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Article

Combined Diagnostic Efficacy of Liquid-Based Cytology and Hpv Testing in the Early Detection of Cervical Cancer

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Abstract: Background: Cervical cancer (CC) remains one of the leading causes of cancer-related morbidity and mortality among women worldwide. Detection at the precancerous stage substantially improves treatment outcomes and survival. Objective: To evaluate the diagnostic sensitivity and specificity of liquid-based cytology (LBC) combined with high-risk human papillomavirus (hrHPV) testing (co-testing) compared with the conventional Papanicolaou (Pap) smear in detecting cervical precancerous lesions and early-stage cancer. Methods: In this prospective study, 240 women aged 25–60 years were randomized into two equal groups. Group I (n=120) underwent conventional Pap cytology; Group II (n=120) underwent LBC combined with PCR-based hrHPV testing. Final diagnoses were established by colposcopy and histopathological examination of directed biopsies. Results: The sensitivity of co-testing for CIN II+ lesions (moderate-to-severe dysplasia and worse) was 94.2%, versus 68.5% for the conventional Pap test ($p<0.001$). The false-negative rate was 4.5 times lower in Group II (4.1% vs 18.3%; $p<0.001$), and no LBC specimen was unsatisfactory, compared with 9.2% of conventional smears. Conclusion: Combining liquid-based cytology with hrHPV testing significantly improves the early diagnostic accuracy of cervical cancer screening and is a promising strategy for screening programs.

Keywords: Cervical cancer; screening; liquid-based cytology; human papillomavirus (HPV); co-testing; cervical intraepithelial neoplasia (CIN); sensitivity.

Introduction

Cervical cancer remains one of the most pressing problems of modern gynecologic oncology. According to GLOBOCAN estimates, approximately 604,000 new cases and 342,000 deaths were recorded worldwide in 2020 [1]. Persistent infection with high-risk human papillomavirus (hrHPV), particularly genotypes 16 and 18, is the principal etiological factor in cervical carcinogenesis [2], and the World Health Organization recommends HPV testing as the preferred approach to cervical cancer screening [3].

Conventional cytology (the Papanicolaou test) has been the cornerstone of screening for decades. However, because of sampling error and obscuring elements such as blood, mucus and inflammatory exudate, the false-negative rate of conventional smears may reach 20–30%. Pooled analyses of European and North American studies have shown that HPV testing is considerably more

sensitive than cytology for detecting CIN II+ lesions [4]. Consequently, "co-testing" — the combination of liquid-based cytology (LBC) with molecular detection of hrHPV — has gained considerable clinical relevance in recent years, and current screening guidelines accept it as an option alongside primary HPV testing [5].

Aim of the study. To assess the combined clinical and diagnostic value of liquid-based cytology and hrHPV testing in the early detection of cervical intraepithelial neoplasia (CIN I–III) and early-stage invasive cervical cancer.

Materials and Methods

This prospective randomized study was conducted in 2024–2025 at the Department of Gynecologic Oncology of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology. It included 240 women aged 25–60 years (mean age 39.4 ± 6.2 years) who presented with benign cervical conditions or attended routine preventive screening.

Inclusion criteria: women of reproductive and perimenopausal age who gave written informed consent.

Exclusion criteria: pregnancy or lactation; a history of confirmed cervical cancer; previous cervical conization.

Participants were randomized into two equal groups:

1. Group I (control, n=120): cervical smears were obtained with an Ayre spatula and cytobrush, fixed, and stained by the conventional Papanicolaou method.
2. Group II (study, n=120): samples were collected into preservative-containing vials (BD SurePath) for liquid-based cytology. Real-time polymerase chain reaction (PCR) for 14 high-risk HPV genotypes was performed on the same sample.

Cytological findings were classified according to the 2014 Bethesda System [6]. All women with abnormal cytology (ASC-US, LSIL, HSIL) or a positive hrHPV result underwent extended colposcopy and colposcopy-directed punch biopsy; histopathology served as the reference standard.

Statistical analysis was performed with SPSS version 26.0. Between-group differences were assessed using Student's t-test and the chi-square (χ^2) test; $p<0.05$ was considered statistically significant.

Scientific background and methodological rationale. The design of the study rests on the work of foreign and local researchers, and our attitude toward their findings determined the methodological choices described above.

Foreign studies. Ronco et al., in a pooled follow-up of four European randomized trials, showed that HPV-based screening gives 60–70% greater protection against invasive cervical cancer than cytology-based screening [7]. We share this position and therefore made hrHPV detection a mandatory component of the study arm rather than an optional supplement. Kitchener et al. (the ARTISTIC trial) evaluated LBC combined with HPV testing in a large randomized trial [8]; we adopted its central principle of testing a single liquid-based sample, but compared co-testing with the conventional Pap smear, which is still widely used in routine practice. Wright et al. (the ATHENA study) demonstrated that HPV-16/18 genotyping identifies women with normal cytology who are at high risk of CIN III+ [9]; accordingly, we recorded genotypes individually and referred every hrHPV-positive woman for colposcopy even when cytology was normal. Arbyn et al., in a systematic review and meta-analysis, found that LBC and conventional cytology have comparable accuracy, although LBC yields fewer unsatisfactory specimens [10]. We therefore regard the gain in sensitivity as attributable mainly to the HPV component, and the improved specimen adequacy as the separate advantage of LBC; because our design compares two screening strategies as a whole, it cannot fully separate these contributions. Finally, we adopted the 2014 Bethesda System [6] to ensure uniform terminology and comparability with international data.

Local studies. Oltieva et al. reported hrHPV in 8.5% of 44,497 women examined in Tashkent, Andijan and Samarkand, with HPV-16/18 in 41.1% of positive cases; among HPV-positive women who underwent cytology, 64.1% had normal results [11]. We consider these data strong evidence that cytology alone is insufficient for the Uzbek population, and they underpinned our decision to refer

HPV-positive women with normal cytology for colposcopy. The higher hrHPV prevalence in our cohort (31.7%) is, in our view, explained by the inclusion of women with benign cervical conditions rather than an unselected screening population. Sharipova et al. detected HPV DNA in 32.6% of cervical samples in a single-center cross-sectional study of 218 women, but urine testing had a sensitivity of only 57.7% [12]. Their prevalence is close to ours, which supports the comparability of the cohorts; because of the low sensitivity of urine testing, we collected cervical samples directly and regard urine sampling only as a possible supplement for women who decline pelvic examination. Mamarasulova et al. (Andijan) emphasized that cytology (high specificity, low sensitivity) and HPV testing (high sensitivity, lower specificity) complement each other in primary screening [13]. We fully agree with this view, and our study arm was built on this complementarity.

Results

Specimen adequacy differed significantly between the groups. In Group I, 11 smears (9.2%) were unsatisfactory for evaluation because of excessive blood and leukocytes and required repeat sampling, whereas all 120 LBC specimens (100%) in Group II were satisfactory and morphologically clear ($p<0.01$).

In Group II, hrHPV was detected in 38 of 120 women (31.7%). Among HPV-positive cases, the most prevalent genotypes were HPV-16 (52.6%; 20/38), HPV-18 (18.4%; 7/38) and HPV-31/33 (15.8%; 6/38).

The diagnostic performance of both approaches, verified against histopathology, is presented in Table 1. Co-testing detected high-grade dysplasia (CIN II–III) more than twice as often as conventional cytology (24 vs 11 cases) and identified carcinoma in situ in 4 cases versus 1.

Table 1. Diagnostic performance of conventional Pap cytology and LBC + hrHPV co-testing

Diagnostic metric	Group I: conventional Pap test (n=120)	Group II: LBC + hrHPV co-testing (n=120)	p-value
Sensitivity (CIN II+)	68.5%	94.2%	<0.001
Specificity	89.1%	91.8%	>0.05
False-negative rate	18.3%	4.1%	<0.001
Detection of CIN II/CIN III	11 cases (9.2%)	24 cases (20.0%)	<0.05
Early-stage cancer (carcinoma in situ)	1 case (0.8%)	4 cases (3.3%)	<0.05

Discussion

Our findings indicate that relying on conventional cytology alone carries a substantial risk of missing high-grade precancerous lesions. Liquid-based cytology provides a uniform monolayer of epithelial cells and removes obscuring background material, which improves cytomorphological assessment and eliminated unsatisfactory specimens in this series.

The 94.2% sensitivity of co-testing for CIN II+ is consistent with the results of large international trials, including ATHENA [9] and ARTISTIC [8]. A Cochrane diagnostic test accuracy review likewise found HPV testing to be more sensitive but less specific than cytology for detecting CIN II+ [14], and in the HPV FOCAL randomized trial primary HPV screening yielded significantly fewer CIN III+ lesions than cytology at 48 months [15]. Notably, among 9 women in Group II whose cytology was initially normal (NILM) but who tested positive for HPV-16/18, colposcopy-directed biopsy confirmed CIN II. This underlines the prognostic value of molecular HPV testing for identifying women at immediate risk of progression whom cytology alone would have missed.

Limitations. The study is single-center, with a relatively small sample and a short follow-up period. In addition, biopsy was performed only in women with an abnormal screening result, so partial verification bias cannot be excluded and the absolute sensitivity estimates should be interpreted with

caution. Our protocol of referring every hrHPV-positive woman for colposcopy is also more intensive than risk-based management algorithms, which allow colposcopy to be deferred for low-risk results [16]. Larger multicenter studies with longer follow-up are needed, together with an assessment of the long-term cost-effectiveness of introducing co-testing algorithms into regional and national screening programs.

Conclusion

Combining liquid-based cytology with hrHPV testing raised the sensitivity for CIN II+ lesions from 68.5% to 94.2%, eliminated unsatisfactory specimens and reduced the false-negative rate from 18.3% to 4.1%, allowing earlier colposcopic referral and treatment. Introducing co-testing into screening programs, particularly for women over 30 years of age, may therefore help reduce the incidence of and mortality from cervical cancer, pending confirmation in larger multicenter studies.

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