DIAGNOSTIC VALUE OF APTIMA HPV COMBINED WITH THINPREP CYTOLOGY TEST IN HIGH-GRADE CERVICAL LESIONS

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ABSTRACT

Objective: *To investigate the diagnostic value of Aptima human papillomavirus (HPV) combined with thinprep cytology test (TCT) in screening high-grade cervical lesions.*

Methods: *A total of 1085 patients with suspected cervical lesions in Beijing Luhe Hospital, Capital Medical University from September 2020 to August 2021 were collected. All patients underwent Aptima HPV, TCT and cervical multipoint biopsy under colposcopy. Patients with positive Aptima HPV were further tested for Optima HPV16/18/45 genotype. Using histopathological results as the 'gold standard, we analyzed and compared the diagnostic value of Aptima HPV and TCT screening alone or in combination in high-grade cervical lesions.*

Results: *The sensitivity and negative predictive value of Aptima HPV combined with TCT were higher than those of single Aptima HPV and TCT (98.83%vs96.21%vs38.48%; 95.12%vs91.95%vs71.37%), The specificity and accuracy were lower than that of Aptima HPV and TCT alone (10.51%vs21.7%vs70.89%;38.4%vs45.25%vs60.65%) (P <0.05). The positive rate of Aptima HPV and TCT elevated gradually with the increase of histopathological grade. The positive rate of Aptima HPV in histopathology diagnosed as HSIL or serious than HSIL group was significantly higher than that of TCT (96.21%vs38.48%, P<0.05). Among the different shunting methods, TCT+ combined with HPV16/18/45+ group had the highest detection rate of histopathology diagnosed as HSIL or serious than HSIL lesions (62.8%), and the OR value was 1.55 times higher than that of TCT+/other HPV+ group, 1.66 times higher than that of TCT+ group, and 1.73 times higher than that of HPV+group (95%CI:4.882-33.940, P <0.05). In all Aptima HPV positive groups, the highest detection rate of histopathology diagnosed as HSIL or serious than HSIL lesions was found in the HPV16/18/45+ group (43.6%), and the OR value was 1.33 times higher than that of the other HPV + groups (95% CI:3.407-23.468,P<0.05).*

Conclusion: *TCT combined with Aptima HPV can significantly improve the screening ability of high-grade cervical lesions, especially TCT combined with Aptima HPV16/18/45 genotype test has better risk prediction ability for histopathology diagnosed as HSIL or serious than HSIL lesions than any single or combined screening, which can be promoted as an opportunistic screening method for clinical cervical cancer.*

Keywords: *Human papillomavirus E6/E7 mRNA, Aptima, thinprep cytology test, cervical cancer screening.*

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Introduction

Cervical cancer is one of the most common malignant tumors in women in developing countries. In 2020, there were about 600,000 new cervical cancer cases and 340,000 deaths worldwide, including about 109,000 new cervical cancer cases and 59,000 deaths in China[1], which seriously threatened the life and health of women. Persistent infection of high-risk HPV is the main risk factor for cervical cancer, and about 95-99% of cervical cancer is associated with persistent infection of high-risk HPV[2]. HPV persists and expresses viral oncogene E6/E7 mRNA, leading to increased genomic instability, accumulation of somatic mutations, and integration of HPV into the host genome leading to cervical cancer lesions. However, this process takes decades, and there is a long and reversible precancerous stage. Early intervention can significantly reduce the incidence and mortality of cervical cancer[3]. This

study investigated the diagnostic value of Aptima HPV based on E6/E7 mRNA detection technology combined with cervical thinprep cytology test for high-grade cervical lesions.

Data and methods

Research object

The clinical data of 1085 patients with suspected cervical lesions admitted to the Department of Gynecology of the hospital from September 2020 to August 2021 were collected.

The Optima HPV, Optima HPV16/18/45 detection, TCT and histopathological results were retrospectively analyzed. Using histopathological results as the 'gold standard, we analyzed and compared the diagnostic value of Aptima HPV and TCT screening alone or in combination in high-grade cervical lesions.

Inclusion criteria:

• The patient had a sexual life history and was 18 years old or older;

• Aptima HPV and TCT combined screening were performed, and if Aptima HPV was positive, Optima HPV16/18/45 genotype was further tested.

• Macroscopic suspicious cervical lesions.

Exclusion criteria:

• Patients with acute and chronic reproductive tract infection;

• Patients had a history of malignancy and chemoradiotherapy;

• History of hysterectomy or cervical surgery;

• Women in pregnancy or puerperium.

TCT

The thinprep cytology test technology was purchased from Beijing Haoluojie Medical Technology Co., Ltd. Cytological sampling brush was rotated clockwise for 3 to 5 weeks to remove exfoliated cells at the cervical squamous columnar junction. The collected cells were stored in PreservCyt cell preservation solution and processed by ThinPrep 2000 system, then smear was prepared, fixed, and stained.

The Bethesda System (TBS) classification standard recommended by The International Cancer Society (NCI) in 2014 was used for cytological diagnosis[4]:

• Negative for intraepithelial lesion and malignancy (NILM);

• Atypical squamous cells undetermined significance (ASC-US);

• Atypical squamous cells cannot exclude a high-grade squamous intraepithelial lesion (ASC-H);

• Low-grade squamous intraepithelial lesion (LSIL);

• High-grade squamous intraepithelial lesions (HSIL);

• Squamous cell carcinoma (SCC);

• Atypical glandular cells (AGC), Atypical glandular cells favor neoplasia (AGC-FN), Adenocarcinoma in situ (AIS), Adenocarcinoma. TCT diagnosed as LSIL or serious than LSIL was defined as positive.

Optima HPV and Aptima HPV16 18/45 genotype detection

The Optima HPV kit purchased from Beijing Haoluojie Medical Technology Co., Ltd. was used to qualitatively detect 14 high-risk types of HPV E6/E7 mRNA without specific typing (including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). Operated according to the instructions, and any positive typing will show positive results (Aptima HPV+).

Positives were further qualitatively detect E6/E7 mRNA for HPV 16, 18 and 45 subtypes by using the Aptima 16/18/45 genotyping kit, but it did not distinguish between subtypes 18 and 45.

Electronic colposcopy

According to the 2012 American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines[5], colposcopy was performed for patients with cytological ASCUS or above and HPV positive, cytological LSIL or above, HPV 16/18 positive, and clinical symptoms of suspected cervical lesions (such as bleeding during sex, macroscopic cervical ulceration or other). Endocervical biopsy with endocervical curettage (ECC) was performed when necessary.

Histopathological results were diagnosed according to the secondary classification of cervical lesions in the WTO Classification of Female Reproductive System Tumors (2014)[4]:

• Normal/inflammatory;

• LSIL (CIN1);

• HSIL (including CIN2, CIN3 and carcinoma in situ);

• Invasive carcinoma of cervix.

High pathological grade were used as the final diagnosis for different sites.

Diagnostic criteria

With histopathology as the 'gold standard, HSIL and above were defined as histopathology positive (≥HSIL) and LSIL and below were defined as histopathology negative (≤LSIL).

The diagnostic value of TCT, Aptima HPV single detection and combined screening for high-grade cervical lesions was analyzed. Sensitivity = number of true positive cases /(number of true positive cases + number of false negative cases) ×100%; Specificity = number of true negative cases /(number of true negative cases + number of false positive cases) ×100%; Positive predictive value = number of true positive cases /(number of true positive cases + number of false positive cases) ×100%; Negative predictive value = number of true negative cases /(number of true negative cases + number of false negative cases) ×100%.

Statistical analysis

SPSS22.0 software was used for data statistical analysis. Age was expressed as mean ± standard deviation ($\bar{x}\pm s$). Counting data were expressed as the number of cases and rate (%). χ^2 test was used for comparison between groups, and odds ratio (OR) was calculated. P<0.05 indicated the difference was statistically significant.

Results

General information

A total of 1085 patients, aged 19 to 72 (41.05±11.69) years old, were enrolled in this study. 180 cases (16.59%) had normal histopathology or inflammation; 562 cases (51.80%) had LSIL (CIN1); 325 cases (29.95%) had HSIL, including 211 cases of CIN2 and 114 cases of CIN3; 18 cases had invasive carcinoma of cervix, including 12 cases of cervical squamous cell carcinoma, 5 cases of cervical adenocarcinoma, 1 case of poorly differentiated carcinoma (no further immunohistochemistry was performed). There were 911 Aptima HPV positive cases (83.96%), including 282 Optima HPV16/18/45 positive cases and 629 other HPV type II positive cases. 348 cases (32.07%) were TCT positive.

Diagnostic value of Aptima HPV and TCT screening alone and in combination for histopathology diagnosed as HSIL or serious than HSIL lesions

As shown in Table 1, a parallel test was used for joint screening, and a positive TCT or Aptima HPV were defined as combined screening positive. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of Aptima HPV, TCT single and combined screening were compared with histopathological gold standard, and the diagnostic value of single test and combined screening for histopathology diagnosed as HSIL or serious than HSIL was evaluated.

Screening methods	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Optima HPV	96.21[a] (330/343)	21.70[a] (161/742)	36.33[a] (330/911)	91.95[a] (161/174)	45.25[a] (491/1085)
TCT	38.48[b] (132/343)	70.89 (526/742)	37.93 (132/348)	71.37 526/737	60.65[b] (658/1085)
Combined screening	98.83[c] (339/343)	10.51 (78/742)	33.8 (339/1003)	95.12[a] (78/82)	38.4[a] (417/1085)
χ^2 value	462.776	678.791	*2.370*	52.145	112.537
P value	<0.001	<0.001	0.306	<0.001	<0.001

Table 1: Comparison of diagnostic efficacy of different screening methods [% (n/N)].

Notes: There was no statistically significant difference between groups marked with the same letter. The difference between groups marked with different letters was statistically significant.

The results showed that the sensitivity and negative predictive value of single TCT test were significantly lower than those of single Aptima HPV test (38.48%vs96.21%; 71.37%vs91.95%), the specificity and accuracy were higher than those of single Aptima HPV test (70.89%vs21.70%; 60.65%vs45.25%), and the differences were statistically significant (P<0.05). There was no significant difference in positive predictive value among groups (P>0.05). The sensitivity and negative predictive value of combined screening were the highest, followed by Aptima HPV test, both of which were strikingly higher than those of single TCT test (98.83%vs96.21%vs38.48%; 95.12%vs91.95%vs71.37%), and the differences were statistically significant (χ^2=462.776, P<0.05; χ^2=52.145, P<0.05).

The specificity of single TCT test was the highest, followed by Aptima HPV test, both of which were markedly higher than that of combined screening (70.89%vs21.7%vs10.51%), and the differences were statistically significant (χ^2=678.791, P<0.05). The accuracy of single TCT screening was higher than that of Aptima HPV screening, both of which were higher than that of combined screening (60.65%vs45.25%vs38.4%), and the differences were statistically significant (χ^2=112.536, P<0.05). The positive predictive value of single TCT screening was the highest, followed by Aptima HPV screening, both of which was higher than that of combined

screening (37.93%vs36.33%vs33.8%), but the difference was not statistically significant (χ^2=2.37, P>0.05). The positive rate of Aptima HPV and TCT in histopathology diagnosed as HSIL or serious than HSIL group was significantly higher than that in LSIL or milder than LSIL group (96.21%vs78.30%;38.48 %vs29.11%), and the differences were statistically significant (χ^2=55.867, P<0.05; χ^2=9.46, P<0.05). The positive rates of Aptima HPV and TCT elevated with the increase of histopathological grade.

The positive rate of Aptima HPV in histopathology diagnosed as HSIL or serious than HSIL group was significantly higher than that of TCT (96.21%vs38.48%), and the differences were statistically significant (χ^2=259.875, P<0.05).

Correlation analysis between different shunt and histopathological results of Aptima HPV, Optima HPV16/18/45 genotypes detection and TCT

As shown in Table 2, in TCT+ group, the detection rate of histopathology diagnosed as HSIL or serious than HSIL lesions was 37.9%, and the OR value of was 1.05 times higher than that of Aptima HPV+ group (95%CI: 2.962-20.414), and the difference was statistically significant (P<0.05).

Different shunt methods	n	≤LSIL (n=742)	≥HSIL (n=343)	X^2	P	OR	95%CI
Optima HPV-	174	161(92.5)	13(7.5)	0.605	0.437	1.532	0.515-4.553
Optima HPV +	911	581(63.8)	330(36.2)	33.114	<0.001	7.426	2.844-19.388
HPV16/18/45+	282	159(56.4)	123(43.6)	41.967	<0.001	8.941	3.407-23.468
Other HPV +	629	422(67.1)	207(32.9)	27.313	<0.001	6.746	2.577-17.660
TCT-	737	526(71.4)	211(28.6)	21.502	<0.001	5.869	2.241-15.367
TCT+	348	216(62.1)	132(37.9)	33.527	<0.001	7.776	2.962-20.414
TCT+/Aptima HPV+	256	133(51.9)	123(48.1)	49.343	<0.001	9.850	3.755-25.833
Other TCT+/HPV+	170	101(59.4)	69(40.6)	34.282	<0.001	8.321	3.145-22.014
TCT+/HPV 16/18/45+	86	32(37.2)	54(62.8)	62.280	<0.001	12.872	4.882-33.940
TCT+/Aptima HPV-	92	83(90.3)	9(9.7)	1.509	0.219	2.005	0.642-6.268
TCT-/ Aptima HPV+	655	448(68.4)	207(31.6)	25.474	<0.001	6.479	2.475-16.961
Other TCT-/ HPV+	459	321(69.9)	138(30.1)	14.499	<0.001	4.739	1.802-12.462
TCT-/HPV 16/18/45+	196	127(64.8)	69 (35.2)	27.458	<0.001	7.217	2.724-19.123
TCT-/ Aptima HPV -	82	78(95.1)	4 (4.9)			1.000	

Table 2: Correlation analysis between different shunt methods and histopathological results [n(%)].

In all Aptima HPV positive groups, the highest detection rate of histopathology diagnosed as HSIL or serious than HSIL lesions was found in the HPV16/18/45 + group (43.6%, 123/282), and the OR value was 1.33 times higher than that of the other HPV + groups (95% CI: 3.407-23.468), and the difference was statistically significant (P<0.05).

Among the different shunting methods, TCT+ combined with HPV16/18/45+ group had the highest detection rate of histopathology diagnosed as HSIL or serious than HSIL lesions (62.8%), and the OR value was 1.55 times higher than that of TCT+/other HPV+ group, 1.66 times higher than that of TCT+ group, and 1.73 times higher than that of HPV+group (95%CI:4.882-33.940), and the difference was statistically significant (P<0.05). Compared with TCT-/Aptima HPV- group, the risk of histopathology diagnosed as HSIL or serious than HSIL lesions was relatively lower in Aptima HPV- group, followed by TCT+/Aptima HPV- group, but the difference was not statistically significant (P>0.05).

Discussion

Persistent infection with high-risk HPV is a necessary condition for cervical cancer. Based on the clear etiology, cervical screening is an important secondary prevention strategy in addition to HPV vaccination. TCT combined with HPV screening is widely used in China.

Cervical smear is one of the main means of cervical screening, which can detect precancerous lesions and early cervical cancer. Compared with traditional Pap smear, TCT has higher sample accuracy and can better identify abnormal cervical cells[6]. However, TCT has high requirements on cell quantity, quality and reader technology, resulting in low reproducibility of the test, low sensitivity of TCT detection, false positives, and easy to cause missed diagnosis and overtreatment of diseases. With the continuous progress of research on the correlation between HPV infection and cervical lesions, a large number of studies have shown that HPV detection has higher sensitivity and negative predictive value than TCT. 10 years of negative HPV test and 3 years of negative cytology test have similar protection level, which is more effective in screening glandular lesions and adenocarcinoma, and is an ideal choice for cervical lesion screening[7-9]. The 2021 WHO Guidelines for the Screening and Treatment of precancerous lesions in cervical cancer proposed HPV-DNA testing as a primary screening method for cervical cancer[10]. More than 70% of women in sexually active period will be infected with HPV, and 90% will be cleared by the immune system within 2 years[2]. When infection persists, the HPV

genome integrates into the host chromosome and induces upregulation of oncogene E6/E7 mRNA expression, producing E6/E7 protein. E6 binds and degrades the tumor suppressor p53 and pro-apoptotic proteins, prevents apoptosis and promotes viral DNA replication. E7 inhibits the release of transcription factors and cyclins from tumor suppressor retinoblastoma-1, leading to cell abnormalities and carcinogenesis[3, 11]. Overexpression of E6/E7 protein can be detected by E6/E7 mRNA transcription. E6/E7 mRNA expression is low in transient infection, but overexpressed in persistent infection. Therefore, the up-regulation of E6/E7 mRNA expression may be closely related to the degree of lesion progression[12]. E6/E7 mRNA transcription is a potential biomarker of disease progression to cervical cancer. Compared with HPV-DNA testing, which only shows the presence or absence of virus, HPV E6/E7mRNA testing can provide a deeper understanding of the activity of virus, overcome the low specificity of HPV-DNA testing in the screening of high-grade cervical lesions[13-14], and avoid excessive referral and intervention for transient HPV infection.

Optima HPV is the only FDA-approved HPV assay kit based on two oncogene E6/E7 mRNA. A study by Liu et al.[15] showed that the positive rate of HPV E6/E7 mRNA detection increased with the severity of cytological or histological findings, in which all samples with high-grade lesions tested positive for HPV mRNA. Burger et al.[16]conducted a systematic review on the performance of HPV mRNA testing, and the results showed that the sensitivity of Aptima HPV testing was up to 90-95%, significantly higher than TCT, and its specificity was 42-61%, higher than HPV DNA screening. In the review report on HPV E6/E7 mRNA detection of CIN2+ lesions, Derbie et al.[13] pointed out that HPV E6/E7 mRNA detection and CIN2+ have diagnostic relevance, especially good specificity, which may be related to the oncogenic power of HPV infection depends on the overexpression of E6/E7 protein.

In this study, the sensitivity and negative predictive value of Aptima HPV test were close to that of combined screening, and significantly higher than that of single TCT test (98.83%vs96.21%vs38.48%; 95.12%vs91.95%vs71.37%), and the specificity and accuracy of single TCT test were higher than those of Aptima HPV test (70.89vs21.70%; 60.65vs45.25%), the differences were statistically significant (P<0.05). The positive rates of Aptima HPV and TCT elevated with the increase of histopathological grade. In histopathology diagnosed as HSIL or serious than HSIL group, the positive rate of Aptima HPV was 96.21%, significantly higher than that of TCT (38.48%) and LSIL or milder than LSIL group (78.30%). The detection rate of histopathology diagnosed as HSIL or serious than HSIL lesions in TCT+ combined with Aptima HPV+ group was 48.1%, which was significantly higher than that in TCT+ group and Aptima HPV+ group (37.9%vs36.2%), and the differences were statistically significant (P<0.05). Therefore, combined screening can significantly improve the identification ability of high-grade cervical lesions, and its negative can provide a better level of protection.

HPV16/18 is the most common pathogenic type associated with cervical cancer, while HPV18/45 is more commonly associated with cervical adenocarcinoma. Other high-risk HPV types, including 35/39/51/56/59/66 and 68, had a relatively low risk of progression to cervical cancer and precancerous lesions. Therefore, classification of HPV-positive women who performed genotype to detect oncogenic types is helpful for risk stratification[17]. In this study, patients with positive Aptima HPV were further tested for Optima HPV16/18/45 genotype. By comparing the results of different shunt methods and histopathology, it was found that TCT+ combined with HPV16/18/45+ group had the highest detection rate of histopathology diagnosed as HSIL or serious than HSIL lesions (62.8%), which was strikingly higer than LSIL or milder than LSIL group, and the OR value was 1.55 times higher than that of TCT+/other HPV+ group, 1.66 times higher than that of TCT+ group, and 1.73 times higher than that of HPV+group (95%CI:4.882-33.940), and the difference was statistically significant (P<0.001). Among 18 patients diagnosed with cervical cancer, the positive rate of Aptima HPV reached 100%, including 2 cases (11.11%) in the other HPV+ group and 16 cases (88.89%) in the HPV16/18/45+ group. Therefore, TCT combined with Aptima HPV detection, especially TCT combined with Aptima HPV16/18/45 mRNA genotype detection technology, can perform risk stratification of cervical lesions and more effectively identify high-grade cervical lesions.

Patients with TCT+/Aptima HPV16/18/45 positive are more likely to develop high-grade cervical lesions. Colposcopy should be referred as early as possible for further evaluation and early intervention, which can effectively reduce the incidence and mortality of cervical cancer. This is consistent with the conclusion of Wang Jiajian and Dong Jie et al.[18] on the feasibility of Aptima HPV

test combined with Aptima HPV-GT test as an opportunistic screening method for cervical cancer.

In conclusion, compared with the single TCT and Aptima HPV test, the combined screening has better diagnostic performance. Especially TCT combined with Aptima HPV16/18/45 genotype test, its negative can provide a better level of protection for women, further risk stratification for Aptima HPV positive patients can more effectively identify high-grade cervical lesions, achieve early intervention of cervical lesions, improve the outcome, and can be popularized in clinical application.

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