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Extended Diagnosis of Cervical Lesions

Chernov D.Y., Tikhonovskaya O.A., Logvinov S.V., Potapov A.V., Gerasimov A.V., Gereng E.A., Akbasheva O.E., Lasukova T.V.

Siberian State Medical University
2 Moscovsky trakt, 634050 Tomsk, Russian Federation

ABSTRACT

Aim. To improve the efficiency of diagnosing cervical pathologies using cytology and polymerase chain reaction (PCR) for human papillomavirus (HPV), taking into account the detection of HPV in upper parts of the endocervix.

Materials and methods. The study involved 60 patients with cervical pathology. The results of the cytological studies were verified according to The Bethesda system; the patients were divided into groups based on the results: Group I (n = 22) – negative for intraepithelial lesion or malignancy (NILM), Group II (n = 18) – low-grade squamous intraepithelial lesion (L-SIL), Group III (n = 12) – high-grade squamous intraepithelial lesion (H-SIL), Group IV (n = 8) – atypical squamous cells of undetermined significance (ASC-US). Standard PCR testing for HPV and PCR of the endocervical homogenate were conducted using the Hybrid Capture Digene test (RF Patent No. 2833119 dated December 14, 2023).

Results. Persistence of HPV in the upper endocervix was detected in 45 (75%) of patients. HPV was diagnosed significantly more often (p = 0.0157) in patients with L-SIL and H-SIL cytology – in 89% (16/18) и 100% (12/12) cases, respectively. Oncogenic HPV serotypes were found in 59% (13/22) of patients with NILM and in 50% (4/8) of patients with ASC-US. High frequency of discrepancies in the profile of the detected HPV strains between standard PCR and homogenate PCR testing was observed and was comparable across all groups: NILM 64% (14/22); L-SIL 61% (11/18); H-SIL 58% (7/12); ASC-US 75% (6/8), p > 0,05. Persistence of HPV in the upper parts of the cervix with negative standard PCR results was detected in 41% (9/22) of patients with NILM. A high viral load in the homogenate was detected more frequently in patients of the H-SIL group (p = 0.0374).

Conclusion. Extended diagnosis allows for a comprehensive assessment of the degree of cervical involvement in the pathology and helps determine the optimal management strategy for women at high risk (H-SIL, recurrent L-SIL, HPV persistence with high viral load).

Keywords: cervical pathology, human papillomavirus, persistence, diagnosis, PCR, cytology, homogenate

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at SibSMU (Minutes No. 9344 dated January 30, 2023).

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✉ *Chernov Denis Y.,* denis.chrnv1@gmail.com

Расширенная диагностика патологий шейки матки

Чернов Д.Ю., Тихоновская О.А., Логвинов С.В., Потапов А.В., Герасимов А.В., Геренг Е.А., Акбашева О.Е., Ласукова Т.В.

Сибирский государственный медицинский университет (СибГМУ)
Россия, 634050, г. Томск, Московский тракт, 2

РЕЗЮМЕ

Цель исследования: повышение эффективности диагностики патологий шейки матки с использованием цитологической диагностики и полимеразной цепной реакции (ПЦР) на вирус папилломы человека (ВПЧ), с учетом выявления персистенции ВПЧ в верхних отделах цервикального канала.

Материалы и методы. В группу исследования включены пациентки (n = 60) с патологией шейки матки. Выполнены цитологические исследования с верификацией диагноза по классификации The Bethesda system и распределены пациентки на группы в соответствии с результатами: I (n = 22) – negative for intraepithelial lesion or malignancy (NILM), II (n = 18) – low-grade squamous intraepithelial lesion (L-SIL), III (n = 12) high-grade squamous intraepithelial lesion (H-SIL), IV (n = 8) atypical squamous cells of undetermined significance (Asc-Us). Проведены стандартная ПЦР-диагностика ВПЧ и ПЦР гомогената эндоцервикального компонента методами Hybrid Capture Digene test (панель 14 онкосеротипов) для выявления ВПЧ в верхних отделах цервикального канала (патент № 2833119 от 14.12.2023).

Результаты. Персистенция ВПЧ в верхних отделах цервикального канала выявлена у 45 (75%) из 60 пациенток. ВПЧ диагностирован достоверно (p = 0,0157) чаще у пациенток с результатами онкоцитологии L-SIL и H-SIL – в 89% (16/18) и 100% (12/12) случаях соответственно. ВПЧ в верхних отделах цервикального канала обнаружен у 59% (13/22) пациенток группы NILM и 50% (4/8) пациенток группы Asc-US. Высока частота расхождений в структуре выявленных штаммов ВПЧ при проведении стандартного ПЦР и ПЦР гомогената, сопоставима для всех групп: NILM 64% (14/22); L-SIL 61% (11/18); H-SIL 58% (7/12); Asc-Us 75% (6/8), p > 0,05. Персистенция ВПЧ в верхних отделах цервикального канала при негативных результатах стандартной ПЦР выявлена у 41% (9/22) пациенток с NILM. Высокая вирусная нагрузка в гомогенате определялась чаще у пациенток группы H-SIL (p = 0,0374).

Заключение. Расширение диагностики позволяет в полной мере оценить степень вовлечения шейки матки в патологический процесс и определить оптимальную тактику ведения у женщин с высокой степенью риска (H-SIL, рецидивы L-SIL, высокая вирусная нагрузка ВПЧ).

Ключевые слова: патология шейки матки, вирус папилломы человека, персистенция, диагностика, ПЦР, цитология, гомогенат

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INTRODUCTION

Squamous intraepithelial and glandular lesions of the cervix are the most common pathologies among women of reproductive age. The leading etiological factor in these cases is human papillomavirus (HPV), followed by integration of viral deoxyribonucleic acid (DNA) into the nuclei of epithelial cells, which is pathogenetically associated with the subsequent cervical cancer development [1]. Cervical cancer remains a major global health concern, as evidenced by the projected increase in new cases to 700,000 by 2030 [2].

HPV affects not only the transformation zone but also the endocervical crypts (in 82.6% of cases). Anatomical features of the cervix, such as length of

up to 4 cm and crypt penetration of up to 4 mm, may be major factors contributing to incomplete excision (80.8% in cases with endocervical involvement) [3, 4]. For this reason, cytology has limited potential in diagnosing precancerous lesions and cervical adenocarcinoma: atypia in the collected material may be minimal or absent, since the process is often located deep within the crypts, while squamous epithelium remains practically unchanged.

There is ongoing debate regarding the optimal timing and methods of screening in women of reproductive age [5], as well as concerning the opportunity of HPV clearance in this population. T. Feng et al. (2023) reported a decrease in frequency and an increase in viral clearance time with age [6]. In contrast, S.N. Adebamowo et al. (2022) argued that both the rate and timing of viral clearance are comparable across all age groups [7]. Meanwhile, K. Louvanto et al. (2010) demonstrated reduction in clearance time with advancing age [8].

The U.S. Preventive Services Task Force guidelines do not recommend HPV screening in women under 30 years due to the high risk of unnecessary medical interventions [9]. However, it is known that HPV testing detects precancerous lesions significantly more often than cytology, and, according to O. Feldstein et al. (2023), it should be considered as the primary diagnostic method [10]. Since most low-grade squamous intraepithelial lesions (L-SIL) regress spontaneously, both the World Health Organization and the clinical guidelines of the Russian Society of Obstetricians and Gynecologists ("Cervical Intraepithelial Neoplasia, Erosion, and Ectropion of the Cervix," 2024) do not recommend active treatment in such cases [11]. Nevertheless, Y.J. Tai et al. (2017) reported that cryotherapy and excisional procedures significantly reduce the risk of lesion progression in women with L-SIL, suggesting an active management approach [12]. At the same time, other studies indicate no necessity for active screening and management of L-SIL among young women [13, 14].

Therefore, there are no clear criteria for predicting the course of squamous intraepithelial lesions and choosing the most appropriate management approach, including the optimal extent of surgical treatment.

The aim of the study was to improve the efficiency of diagnosis of cervical pathologies using cytological screening and polymerase chain reaction (PCR) for HPV, taking into account the detection of HPV in upper parts of the endocervix.

MATERIALS AND METHODS

The study involved 60 patients with cervical pathology, mean age 34.4 ± 8.6 years. The study was approved by the Ethics Committee at Siberian State Medical University (Minutes No. 9344 dated January 30, 2023) and conducted in accordance with the Declaration of Helsinki and the Rules for Clinical Practice in the Russian Federation approved by the Order of the Russian Ministry of Health (No. 266, dated June 19, 2003). All patients gave their informed consent to participate in the study.

A standard cytological examination with verification using the Bethesda system was performed. The material for the cytological examination was obtained in accordance with the clinical guidelines of the Russian Society of Obstetricians and Gynecologists "Cervical intraepithelial neoplasia, erosion, and ectropion of the cervix," 2024.

All patients were divided into groups based on the cytology results. Group 1 (n = 22) – negative for intraepithelial lesion or malignancy (NILM), mean age 37 ± 5.4 years. Group 2 (n = 18) – low-grade squamous intraepithelial lesion (L-SIL), mean age 33.7 ± 6.8 years. Group 3 (n = 12) – high-grade squamous intraepithelial lesion (H-SIL), mean age 41.4 ± 9.2 years. Group 4 (n = 8) – atypical squamous cells of undetermined significance (ASC-US), mean age 43 ± 7.5 years.

A mandatory part of the examination was a PCR test (Hybrid Capture Digene test) for high-oncogenic-risk HPV with quantitative determination of viral DNA (a panel of 14 oncoserotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). The viral load was considered to be low at < 3.0 LgDNA / 10^5 cells, moderate – at 3.0–5.0 LgDNA / 10^5 cells, high at ≥ 5.0 LgDNA / 10^5 cells. The material for PCR test was obtained in accordance with the clinical guidelines of the Russian Society of Obstetricians and Gynecologists "Cervical intraepithelial neoplasia, erosion, and ectropion of the cervix," 2024.

To detect HPV persistence in the upper parts of the endocervix, fragments of the cervix obtained during the following procedures were also used for HPV testing:

Excisional biopsy in women with cervical ectopia and NILM cytology, with or without HPV infection.

Targeted mono-/multifocal biopsy in the initial detection of H-SIL.

Excisional biopsy in L-SIL, benign hyperplastic lesions, recurrent ASC-US, and infection with high-risk HPV with a high viral load.

Diathermoelectroexcision as the procedure of choice for H-SIL, as well as recurrences due to HPV infection with a high viral load.

Detection of HPV persistence in the upper parts of the cervical canal (RF Patent No. 2833119, December 14, 2023). A tissue specimen, necessarily including the upper parts of the endocervix, was placed in a sterile test tube with saline (0.9% NaCl). Over the first 2–4 hours, the specimen was homogenized in saline using a rotary homogenizer, followed by centrifugation for 15 minutes at 3,000 rpm. Supernatant was used for subsequent PCR analysis, which made it possible to perform PCR test of the distal parts of the cervix, inaccessible for analysis during traditional PCR material sampling.

Statistical analysis was performed using the Statistica 10.0 software based on contingency table analysis. Qualitative variables were presented as the absolute values and percentages (*n*, %). The McNemar test was used to compare paired binary data (standard PCR and PCR homogenate results from the same patients in the same groups). The Fisher's exact test was used to assess the statistical significance of differences in the frequency of detected HPV strains, as well as PCR diagnostic results between independent groups. The significance level p for all analytical procedures was 0.05.

RESULTS

Standard PCR testing detected HPV in 30 (50%) out of 60 patients. HPV was detected more frequently in patients of the L-SIL group ($p < 0.001$). PCR of the homogenate revealed HPV with greater frequency ($p = 0.0098$), and persistence of HPV in the upper parts of the endocervix was detected in 45 (75%) out of 60 patients. HPV was detected more often in patients with L-SIL and H-SIL ($p = 0.0157$). HPV was detected prevalently by homogenate PCR than by standard PCR in patients of the NILM group ($p = 0.046$). The frequency of HPV detection in PCR studies is presented in Table 1.

Discrepancies in the profile of HPV strains detected by standard PCR testing and PCR testing of the homogenate were observed in 38 (63%) out of 60 patients.

Table 1

HPV Detection by Standard PCR Testing and PCR Testing of the Homogenate in Patients with Different Cytology Results, *n* (%)

Method	Groups			
	I ($n = 22$)	II ($n = 18$)	III ($n = 12$)	IV ($n = 8$)
Standard PCR	5 (23%)	18 (100%)*	7 (58%)	0 (0%)
PCR of the homogenate	13 (59%)#	16 (89%)*	12 (100%)*	4 (50%)

* statistically significant differences within the method, # statistically significant differences within a group (here and in Table 2)

Discrepancies in the detected HPV strains were observed in 14 (64%) out of 22 patients in the NILM group, 11 (61%) out of 18 patients in the L-SIL group, 7 (58%) out of 12 patients in the H-SIL group, and 6 (75%) out of 8 patients in the ASC-US group ($p > 0.05$). Persistence of HPV in the upper cervical canal with a negative standard PCR result was detected in 18 (30%) out of 60 patients ($p = 0.0074$): in 9 (42%) out of 22 patients in the NILM group, in no patients in the L-SIL group (since all patients in this group had a positive standard PCR result), in 3 (25%) out of 12 patients in the H-SIL group, and in 6 (75%) out of 8 patients in the ASC-US group.

Persistence of HPV with high viral load in the homogenate was detected in 3 out of 22 patients (14%) in the NILM group, in 7 out of 18 patients (39%) in the L-SIL group, in 7 out of 12 patients (58%) in the H-SIL group, and in 2 out of 8 patients (25%) in the ASC-US group. The frequency of HPV persistence with high viral load in the homogenate was significantly higher in the H-SIL group than in the other groups ($p = 0.0374$). No differences in the frequency of multiple HPV detection in the homogenate were found between the groups (NILM 23%, 5/22; L-SIL 39%, 7/18; H-SIL 25%, 3/12; ASC-US 0%, $p > 0.05$). Serotype 16 was significantly prevalent in the L-SIL group (Table 2) according to both standard PCR and homogenate PCR results ($p < 0.001$). Serotypes 35, 45, 51, and 68 were detected in single cases.

Table 2

Frequency of Detecting High-Risk HPV Strains by Standard PCR Testing and PCR Testing of the Homogenate in Patients with Different Cytology Results, *n* (%)

HPV strains	Groups							
	I ($n = 22$)		II ($n = 18$)		III ($n = 12$)		IV ($n = 8$)	
	Stand.	Hom.	Stand.	Hom.	Stand.	Hom.	Stand.	Hom.
16	3 (14%)	8 (36%)	13 (72%)*#	16 (89%)*#	3 (25%)	8 (67%)	0	4 (50%)
18	0	0	0	0	2 (17%)	3 (25%)	0	0

End of table 2

HPV strains	Groups							
	I (n = 22)		II (n = 18)		III (n = 12)		IV (n = 8)	
	Stand.	Hom.	Stand.	Hom.	Stand.	Hom.	Stand.	Hom.
31	0	5 (23%)	4 (22%)	4 (22%)	0	0	0	0
33	2 (9%)	2 (9%)	4 (22%)	5 (28%)	2 (17%)	3 (25%)	0	0

Note. Stand. – frequency of detecting HPV strains by standard PCR testing; Hom. – frequency of detecting HPV strains by PCR testing of the homogenate

DISCUSSION

The results demonstrate the potential for improving the effectiveness of extended diagnosis of cervical pathology by assessing the involvement of the upper parts of the cervical canal in the pathological process. The high frequency of HPV persistence in the upper parts of the cervical canal in all groups, particularly in patients with negative standard PCR results, demonstrates limitations of traditional screening methods. Thus, 59% of patients with NILM cytology and 50% patients with ASC-US were found to have HPV persistence in the upper parts of the endocervix, which is consistent with the data from T. Malagón et al. (2020), indicating a high risk of developing precancerous lesions even with normal cytology [15].

We found that HPV 16, 31, and 33 are the most frequently diagnosed strains in homogenate samples, regardless of cytology results. According to W.D. Kang et al. (2024), the detection of these HPV strains may require closer monitoring in women with L-SIL due to a higher risk of dysplastic progression [16]. The choice of the management strategy for patients with L-SIL remains controversial. On the one hand, according to C. Buick et al. (2020), the high probability of spontaneous HPV elimination in young women justifies a wait-and-see approach [13], on the other hand, the detection of high-risk strains, particularly HPV 16, 31, and 33, may justify the use of excisional treatment, which is confirmed by the studies of Y.J. Tai et al. (2017) and C. Firnhaber et al. (2017) [12, 17].

Multiple HPV infection was detected in approximately one in three patients in the NILM, L-SIL, and H-SIL groups following homogenate testing. According to D. Zhou et al. (2024), single-type infection (particularly with HPV16) predominates in H-SIL lesions, whereas multiple HPV infection is more characteristic of L-SIL [18]. A retrospective study by X. Tao et al. (2022) including women with L-SIL found that the proportion of histologically confirmed H-SIL was significantly greater in the presence of multiple HPV infection [19]. In contrast, data from X. Ni et al. (2023) suggested that multiple-type infection was associated with a lower risk of H-SIL and, simultaneously, a higher rate of spontaneous viral clearance [20]. These findings support the concept of complex interactions between different HPV types, which requires further investigation. It seems perspective to investigate the role of impaired immune barriers and their impact on antigen-presenting cells and macrophage subpopulations in the cervical canal, as they may play a key role in the pathogenesis of endocervical HPV persistence.

The results indicate high frequency of pathological endocervical involvement which is particularly important in planning organ-preserving treatment and determining the extent of excision, as margin status combined with HPV persistence after surgery are key risk factors for recurrence [21]. Based on the obtained data, the conventional approach of determining the excision volume based solely on the type of the transformation zone cannot be considered optimal due to the high rate of latent endocervical HPV persistence.

CONCLUSION

The results of the study demonstrate high frequency of HPV persistence in the upper parts of the endocervix among patients with cervical pathology and underscore the necessity of a personalized treatment approach. This approach should account for the patient's age, reproductive plans, and HPV infection type when planning organ-preserving treatment, especially in high-risk groups (with H-SIL, recurrent L-SIL, or a high HPV viral load). Further data collection is warranted to establish statistically significant patterns and to develop personalized algorithms for the diagnosis and management of cervical pathology. These algorithms should integrate cytology findings and HPV status with immunohistochemical detection of cellular proliferation markers (p16/INK4a) and potentially include the assessment of local cervical immunological barrier impairments, including evaluating dendritic cell activity and macrophage subpopulations.

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Author Contribution

Chernov D.Y., Tikhonovskaya O.A. – conception and design. Tikhonovskaya O.A., Logvinov S.V. – critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication. Chernov D.Y., Potapov A.V., Gerasimov A.V., Gereng E.A., Akbasheva O.E., Lasukova T.V. – acquisition and processing of the data.

Author Information

Chernov Denis Y. – Postgraduate Student, Division of Obstetrics and Gynecology, Siberian State Medical University, Tomsk, denis.chrnv1@gmail.com, https://orcid.org/0000-0002-1521-9668

Tikhonovskaya Olga A. – Dr. Sci. (Med.), Professor, Division of Obstetrics and Gynecology, Siberian State Medical University, Tomsk, tikhonovskaya2012@mail.ru, https://orcid.org/0000-0003-4309-5831

Logvinov Sergey V. – Dr. Sci. (Med.), Professor, Head of the Division of Histology, Embryology, and Cytology, Siberian State Medical University, Tomsk, sLogvinov@mail.ru, https://orcid.org/0000-0002-9876-6957

Potapov Alexey V. – Dr. Sci. (Med.), Professor, Division of Histology, Embryology, and Cytology, Siberian State Medical University, Tomsk, potalex@mail.ru, https://orcid.org/0000-0002-0468-3959

Gerasimov Aleksander V. – Dr. Sci. (Med.), Associate Professor, Professor of the Division of Histology, Embryology, and Cytology, Siberian State Medical University, Tomsk, av-gerasimov62@yandex.ru, https://orcid.org/0000-0002-8526-6187.

Gereng Elena A. – Dr. Sci. (Med.), Associate Professor, Professor of the Division of Morphology and General Pathology, Siberian State Medical University, Tomsk, e-gereng@mail.ru, https://orcid.org/0000-0001-7226-0328

Akbasheva Olga E.– Dr. Sci. (Med.), Professor, Division of Biochemistry and Molecular Biology with a Clinical Laboratory Course, Siberian State Medical University, Tomsk, Akbashoe@yandex.ru, https://orcid.org/0000-0003-0680-8249

Lasukova Tatyana V. – Dr. Sci. (Biology), Professor, Division of Normal Physiology, Siberian State Medical University, Tomsk, tlasukova@mail.ru, http://orcid.org/0000-0003-3274-6010

(✉) **Chernov Denis Y.,** denis.chrnv1@gmail.com

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