- and myometrium). The combination of uterine fibroids with adenomyosis and/or endometrial hyperplasia in patients with CIN III (47.6%) and cervical cancer (59.1%) ($p < 0.05$) is significantly more common than the combination with other cervical pathologies. This fact is apparently due to the mutually stimulating influence of pathological processes in the endo- and myometrium on the

condition of the cervix, which is realized through the mechanisms of intercellular interactions of growth factors [15].

Objective of the study. To evaluate the effectiveness of cytological, immunocytochemical, and HPV testing for the detection of cervical precancer and cancer, and to study the pathological and morphological features of cervical repair processes in the presence of HPV infection**.**

Materials and methods. All 167 women were examined according to a standard protocol: clinical examination, collection of smears in SurePath vials (BD, USA), preparation of Papanicolaou-stained cytological preparations using a TriPath processor (BD, USA), and smear evaluation using the Bethesda system [1,13]. Three groups of women were selected: 1) 91 women to evaluate the effectiveness of HPV testing using the PCR-NV method and liquid-based cytology in detecting HPV-associated cervical pathology in women aged 30 years and older. 2) 148 women to evaluate the effectiveness of a combination of methods: liquid-based cytology, double immunostaining of p16/Ki67 and HPV testing using the PCR-NV method for HPV-associated cervical pathology. 3) 61 women to study the morphological and immunohistological features of different types of SEMS. At the first stage, 91 patients aged 17 to 56 years were included in the study with the following examinations: 1) detection of cervical pathology after liquid cytology; 2) performing colposcopy with targeted sampling of altered or suspicious areas of the cervical canal for histological examination; 3) conducting a molecular biological study to study the expression of p16/Ki-67 markers and HPV DNA genotypes in cytological preparations prepared from residual material.

Study results. In the second stage, the effectiveness of p16/Ki67 dual staining in combination with liquid-based cytology and HPV testing using the NR-PCR method for detecting cervical pathology was assessed. Cytological and biopsy specimens from 148 women with cervical pathology were examined. Cytological examination of cervical smears prepared using liquid-based cytology was performed. Depending on the cytological diagnosis, all patients were divided into five groups: H-SIL (57 women), L-SIL (39), ASC-US-H (4), ASC-US-R (26), and NILM (22).

Next, double immunostaining of cytological specimens was performed using two antibodies: p16 and Ki67. p16/Ki67 expression was detected both in isolated atypical cells and in aggregates of atypical squamous epithelial cells. The number of positive cells with double staining did not exceed 30% of the total number of cells in L-SIL and ranged from 30% to 100% in H-SIL. In NILM, individual p16-positive cells were detected, as well as atrophic and dystrophic changes, which allowed them to be classified as “senescent” cells [9,14]. Based on the results of double immunostaining,

the diagnosis of ASC-US-R and ASC-US-H was changed to H-SIL (7 women), L-SIL (4), or NILM (19). In addition, in three cases, L-SIL was changed to H-SIL, since the number of atypical cells with double staining amounted to 90% of all cells in the complex. In one case, the cytological diagnosis of L-SIL was changed to NILM due to the lack of expression of the p16 and Ki67 tumor markers in the cells of the squamous epithelium of the cervix. The histological result of "chronic cervicitis" confirmed the correctness of the diagnosis change. The double immunostaining method does not require counting positive cells, according to the manufacturer's instructions. However, we observed a direct correlation between the number of p16/Ki-67–positive cells and the degree of cervical lesion. Thus, in cytological preparations diagnosed with H-SIL, the content of double-stained positive cells in the atypical squamous epithelial cell complexes of the cervix was 80-100%. Our observations coincided with the results of Yoshida T [1,3,14]. IHC analysis of samples with CIN≥II showed increased expression of the p16 protein throughout the entire depth of the epithelial layer, and Ki67 in 60% to 100% of cervical epithelial cells. HPV DNA was detected in cytological material using the PCR-NV method on a Cobas 4800 device, and the results were compared with the histological conclusion. In smears with a diagnosis of NILM, HPV DNA was detected in 1 sample out of 22 (4.55%). In samples with a diagnosis of L-SIL, the test was positive in 34 cases out of 39 (87.18%). The most frequently observed combination was a common pool of 12 types of highly oncogenic HPV (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and HPV DNA type 16 - in 23 out of 34 smears (67.65%). In samples with a diagnosis of L-SIL, HPV DNA was detected in 34 cases out of 39 (87.18%). HPV DNA was detected in 53 of 57 samples (92.98%) with H-SIL assays, primarily HPV type 16 (40 of 53 cases, 75.47%). In samples diagnosed with ASC-US-R, it was detected in 8 of 26 cases (30.77%), and ASC-US-H in 2 of 4 cases (50.0%). Moreover, the most common pool of 12 high-oncogenic HPV types was detected in 8 of 11 (72.72%) of the 70 samples.

Conclusions. It has been established that a combination of methods should be used for the early diagnosis and screening of HPV-associated cervical pathology: liquid-based cytology, HPV testing using the PCR-NV method, and ICC with dual p16/Ki67 staining. This significantly increases their sensitivity and specificity. Screening for cervical cancer in women under 30 years of age should begin with liquid cytology, and in women over 30 years of age – with HPV testing, which is determined by the evolution of the pathological process and economic factors.

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