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Original Research

Discriminating Performance of Early Uterine and Cervical Artery Pulsatility and Resistivity In Pre-Invasive Cervical Lesions

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Abstract

Objectives: The aim of the present study was to investigate the diagnostic effectiveness of uterine and cervical vascularity alone or in combination with human papillomavirus (HPV) DNA testing and with cytology.

Methods: Data were prospectively collected from 129 patients in an outpatient clinic of a secondary setting. Routine liquid-based cervical cytology and HPV-DNA testing were obtained. An abnormal result of any of these high-risk types was viewed as positive. Pulsatility (PI) and resistance (RI) indices of uterine (UA) and cervical (CA) arteries were assessed by Doppler sonography. Pathological diagnosis was considered as the gold standard for assessment. Diagnostic efficiency of alone and joint screening of the three indices for discriminating cervical intraepithelial neoplasia (CIN-I) or above from below was assessed.

Results: UA-RI and CA-RI were significantly lower in the HPV (+) group than in the controls (p=0.02 and p=0.03, respectively). In subsequent sub-analysis among patients with positive HPV-DNA, UA-PI was significantly higher in the HPV-16 (+) group than in the HPV-18 (+) group (p=0.04). High-risk HPV (Hr-HPV) testing had the highest sensitivity compared with Doppler and cytology (76.5%, 64.7%, and 58.5%, respectively). Combining CA-RI with cytology or Hr-HPV significantly reduced the sensitivity (23.5% and 29.4, respectively) but improved the specificity from 54.4% to 69.8% and 40.9% to 70.7%, respectively. Combining UA-PI with Hr-HPV slightly increased the positive predictivity when compared with testing Hr-HPV alone (36.1% vs. 33.3%).

Conclusion: The potential of the Doppler indices of UA and CA was doubtful in discriminating CIN-I or above lesions in the early period. In addition, RI of UA and CA differed with regard to the presence of HPV infection, whereas CA-RI differed in high-risk HPV cases.

Keywords: Cervical intraepithelial neoplasia; cervical smears; doppler ultrasonography; human papilloma virus; uterine artery.

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Cervical cancer is the second most common cancer in less developed regions; the average risk of death before age 75 years is three times lower in developed regions than in less developed regions, thus bringing a higher burden for developing countries.[1]

An estimate of 12.820 new cervical cancer cases and 4210 deaths in the United States was reported in 2017.[2] Cervical cancer is the second leading cause of death due to cancer in women aged 20 to 39 years, accounting for 1 out of every 10 cancer deaths and emphasizing the need to improve screening rates in this age range.[2]

Tens of thousands of invasive cervical cancer cases have been prevented owing to national organized screening programs for cervical cancer, and the beneficial impact of

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screening was consistently increased in time.[3] Innovative approaches in cervical cancer prevention improved patient outcomes as in shifting screening algorithms from cytology-based to human papillomavirus (HPV)-based screening.[4]

High-risk HPV (Hr-HPV) is known as the essential factor for cervical cancer development, and only a small percentage of HPV-infected cases will progress to high-grade cervical intraepithelial neoplasia (CIN-I) or cancer after a long latency period.[5] Recent meta-analysis showed that the specificity of the HPV-DNA testing is age-related, and the specificity to detect CIN-II and above-grade lesions only overlaps with cytology in women aged ≥30 years despite its high sensitivity.[6] Women with positive Hr-HPV and negative cytology have relatively higher false-positivity.[7] In addition, colposcopic interpretation, which is the current gold standard of diagnosis of pre-invasive lesions, has variable accuracy between different operators.[8] On the other hand, it is known that the angiogenesis and the vascularity of cervical cancer correlate well with the individual tumor characteristics and prognostic factors for recurrence.[9, 10]

It is needed to improve the efficacy of the screening to obtain better outcomes and decrease the invasive cancer incidence. However, the relationship between the angiogenesis of the pre-invasive lesions, in particular, and the HPV-DNA testing is scarce in the literature. Therefore, we speculated that assessing cervical vascularity may alter the management of certain individuals with specific conditions in the early period with regard to HPV-DNA testing alone or in combination with cytology. Thus, our study aimed to evaluate the diagnostic performance of combining the uterine and cervical blood flow assessed by color Doppler ultrasound with the presence of Hr-HPV and/or cytology.

Methods

A total of 129 patients who were admitted to gynecologic outpatient clinics in a secondary state hospital for a routine control between 2015 and 2016 were enrolled in this prospective study.

Women <30 and >65 years, who were hysterectomized for any causes, and with a history of any vaginal medical application or oral contraceptive use, cervical precancerous lesions or cervical conization, embolization of the uterine arteries (UAs), and previous radiochemotherapy were excluded from the study. Patients with postmenopausal status or in the menstrual or gestation period were also excluded prior to the study. Data were prospectively collected including age, parity, and body mass index (BMI). Routine liquid-based cervical cytology and HPV-DNA testing were obtained from all patients. HPV typing method HybriBio medical nucleic acid molecule hybridization technique and its reagents (introduced from HybriBio, Hong Kong, China) were applied to typing and detect the 21 most common HPV genotypes including 15 types of Hr-HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, and 68) and 6 types of low-risk types (6, 11, 42, 43, 44, and 8304). A positive result of any of the high-risk types was viewed as positive. Adequate colposcopy was performed by a gynecologist (O.D.) highly experienced with colposcopy according to the ASCCP 2013 guideline and clinical suspicion.[11] Pathological diagnosis was accepted as the gold standard for assessment. Patients were referred to tertiary care centers servicing as a referral center for gynecological oncology with regard to colposcopy results, if necessary.

A transvaginal ultrasound was routinely performed by using a Voluson 730 (GE Ultrasound, Glattbrugg, Switzerland), a GE E8 (GE Ultrasound), and an Acuson Sequoia (Siemens AG, Erlangen, Germany) equipped with a 4–9 MHz endovaginal probe with color and pulsed Doppler capabilities. Measurements of Doppler flow characteristics were obtained from UA and CA on the one side that could be measured most easily including pulsatility index (PI) and resistance index (RI). PI and RI values were automatically calculated for each artery identified. The lowest RI and the lowest PI found for each artery were used for analysis. Color Doppler ultrasonography (USG) assessment of CA and UA was performed by the same USG device and by the same radiologist with particular ultrasound Doppler study expertise at one place. Ethical approval for the current study was obtained from the local Institutional Ethics Review Board.

Descriptive statistics for continuous variables were expressed as mean±standard deviation or median (minimum–maximum), whereas nominal variables were expressed as number and percentage (%). The significance of the difference between the mean values of the groups was evaluated using the Student's t-test, whereas the significance of the difference in the median values was evaluated using the Mann–Whitney U test. Categorical data were compared by chi-square distribution. One-way ANOVA was used to test the differences among the HPV (+) groups using Tukey as the post hoc test. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS for Windows version 22 software (SPSS Inc., Chicago, IL, USA).

Results

Patients with positive and negative HPV-DNA testing did not differ between each other in terms of age, BMI, parity, and cigarette use (Table 1).

Colposcopy was performed in a total of 78 out of 129 cases based on cytology results (n=39, 30.2%) and Hr-HPV (n=39, 30.2%). Of those, 28 (35.9%) cases were diagnosed with inflammation, 26 (33.3%) cases with CIN-I, 18 (23%) cases

with high level CIN, and 6 (7.7%) cases with cervical cancer. Histology of CIN-I and higher was defined as positive. Table 2 shows the comparison of the pathological coincidence rate between high-risk HPV and cytology.

Of the 129 cases, 39 were confirmed with Hr-HPV infection. The positive rate was 30.2%, pathological coincidence rate with a CIN-I or above was 64.1%, and 30.7% for a high level CIN or above. Hr-HPV positivity was 50% (25/50) for cases with CIN-I and above and 50% (12/24) for cases with a high level CIN or above.

Table 1. Characteristics of the patients

	HPV (+) group (n=67)	HPV (-) group (n=62)	p
Age (year)	42.86±9.49	42.04±9.49	0.61
BMI (kg/m^2)	26.93±4.48	28.31±3.66	0.054
Parity	2 (0-7)	3 (1–7)	0.24
Cigarette use (%)	21 (43.5)	27 (30.9)	0.14

Patients were divided into three groups for the Doppler (PI and RI) of UA and CA. Group 1 consisted of 39 patients with positive Hr-HPV, group 2 had 28 patients with positive HPV other than types 16 and 18, and group 3 was composed of 62 patients with negative HPV-DNA as a control group. CA-RI was statistically significantly lower in group 1 than in controls (p=0.0146) (Table 3).

For a detailed sub-analysis, patients were categorized as HPV (+) and HPV (–) in addition to HPV-16 (+), HPV-18 (+), and HPV other (+) groups in Table 4. RI of UA and also CA-RI was significantly lower in the HPV (+) group than in the controls (p=0.02 and p=0.03, respectively). In subsequent sub-analysis among patients with positive HPV-DNA (+), PI of UA was significantly higher in the HPV-16 (+) group than in the HPV-18 (+) group (p=0.04).

Cut-off values discriminating CIN-I or above from others by using receiver operating characteristic curve analysis of CA-RI, UA-RI, and UA-PI were 0.68 (area under the curve (AUC): 0.647), 0.84 (AUC: 0.545), and 2.40 (AUC: 0.534), respectively.

Table 2. Distribution of pathology results based on cytology results and Hr-HPV positivity

Cytology (n=39)	Pathological results					
	Inflammation (%)	CIN I (%)	CIN II (%)	CIN III (%)	Ca (%)	Pathological coincidence rate ≥ CIN, n/total (%)
Inflammation (n=7)	3 (42.8)	3 (42.8)	1 (14.4)	0	0	57.1
ASCUS (n=2)	1 (50)	1 (50)	0	0	0	50
LGSIL (n=25)	10 (40)	8 (32)	3 (12)	2 (8)	2 (8)	60
ASC-H (n=2)	0	0	1 (50)	1 (50)	0	100
HGSIL (n=3)	0	1 (33.3)	1 (33.3)	0	1 (33.3)	100
Hr-HPV (+) (n=39)	14 (35.9)	13 (33.3)	6 (15.4)	3 (7.7)	3 (7.7)	64.1

Table 3. Comparison of Doppler indices

	Group 1 vs Group 3			Group 2 vs Group 3			Group1 vs Group 2		
	Mean±SD		p	Mean±SD		P	Mean±SD		p
UA PI	2.53±0.85	2.52±0.55	0.80	2.29±0.39	2.53±0.55	0.29	2.53±0.85	2.29±0.39	0.07
UA RI	0.87±0.07	0,86±0.04	0.31	0.89±0.07	0,86±0.04	0.55	0.87±0.07	0.89±0.07	0.74
CA PI	1.78±0.63	1.63±0.28	0.19	1.66±0.62	1.63±0.28	0.14	1.78±0.63	1.66±0.62	0.14
CA RI	0.66±0.86	0.70±0.06	0.0146*	0.63±0.12	0.70±0.06	0.10	0.66±0.86	0.63±0.12	0.13
Age	40.68±8.50	42.11±8.13	0.31	46±10.1	42.11±8.13	0.08	40.68±8.50	46±10.1	0.0266*
BMI (kg/m^2)	26.05±3.90	28.32±3.63	0.0035*	28.19±5.01	28.32±3.63	0.88	26.05±3.90	28.19±5.01	0.23
Cervical length (mm)	21.3±7.15	17.37±1.87	<0.0001*	18.29±7.01	17.37±1.87	0.14	21.3±7.15	18.29±7.01	0.0027*
Parity	2.87±1.45	2.98±1.31	0.54	2.39±1.16	2.98±1.31	0.14	2.87±1.45	2.39±1.16	0.41

UA: Uterine artery; CA: Cervical artery; RI: Resistance index; PI: Pulsatility index; BMI: Body-mass index; Group 1: Cases with positive Hr-HPV; Group 2: Cases with positive HPV other than type 16 and 18; Group 3: Cases with negative HPV; *: p<0.05.

Table 4. Comparison of Doppler Indices according to HPV types

	HPV (+) (n=67)	HPV (-) (n = 62)	p	HPV 16 (+) group (n=28)	HPV 18 (+) group(n= 11)	HPV others (+) group (n= 28)	p
UA RI	0.84±0.35	0.86±0.59	0.02	0.87±0.07	0.85±0.05	0.84±0.05	0.27
UA PI	2.43±0.71	2.52±0.55	0.40	2.69±0.91*	2.10±0.49*	2.28±0.39	0.04
CA RI	0.65±0.10	0.70±0.60	0.03	0.68±0.09	0.63±0.04	0.63±0.12	0.20
CA PI	1.73±0.63	1.63±0.28	0.25	1.75±0.58	1.85±0.79	1.66±0.62	0.68

UA: Uterine artery; CA: Cervical artery; RI: Resistance index; PI: Pulsatility index; *: The mean difference is significant at the 0.05 level.

Table 5. Diagnostic performance of Doppler indices when combined with cytology results and the presence of Hr-HPV in discriminating CIN-I or above from below

	Sensitivity (%)	Specificity (%)	Positive predictivity of the test (%)
CVS	58.5	54.4	33.3
Hr-HPV	76.5	40.9	33.3
Doppler (CA RI)	64.7	61.4	18.2
CVS + Doppler (CA RI)	23.5	69.8	22.2
Hr-HPV + Doppler (CA RI)	29.4	70.7	25.0
Hr-HPV + CVS + Doppler (CA RI)	26.7	71.7	26.6
Doppler (UA PI)	63.8	61.2	47.5
CVS + Doppler (UA PI)	35.7	64.3	23.0
Hr-HPV + Doppler (UA PI)	31.8	68.2	36.1
Hr-HPV + CVS + Doppler (UA PI)	26.7	73.3	24.6
Doppler (UA RI)	60.4	51.8	20.8
CVS + Doppler (UA RI)	55.6	54.4	24.8
Hr-HPV+ Doppler (UA RI)	44.8	58.5	26.4
Hr-HPV+ CVS + Doppler (UA RI)	35.6	64.8	24.8

CVS: Cervico-Vaginal Smear Test; Hr-HPV: High risk – HPV; UA: Uterine artery; CA: Cervical artery; RI: Resistance index; PI: Pulsatility index.

Table 5 represents the sensitivity, specificity, and performance of the Doppler indices in assessing the diagnostic efficiency of alone and joint screening of the three indices for discriminating CIN-I or above from below. Cytology showed a moderate sensitivity of 58.5% and specificity of 54.4%, whereas testing Hr-HPV alone indicated a good sensitivity of 76.5% and moderate specificity of 40.9%. Combining Doppler indices with cytology and/or Hr-HPV testing significantly reduced the sensitivity and positive predictivity but improved the specificity. Combining the measurement of UA-PI with Hr-HPV slightly increased the positive predictivity when compared with testing Hr-HPV alone (36.1% vs. 33.3%).

Discussion

To our knowledge, this was the first study to evaluate the diagnostic performance of measuring PI and RI of UA and CA in colposcopically verified pre-invasive cervical cancer lesions and to investigate the relationship of cytology and Hr-HPV. Assessing the angiogenesis of the pre-invasive lesions alone represented higher sensitivity than cytology but lower than Hr-HPV testing in discriminating CIN-I or above in the present cohort study. In addition, including the uterine and cervical blood flow Doppler indices into the routine evaluation showed poor positive predictive performance.

Blood flow detection is practical and instant from the clinical point of view in daily practice. It is well shown that color Doppler sonography is effective in evaluating cervical carcinoma vascularization, showing the correlation with specific tumor characteristics, and predicting the therapeutic response to treatment.[9] Liberal use of transvaginal and transrectal ultrasound is being frequently used to determine the extent and size of the cervical tumor since transvaginal ultrasound is a non-invasive and easy to use method with almost no cost.[12, 13] It has been proven that vascularity of the invasive tumor assessed by transvaginal color Doppler ultrasound highly correlates with tumor size, parametrial invasion, lymph node metastasis, and response to neoadjuvant chemotherapy in histologically proven cervical carcinomas.[14, 15]

Assessing the velocimetric indices of UA and CA in the early period revealed some important changes in the present study. CA-RI was found to be significantly lower in patients with positive HPV and, in particular, with positive Hr-HPV. Although positive predictivity was found to be low when embedded into the joint screening, we believe that assessing the CA-RI may still warn clinicians since it was shown that increased vascularization and therefore the lower RI is related to cervical cancer as a prognostic and response to treatment factor.[9, 16] Dalstein et al. [17] followed 781 women for a median period of 22 months, and more than half of the women with positive Hr-HPV at entry were cleansed at 7.5 months. They found that the outcome is strongly related

to the viral load at entry and the persistence. We speculate that the viral load or persistence may have resulted with a difference in CA-RI in the current study. The changes in cervical blood flow detected by Doppler sonography may predict the persistence and reflect the viral load that should be evaluated in future studies.

Landt et al.[18] evaluated the difference in concentrations of circulating angiogenic factors at different clinical tumor stages. Although all angiogenic factors were found within the normal ranges, the changes in angiogenin, endostatin, and endoglin levels were significantly different between non-invasive, invasive, and recurrent stages in cervical cancer. We believe that the differences in Doppler indices of UA and CA between Hr-HPV positivity and specific HPV genotypes in the present study are consonant with Landt et al. Doppler sonography was successfully used in an animal study by Goertz et al. [19] to detect changes in tumor blood flow after the injection of human melanoma cells and after anti-vascular molecular therapy. Although joint screening with Doppler indices failed in the present study, a similar approach to Goertz et al. may be used by combining Doppler flow assessment of CA and UA with the serum angiogenic factors to select patients for antiangiogenic therapy.

The analysis of the difference in Doppler indices revealed that only UA-PI was different between HPV-16, HPV-18, and other HPV positive cases in the present study. UA-PI was significantly lower in patients with positive HPV-18 testing than in those with HPV-18 and other HPV type positive cases. Cremoux et al. [20] analyzed the prognostic value of HPV genotypes in cervical cancer in their large retrospective study. The outcome of HPV-16- and HPV-18-associated tumors was not significant at a long follow-up; however, it has been shown that HPV-18-associated tumors frequently had earlier relapse than HPV-16, and adenocarcinoma was preferentially related to HPV-18. The authors consider that the link between specific HPV genotypes and prognosis is also theoretically important in future immunotherapy options.[20]

Liang et al.[21] recently investigated the diagnostic performance of a triple-screening approach. They performed cytology and Hr-HPV testing and measured vascularization index (VI) by three-dimensional (3D) color power angiography to all eligible patients, and colposcopic biopsy was performed in patients with a positive result of any of those three examinations. VI was defined and categorized according to the shape and distribution of cervical vessels and branches with 3D reconstruction. They found that combining cytology and HPV testing with 3D vascular morphology significantly improves the accuracy of screening for cervical cancer. Their inclusion of angiogenesis as a criterion for colposcopic biopsy was the leading feature when compared with the current study and their previous study.[22]

The small size of this cross-sectional study and unilateral measurements were the other limitations of the present study. The inter- and intra-observer reproducibility was not assessed prior to the study; however, we believe that it has an irrelevant effect on the results since all the measurements were made by only one expert radiologist. We recommend future studies to include bilateral measurements with a large-sized longitudinal study.

Conclusion

Embedding the uterine and cervical blood flow Doppler indices into the routine cervical cancer screening showed poor positive predictive performance. The potential of the blood flow assessment by Doppler sonography was doubtful in discriminating CIN-I or above lesions in the early period. On the other hand, RI of UA and CA differed with regard to the presence of HPV infection, whereas CA-RI also differed in high-risk HPV cases. The initial findings of specific changes in blood flow indices depending on HPV infection may be used in future studies as markers to monitor persistence and viral load or to select patients for novel antiangiogenic therapies.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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