studies and indicate that further systematic study of pre-conceptual maternal prognostic factors of fetal distress in labor is required in order to develop preventive pregravidarial programs.

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DOI 10.25789/YMJ.2025.89.03

UDC 618.14-006.6+613.24

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OPTIMIZING EARLY DETECTION OF UTERINE CANCER IN WOMEN WITH RISK FACTORS

The article describes the stages of early detection of uterine body cancer in patients with morbid obesity. It has been proven that genetic testing for oncogenic mutations of endocervical canal scrapings with a negative cytological conclusion regarding cervical cancer is effective for subsequent screening of uterine body cancer. In morbid obesity, the diagnostic sensitivity of mutation screening for uterine body cancer increases when examining endocervical canal scrapings. When oncogenic mutations are detected in samples from the endocervical canal, the next step is recommended to conduct a cytological examination of endometrial biopsies with sampling using brush technology.

Keywords: uterine body cancer, morbid obesity, oncogenic mutations, liquid cytology, endometrial biopsy.

For citation: Grafskaya M.Yu., Verenikina E.V., Maksimov A.Yu., Demidova A.A., Karasenko N.V., Ermilova M.V. Optimizing early detection of uterine cancer in women with risk factors. Yakut Medical Journal. 2025; 89(1): 12-15. https://doi.org/10.25789/YMJ.2025.89.03

Introduction. Among oncogynecological diseases, uterine cancer is the most common in countries with a high level of economic development and the second most common worldwide [1]. At the same time, there is a steady trend of constant growth in the prevalence of uterine cancer in the world, despite the improvement of the preventive and diagnostic system for timely detection of endometrial tumor pathology [4].

Obesity is a recognized risk factor for uterine cancer. The correlation between obesity and cancer of the uterine body is the closest in comparison with malignant diseases of other localization [2]. Based on a meta-analysis of thirty randomized prospective studies, each increase in body mass index (BMI) by 5 kg/m^2 is associated with a 54% increased risk of developing uterine cancer with a 95% confidence interval of 47 to 61% [7]. Given that

the prevalence of obesity among women is growing every year everywhere in all countries, the development of effective tactics for early detection of uterine cancer in women with increased body weight is an urgent task. In morbid obesity with a BMI exceeding more than 40 kg/m2, women, due to psychological problems, are poorly motivated to regularly visit gynecologists, which affects the detection of more advanced forms of uterine body cancer in the initial diagnosis of cancer [8]. In addition, morbid obesity increases the risk of death of patients with uterine cancer by 6 times [3]. Therefore, the development of methods for early diagnosis of uterine cancer in women with morbid obesity is aimed at solving an important socio-medical problem.

Scraping of the cervical epithelium and endocervical canal in liquid cytology is traditionally used to diagnose cervical cancer. Meanwhile, in the last decade, the biological material obtained during the Pap test, in case of a negative result for cervical cancer, has been used to diagnose cancer of the uterine body or ovaries [9]. At the same time, the DNA concentration of circulating tumor cells, oncogenic mutations are determined in endocervical scrapings, and a mass spectrometric analysis of the protein profile is performed [6,9]. The basis for an additional search was the results of cytological, histological and molecular genetic studies confirming that in endometrial or ovarian cancer, circulating cancer cells from tumors of other localization are concentrated in the cervical canal of the uterus [5].

Since the Pap test during gynecological examinations is performed much more often than an aspiration biopsy of the endometrium, and in liquid cytology, stabilizing solutions do not destroy cells and preserve them, the standard technique may have a much wider potential than the traditional format of its use. Expanding the diagnostic tasks when using a single biologicalcsubstrate is especially important for the contingent of patients who are provoked in relation to uterine cancer by a risk factor in the form of morbid obesity and who experience psychological obstacles to frequent and thorough examinations by gynecologists.

In connection with the above, **the aim of the work** was to develop a step-by-step complex diagnostic algorithm for early detection of uterine cancer in patients with morbid obesity.

Materials and methods. The work includes the results of the examination of 378 patients of the main group with verified uterine body cancer, who were divided into two subgroups depending on the presence of morbid obesity. The 1st subgroup included 103 women with morbid obesity (BMI over 40 kg/m^2), and the 2nd subgroup included 275 patients without obesity (BMI from 18,5 to 30 kg/m^2). Cancer of the uterine body was verified by the results of targeted curettage of the uterine walls, followed by histological examination of samples. The control group included 226 women of similar age, but without cancer pathology, based on the results of preventive examinations during a dispensary examination. The 1st control subgroup consisted of 47 women with morbid obesity and the 2nd control subgroup - 179 patients without obesity.

The criteria for inclusion of patients in the main group were as follows: newly diagnosed uterine cancer, endometrial histological type, collection of diagnostic material from the endocervical canal and endometrial biopsy before starting specific antitumor treatment, BMI in the range of 18,5-30 kg/m^2 and more than 40 kg/m^2, written informed consent to inclusion in the study.

Exclusion criteria: BMI in the range of 30-40 kg /m^2, cervical cancer, infection with human papillomavirus based on the results of a study of scrapings from the cervix, tumors of a different localization in relation to the uterine body, decompensation of somatic diseases.

During the study, the ethical principles of the Helsinki Declaration of the World Medical Association were observed, and the approval of the Local Ethical Committee of the Federal State Budgetary Institution " National Medical Research Center of Oncology " of the Ministry of Health of the Russian Federation was obtained.

The age of women in the 1st main group was 59,7±0,85 years (range from 32 to 79 years), the 2nd main group – 62,3±0,49 years (range from 29 to 84 years), the 1st control group – 58,6±0,66 years (range from 33 to 76 years) and the 2nd control group – 59,4±1,12 years (range 37-78 years). There were no intergroup differences in age between the groups.

BMI in the 1st main group corresponded to 41,8±1,71 kg/m^2, the 2nd main group – 24,7±1,92 kg/m^2, the 1st control group – 40,9±1,67 kg/m^2, and in the 2nd control group – 22,3±1,38 kg/m^2. In all patients of the 1st main and 1st control groups, the presence of insulin resistance syndrome was noted.

In women of the main and control groups, a sample from the endocervical canal was obtained using a brush brush from the Cytoscreen kit (Hospitex, Italy). The resulting material was stabilized with a special solution "Cyto-screen solution", the cells were washed off in a shakere, and the density of the cell suspension was determined by nephelometry. Cytological examination of the stained smear on glass was performed using light microscopy. Human papillomavirus infection was determined by immunocytochemical method.

For endometrial sampling Tao, a Tao-Brush IUMC brush (Cook Medical Inc., USA) was used. Previously, the length of the uterine cavity was determined using a uterine probe. The limiter was set to the intended insertion depth and a brush in a cover was carefully inserted through the cervix to the level of the uterine floor. Then the outer shell was pulled back, and the brush was rotated five times 360° clockwise and counterclockwise. Next, the outer cover was returned back to the brush and the selection device was removed from the uterine cavity. A sample of endometrial tissue was placed in a stabilizing solution.

DNA was isolated from a buffer with tissue samples of the endocervical canal and endometrium, following the manufacturer's recommendations, using the QIAamp DNA micro DNA purification kit (Qiagen). The quantity and quality of the isolated DNA were determined, the samples were stored at a temperature of -80°C until the implementation of the laboratory stage. Further, the presence of oncogenic mutations in the genes *AKT1, APC, BRAF, CDKN2A, CTNNB1, EGFR, FBXW7, FGFR2, KRAS, MAPK1, NRAS, PIK3CA, PIK3R1, POLE, PPP2R1A, PTEN, RNF43*, and *TP53* biological samples of the endocervix and endometrium was evaluated by three multiplex PCRs using the SSafe-Sequencing System (SSE-SeqS) technology. At the same time, segments with a length from 110 to 142 bp of the studied genes was amplified using 139 pairs of primers. This approach made it possible to identify non-overlapping amplicons and detect low-frequency mutations by assigning a unique identifier to each matrix molecule. PCR fragments with the same unique identifier were considered mutant only if 95% or more contained the same mutation.

The mutation screening test was considered positive in the study of samples obtained with the PAP test or the TAO test if at least one of the genes was found to have a mutation. In addition, the results of cytological studies of biological samples obtained using brush-brush PAP and Tao were taken into account.

Statistical analysis of the study results was performed using STATISTICA 12.0 software (StatSoft, USA).

Results and discussion. In all patients of the main and control groups, cytological examination of scrapings from the cervix and endocervical canal tested negative for detection of cervical cancer and infection with human papillomavirus. When determining oncogenic mutations in cells concentrated in the endocervical canal, positive results in the 1st main subgroup were detected in 82,5% (n=85), and in the 2nd main subgroup in 72,4% (n=199) (Table 1). Consequently, in patients with verified uterine cancer, the detection of mutations of genes that contribute to the development of tumors in biological samples from the endocervical canal was high. The number of patients suffering from uterine cancer with a positive Pap test result for oncogenic mutations was higher (p=0,042) compared to patients without morbid obesity. In the control groups of healthy women, the detection of oncogenic mutations in endocervical canal scrapings was rare regardless of the presence of morbid obesity (Table 1).

The results of cytological examination of endometrial biopsies revealed uterine body cancer in the 1st main subgroup in 83,5% (n=86), and in the 2nd main subgroup in 82,2% (n=86) (Table 2). No intergroup differences were found based on the results of cytological examination of endometrial biopsies depending on the presence of morbid obesity (p=0,76). In the control group, cytological examination of endometrial biopsies showed no positive results, which indicated 100% specificity of the test (Table 2).

The results of the mutation screening test in the study of endometrial biopsies in the 1st main group were similar to the results of the cytological study. In the 2nd main subgroup, the results of the genetic study allowed us to obtain positive results regarding the detection of uterine cancer in an additional 10 women compared to the cytological conclusion (Table 3).

Table 1

Number of patients with positive and negative results of the test for mutational screening of uterine cancer in the study of endocervical canal scrapings in clinical groups

Group	PAP Test Mutation Screening	Main Group (UC)	Control group (healthy)
1 subgroup (MO)	Positive	85	4
	Negative	18	43
	Total	103	47
2 Subgroup (no MO)	Positive	199	7
	Negative	76	172
	Total	275	179

Note: UC -uterine cancer, MO - morbid obesity

Table 2

Number of patients with positive and negative results of detection of uterine cancer in cytological studies and endometrial biopsies in clinical groups

Group	TAO Test	Main Group (UC)	Control group (healthy)
1 subgroup (MO)	Positive	86	0
	Negative	17	47
	Total	103	47
2 subgroup (no MO)	Positive	226	0
	Negative	49	179
	Total	275	179

Table 3

Number of patients with positive and negative results of the mutation screening test in the study of endometrial biopsies in clinical groups

Group	TAO Test Mutation Screening	Main Group (UC)	Control group (healthy)
1 subgroup (MO)	Positive	88	0
	Negative	15	47
	Total	103	47
2 subgroup (no MO)	Positive	236	0
	Negative	39	179
	Total	275	179

Table 4

Informative value of mutational screening of uterine cancer in the study of endocervical canal scrapings and endometrial biopsies

Test Parameters	PAP test Mutation screening		TAO test Mutation screening	
	1 main subgroup (UC+MO)	2 main subgroup (UC)	1 main subgroup (UC+MO)	2 main subgroup (UC)
Diagnostic sensitivity, %	82,5	72,4	85,4	85,8
Diagnostic specificity, %	91,5	96,1	100,0	100,0
Diagnostic accuracy, %	85,3	81,7	90,0	91,4
AUC	0,870	0,842	0,927	0,929
Positive predictive value, %	95,5	96,6	100,0	100,0
Negative predictive value, %	70,5	69,4	75,8	82,1

Note: UC – uterine cancer, MO - morbid obesity, AUC – area under the ROC curve

The informative value of the test for mutational screening of uterine cancer in the study of endocervical canal samples and endometrial biopsies is presented in Table 4.

Of course, diagnostic accuracy in detecting uterine cancer was higher when cytological and genetic studies of endometrial biopsies were performed simultaneously (90% in the 1st main subgroup and 91,4% in the 2nd main subgroup). However, it should be noted that the effectiveness of genetic testing for oncogenic mutations in endocervical canal samples in detecting uterine cancer was high (in the 1st main subgroup 85,3% and in the 2nd main subgroup 81,7%). This circumstance allows us to recommend conducting a genetic study of the substrate obtained during the Pap test to detect cancer of the uterine body. Additional mutational screening after liquid Pap cytology using cervical scrapings is particularly important in women who are compromised for risk factors, including morbide obesity. After detection of oncogenic mutations in the endocervical scraping, the next step is to conduct cytological examination of endometrial biopsies obtained using a brush-brush Tao. Additional genetic testing of endometrial biopsies after receiving a cytological conclusion does not increase diagnostic efficiency, so its implementation is not economically justified.

Conclusions

1. In morbid obesity, the diagnostic sensitivity of mutational screening for endometrial cancer using endocervical canal scrapings is higher than in non-obese patients (82,5% versus 72,4%, p=0,042), which should be taken into account when organizing a step-by-step examination of women.
2. In case of a negative cytological conclusion regarding cervical cancer in patients with morbid obesity, the next recommended step is screening for endometrial cancer using genetic testing of endocervical canal scrapings for oncogenic mutations.
3. In case of detection of oncogenic mutations in endocervical canal samples, a cytological examination of endometrial biopsies taken using brush technology is indicated as a further step in diagnosing endometrial cancer.
4. The developed step-by-step complex diagnostic algorithm is effective for the early detection of endometrial cancer in patients with morbid obesity.

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