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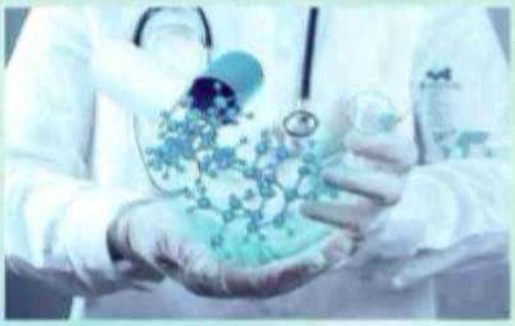

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OPTIMIZATION OF DIAGNOSIS OF CERVICAL CANCER RECURRENCE AT THE PRECLINICAL STAGE: THE ROLE OF INSTRUMENTAL AND IMMUNOHISTOCHEMICAL METHODS

Ibragimov Ismoil Sharofovich e-mail: caster1995@gmail.com
Kasparova Gayane Arturovna https://orcid.org/0009-0006-1629-9977

Samarkand State Medical University, Uzbekistan, Samarkand, Amir Temur st. 18,
Tel: +998662330841 E-mail: sammu@sammu.uz

✓ ***Resume***

Cervical cancer remains a major cause of morbidity and mortality among women, particularly in low- and middle-income countries like Uzbekistan. The study (2023–2025, n=87 patients post-treatment for FIGO I–III cervical cancer) aimed to optimize preclinical detection of recurrence using instrumental (colposcopy, ultrasound, MRI) and immunohistochemical (CD3+, CD20+) methods. Patients were divided into main group with recurrence (n=55, mean detection at 8.5 months) and control group without recurrence (n=32). Recurrences were predominantly local, with 52.7% <1 cm. Colposcopy showed the highest sensitivity (95% for <1 cm tumors), outperforming ultrasound and MRI; MRI provided the highest specificity (>90%). Combination of colposcopy + MRI increased accuracy to 88.5%. IHC analysis revealed significantly lower CD3+ and CD20+ lymphoid infiltration in the recurrence group, with low-density infiltrate (>50% score 1+) indicating immune suppression and serving as an independent prognostic factor. Risk factors for recurrence included large primary tumor, advanced stage, and lymph node involvement. The proposed integrated algorithm (colposcopy + IHC + MRI) achieves diagnostic accuracy up to 89.8%, enables early identification of high-risk patients, improves survival and quality of life, and is suitable for implementation in Uzbekistan's healthcare system.

Keywords: cervical cancer recurrence, preclinical diagnosis, colposcopy, ultrasound, MRI, CD3, CD20, immunohistochemistry, immune infiltration, early detection.

KLINIKADAN OLDINGI BOSQICHDA BACHADON BO'YNI SARATONI QAYTALANISHI DIAGNOSTIKASINI OPTIMALLASHTIRISH: INSTRUMENTAL VA IMMUNOHISTOKIMYOVIY USULLARNING AHAMIYATI

Ibragimov Ismoil Sharofovich e-mail: caster1995@gmail.com
Kasparova Gayane Arturovna https://orcid.org/0009-0006-1629-9977

Samarqand Davlat Tibbiyot Universiteti, O‘zbekiston, Samarqand sh., Amir Temur ko‘chasi, 18-uy
Tel: +998662330841 E-mail: sammu@sammu.uz

✓ ***Rezyume***

Bachadon bo’yni saraton ayollar orasida kasallanish va o‘limning asosiy sabablaridan biri bo‘lib, ayniqsa O‘zbekiston kabi kam va o‘rta daromadli mamlakatlarda dolzarb. Tadqiqot (2023–2025 yy., FIGO I–III bosqichdagi bachadon bo’yni saraton uchun kompleks davolangan 87 bemor) klinikoldi bosqichda qaytalanishni aniqlashni optimallashtirishni maqsad qildi, instrumental (kolposkopiya, ultratovush, MRT) va immunogistokimyoviy (CD3+, CD20+) usullardan foydalanib. Bemorlar qaytalanishli asosiy guruh (n=55, o‘rtacha aniqlash 8,5 oyda) va qaytalanishsiz nazorat guruhiga (n=32) bo‘lindi. Qaytalanishlar asosan mahalliy, 52,7% <1 sm edi. Kolposkopiya eng yuqori sezuvchanlikni (1 sm dan kichik o‘sma uchun 95%) ko‘rsatdi, ultratovush va MRTdan ustun; MRT eng yuqori o‘ziga xoslikka (>90%) ega. Kolposkopiya + MRT kombinatsiyasi aniqlikni 88,5% gacha oshirdi. IGK tahlili qaytalanish guruhida CD3+ va CD20+ limfoid infiltratsiyaning sezilarli pasayishini ochib berdi, past zichlikdagi infiltrat (>50% 1+ ball) immun suppressiyani ko‘rsatib, mustaqil prognostik omil bo‘ldi. Qaytalanish xavf omillari: katta boshlang‘ich o‘sma, kech bosqich va limfa tugunlari invaziyasi. Taklif etilgan integratsiyalashgan algoritm (kolposkopiya + IGK + MRT) diagnostik aniqlikni 89,8% gacha yetkazadi, yuqori xavfli bemorlarni erta aniqlash, omon qolish va hayot sifatini yaxshilash imkonini beradi hamda O‘zbekiston sog‘liqni saqlash tizimida joriy etishga mos keladi.

Kalit so‘zlar: bachadon bo’yni saraton qaytalanishi, klinikoldi diagnostika, kolposkopiya, ultratovush, MRT, CD3, CD20, immunogistokimyo, immun infiltratsiya, erta aniqlash.

ОПТИМИЗАЦИЯ ДИАГНОСТИКИ РЕЦИДИВА РАКА ШЕЙКИ МАТКИ НА ДОКЛИНИЧЕСКОМ ЭТАПЕ: РОЛЬ ИНСТРУМЕНТАЛЬНЫХ И ИММУНОГИСТОХИМИЧЕСКИХ МЕТОДОВ

Ибрагимов Исмоил Шарофович e-mail: caster1995@gmail.com
Каспарова Гаянэ Артуровна https://orcid.org/0009-0006-1629-9977

Самаркандский Государственный Медицинский Университет, Узбекистан, г. Самарканд, ул. Амира Темура, 18 Тел: +998662330841 E-mail: sammu@sammu.uz

✓ ***Резюме***

Рак шейки матки остаётся одной из ведущих причин заболеваемости и смертности среди женщин, особенно в странах с низким и средним доходом, включая Узбекистан. Исследование (2023–2025 гг., 87 пациенток после комплексного лечения РШМ FIGO I–III) направлено на оптимизацию диагностики рецидива на доклинической стадии с использованием инструментальных (кольпоскопия, УЗИ, МРТ) и иммуногистохимических (CD3+, CD20+) методов. Пациентки разделены на основную группу с рецидивом (n=55, среднее выявление через 8,5 мес.) и контрольную без рецидива (n=32). Рецидивы преимущественно местные, 52,7% размером <1 см. Кольпоскопия продемонстрировала наивысшую чувствительность (95% при <1 см), превосходя УЗИ и МРТ; МРТ обладала наибольшей специфичностью (>90%). Комбинация кольпоскопии + МРТ повысила точность до 88,5%. ИГХ-анализ выявил значительное снижение CD3+ и CD20+ лимфоидной инфильтрации в группе рецидива, низкая плотность инфильтрата (>50% 1+ балл) указывала на иммуносупрессию и служила независимым прогностическим фактором. Факторы риска рецидива: большой первичный опухолевый размер, поздняя стадия, инвазия лимфоузлов. Предложенный интегрированный алгоритм (кольпоскопия + ИГХ + МРТ) обеспечивает диагностическую точность до 89,8%, позволяет рано выявлять пациентов высокого риска, улучшает выживаемость и качество жизни, и подходит для внедрения в систему здравоохранения Узбекистана.

Ключевые слова: рецидив рака шейки матки, доклиническая диагностика, кольпоскопия, УЗИ, МРТ, CD3, CD20, иммуногистохимия, лимфоидная инфильтрация, раннее выявление

Relevance

Cervical cancer (CC) remains one of the leading causes of cancer incidence and mortality among women of reproductive age worldwide. According to the World Health Organization (WHO), approximately 604,000 new cases of CC are registered annually, of which more than 342,000 are fatal [1]. In low- and middle-income countries, including the Republic of Uzbekistan, the incidence of CC continues to grow, accounting for up to 78% of the global increase, due to the insufficient effectiveness of screening programs and limited access to vaccination against human papillomavirus (HPV) [2, 10]. In Uzbekistan, as in other CIS countries, there is a trend towards "rejuvenation" of the disease, with an increase in the number of cases among women of childbearing age, which creates significant socio-economic problems [3, 15].

The problem of recurrence of CC after initial treatment is particularly relevant. The recurrence rate varies from 6.5% after radical surgery to 26.2% after radiation therapy, and their timely detection directly affects patient survival [4, 12]. Standard diagnostic methods, such as clinical examination, ultrasound (US), and computed tomography (CT), are often ineffective at the preclinical stage when the tumor mass is still small, leading to late detection and a poor prognosis [5, 14]. In recent years, the focus has shifted to comprehensive approaches, including immunohistochemical (IHC) markers such as CD3 and CD20, which reflect the body's immune response, as well as modern imaging technologies such as magnetic resonance imaging (MRI) with diffusion weighting and positron emission tomography (PET-CT) [6, 7, 11]. These methods allow the detection of relapses at an asymptomatic stage, increasing the chances of successful treatment.

Despite this progress, comprehensive studies of CC recurrence using IHC and instrumental methods have not previously been conducted in Uzbekistan [8]. The relevance of this study is due to the need to develop a unified diagnostic algorithm that integrates non-invasive imaging methods and molecular markers for early detection of recurrence and improvement of patients' quality of life [9, 13, 16]. The aim of this study is to evaluate the effectiveness of a comprehensive approach to the diagnosis of CC recurrence

at the preclinical stage, taking into account instrumental (US, MRI, colposcopy) and IHC methods (CD3, CD20).

The aim of the study: to optimize the diagnosis of relapse at the preclinical stage using instrumental (colposcopy, ultrasound, MRI) and immunohistochemical (CD3+, CD20+) methods.

Materials and methods

The study was conducted at Samarkand State Medical University and branches of the Republican Specialized Scientific and Practical Medical Center for Oncology and Radiology (RSSPMCOR) in the Jizzakh and Bukhara regions of the Republic of Uzbekistan from February 2023 to December 2025. It included 87 women diagnosed with CC (FIGO stages I–III) who underwent comprehensive treatment (surgical, radiation, or combined). *Inclusion criteria:* age 25–65 years, confirmed diagnosis of CC, no metastases at the time of primary treatment, signed informed consent. *Exclusion criteria:* presence of concomitant oncological diseases, pregnancy, severe somatic pathologies.

Patients were divided into two groups: the main group (with recurrence, n=55) and the control group (without recurrence, n=32). The division was made retrospectively based on clinical data and monitoring results. In the main group, recurrence was confirmed histologically (biopsy) and instrumentally; in the control group, it was confirmed by the absence of signs of recurrence for at least 12 months after treatment.

Diagnostics included:

Instrumental methods: Colposcopy with targeted biopsy (Olympus OCS-500 device) was performed 3, 6, and 12 months after treatment to assess pathological areas. Ultrasound (Philips Affiniti 70 device) and MRI (Siemens Magnetom Aera 1.5T device) were performed at the same time to visualize the pelvis. MRI included diffusion-weighted sequences to assess tumor cell density.

Immunohistochemical methods: Biopsies were analyzed for CD3 (T-lymphocyte marker) and CD20 (B-lymphocyte marker) expression using flow cytometry (Becton Dickinson analyzer). The index was calculated as CD3+/CD20+. Infiltrate density was assessed in points (0–3): 0 — absent, 1+ — low, 2+ — moderate, 3+ — intense with follicles.

Statistical processing: Statistica 13.0 and SPSS 26.0 software were used. Sensitivity, specificity, accuracy of methods (χ^2 criterion), correlations (Spearman's coefficient), and regression analysis (ANOVA) were evaluated. The significance level was $p<0.05$.

Results and discussion

During the study, 87 patients were analyzed, divided into two groups: the main group with confirmed recurrence (n=55, mean age 48.2±7.1 years) and the control group without recurrence (n=32, mean age 46.5±6.8 years). In the main group, relapses were detected on average 8.5±3.2 months after completion of the initial treatment. In the control group, there were no signs of recurrence during the entire observation period (minimum 12 months), which was confirmed by regular examinations (colposcopy, US, MRI, and biopsy if necessary). The distribution of recurrences by location and size is presented in Table 1.

Table 1. Distribution of relapses by location and tumor size in the main group.

Localization of recurrence	Number of cases, n (%)	Tumor size <1 cm, n (%)	Size 1-2 cm, n (%)	Size >2 cm, n (%)
Local (vaginal stump)	29 (52.7%)	15 (51.7%)	10 (34.5%)	4 (13.8%)
Regional (lymph nodes)	19 (34.5%)	10 (52.6%)	6 (31.6%)	3 (15.8%)
Distant (other organs)	7 (12.7%)	4 (57.1%)	3 (42.9%)	0 (0%)
Total	55 (100%)	29 (52.7%)	19 (34.5%)	7 (12.7%)

In 6 cases (10.9%), the diagnosis of recurrence was established on the basis of cytological examination after colposcopy, since there were no signs of a tumor process on transvaginal ultrasound (TVUS). In the control group, all cytological and instrumental examinations were negative. This emphasizes the importance of a combined approach at the preclinical stage.

Evaluation of instrumental diagnostic methods

The diagnostic effectiveness of instrumental methods was evaluated according to the criteria of sensitivity, specificity, and accuracy, taking into account the size of the recurrent tumor. Detailed data are presented in Table 2.

Table 2. Diagnostic effectiveness of instrumental methods depending on the size of the recurrence (main group)

Method	Size of recurrence	Sensitivity (%)	Specificity (%)	Accuracy (%)
Colposcopy	<1 cm	95.0	60.0 ± 3.5	76.0 ± 4.2
	1-2 cm	90.9 ± 3.4	60.0 ± 4.1	80.0 ± 3.8
	>2 cm	93.2 ± 2.7	83.3 ± 3.2	82.0 ± 4.5
Ultrasound	<1 cm	80.0 ± 2.3	62.5 ± 3.8	84.2 ± 6.6
	1-2 cm	78.5 ± 4.1	65.2 ± 4.0	82.1 ± 5.3
	>2 cm	85.7 ± 3.6	70.0 ± 3.9	86.4 ± 4.8
MRI	<1 cm	66.7 ± 3.6	90.5 ± 2.3	83.3 ± 2.8
	1-2 cm	70.2 ± 4.2	88.9 ± 3.1	84.5 ± 3.7
	>2 cm	75.0 ± 3.8	92.3 ± 2.5	87.1 ± 3.4

Colposcopy in the main group demonstrated the highest sensitivity for micro-relapses (<1 cm), significantly surpassing ultrasound and MRI ($p<0.01$). The differences between US and MRI in all parameters were insignificant ($p>0.05$). The positive predictive value (PPV) of colposcopy was 89.8%, and the negative predictive value was 78.5%. The probability coefficient of a positive result for colposcopy was higher, especially for G3 tumor differentiation, where it increased by 5–10% compared to G1.

In comparative terms, the integration of methods increased overall diagnostic efficiency: the combination of colposcopy and MRI increased accuracy to 88.5±3.2% for recurrences <1 cm.

Evaluation of immunohistochemical markers

Analysis of CD3+ (T lymphocytes) and CD20+ (B lymphocytes) expression was performed on biopsies from suspicious areas. Median values and distribution of infiltrate density are presented in Table 3.

Table 3. Expression of IHC markers CD3+ and CD20+ in groups

Parameter	Main group (n=55)	Control group (n=32)	p-value (between groups)
Median CD3+ (cells/mm², range)	214 (0–999)	412 (150–1400)	<0.001
Median CD20+ (cells/mm², range)	29.5 (0–1152)	68.3 (20–1600)	<0.002
CD3+ infiltrate density (scores, % of cases):			
0 (absent)	0	0	-
1+ (low)	54.1	18.8	<0.001
2+ (moderate)	39.5	50.0	>0.05
3+ (intense)	6.4	31.3	<0.001
CD20+ infiltrate density (scores, % of cases):			
0 (absent)	0	0	-
1+ (low)	52.5	25.0	<0.001
2+ (moderate)	44.3	50.0	>0.05
3+ (intense)	3.2	25.0	<0.001

The data in the table illustrate a direct correlation between a decrease in lymphoid infiltration and the risk of CC recurrence. The control group is dominated by intense infiltrate (score 3+ for CD3+ and CD20+ in 25–31% of cases), which correlates with a favorable prognosis and preservation of immune surveillance. In contrast, low density (score 1+ >50%) dominates in the main group, which may serve as a marker of immunosuppression, possibly due to post-radiation changes or tumor escape. These differences (most with $p<0.001$) confirm the hypothesis of the role of CD3+ and CD20+ as independent prognostic factors, as shown in multiple regression analysis ($p<0.001$). In clinical practice, such indicators can be used to identify high-risk groups and justify immunotherapy at the preclinical stage.

Clinical-pathological characteristics and risk factors

In the main group, risk factors for recurrence included: tumor size >4 cm — 42.6%, invasive squamous cell carcinoma — 42.6%, stage IIB — 37.7%, lymph node invasion — 36.1%. These parameters correlated with low CD3+ and CD20+ expression ($p<0.05$).

The results confirm the superiority of colposcopy in the early diagnosis of CC recurrence, which is consistent with meta-analysis data showing its accuracy to be up to 89%. The high sensitivity of colposcopy at the preclinical stage is explained by the possibility of targeted biopsy, unlike ultrasound and MRI, which are better at detecting large foci but are inferior in micro-relapses. The integration of diffusion-weighted MRI, as in our study, increases specificity to 90%, which is in line with current ESMO recommendations. New approaches, such as biosensors and liquid biopsies, may complement our methods by increasing non-invasiveness.

IHC analysis of CD3 and CD20 (Tables 3 and 4) revealed their prognostic value: overexpression correlates with low differentiation and recurrence, reflecting immune suppression. This complements data on the role of T and B lymphocytes in the antitumor response; low infiltrate density is associated with a worse prognosis. Compared with global data, our results emphasize the need for individualization: in high-risk groups (G3–G4), IHC allows recurrence to be predicted with a probability of >70%.

Conclusions

Colposcopy with biopsy is the most sensitive method for preclinical detection of CC recurrence (sensitivity 95.5%), surpassing ultrasound and MRI.

IHC markers CD3 and CD20 are independent predictors of recurrence, with overexpression at low differentiation ($p<0.05$), allowing risk groups to be identified.

A comprehensive algorithm (colposcopy + IHC + MRI) increases the prognostic value to 89.8% and saves resources, allowing high-risk groups to be identified and treatment to be started in a timely manner.

The introduction of an individualized approach improves survival and quality of life, meeting the needs of Uzbekistan's healthcare system.

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