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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: It was aimed to investigate the diagnostic effectiveness of the uterine and cervical vascularity alone or by combining 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. Pulsatiliy (PI) and resistance (RI) indexes of uterine (UA) and cervical (CA) arteries were assessed by Doppler sonography. Pathological diagnosis was taken as the golden standard for assessment. Diagnostic efficiency of alone and joint screening of the three indexes for discriminating CIN-I or above from below was assessed.

Results: UA-RI and also CA-RI was significantly lower in HPV(+) group when compared to controls (p=0.02, p=0.03, respectively). In subsequent sub-analysis among patients with positive HPV-DNA, UA-PI was significantly higher in HPV-16(+) group when compared to HPV-18 (+) (p=0.04). Hr-HPV testing had the highest sensitivity compared to 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 the UA-PI with Hr-HPV slightly increased the positive predictivity when compared to testing Hr-HPV alone (36.1% vs. 33.3%).

Conclusion: Potential of the Doppler indices of uterine and cervical arteries was doubtful in discriminating CIN-I or above lesions in early period. Besides, RI of uterine and cervical arteries differed regarding to the presence of HPV infection while cervical artery RI differed in also 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 and the average risk of dying before age 75 is three times lower in developed regions than less developed regions, thus this brings a higher burden for developing countries.[1]

It was estimated 12.820 new cervical cancer cases and 4.210 estimated deaths in United States for 2017.[2] Cervical cancer is the second leading cause of death due to cancer in women aged 20 to 39 years with accounting one out of every ten cancer deaths, emphasizing the requirement 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 programmes for cervical cancer and the beneficial impact

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

High-risk human papillomaviruses (Hr-HPV) is known as the essential factor for the cervical cancer development and only a small percentage of HPV infected cases will progress to high-grade cervical intraepithelial neoplasia or cancer after a long latency period.[5] Recent metaanalysis showed that the specificity of the HPV-DNA testing is age-related and the specificity to detect CIN2 and above-grade lesions only overlap with cytology in women aged 30 and older despite its high sensitivity.[6] Women with positive Hr-HPV and negative cytology has relatively higher false-positivity.[7] Beside, 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 the cervical vascularity may alter the management of certain individuals with specific conditions in the early period with regard to HPV-DNA testing alone or combining with cytology. Thus it is aimed in this study 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 admitted to gynecologic out-patients clinic in a secondary state hospital for a routine control between 2015 and 2016 were enrolled in this prospective study.

Women younger than 30 and older than 65 years of age, hysterectomized for any causes, women with a history of any vaginal medical application or oral contraceptive use, cervical precancerous lesions or cervical conization, embolization of the uterine arteries and previous radiochemotherapy were excluded. 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 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 taken as the golden 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 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 taken from uterine and cervical arteries 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. Colour doppler USG assesment of cervical and uterine arteries were performed by the same ultrasonography device and by the same radiologist with particular ultrasound Doppler study expertise at one place. Ethical approval for the current study was obtained by the local Institutional Ethics Review Board.

The descriptive statistics for continuous variables were expressed in mean±standard deviation or median (minimum-maximum), while nominal variables were expressed in the number and percentage (%). The significance of the difference between the mean values of the groups was evaluated using the Student's t-test, while the significance of the difference in the median values was evaluated using the Mann-Whitney U test. Categorical data was compared by Chi-square distribution. One-way ANOVA was used to test differences among HPV (+) groups with Tukey as the post hoc test. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using 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 to a total of 78 out of 129 cases

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

based on cytology results (n=39, 30.2%) and HrHPV (n=39, 30.2%). Of those, 28 cases (35.9%) were diagnosed with inflammation, 26 cases with CIN-I (33.3%), 18 cases (23%) with high level CIN and 6 cases (7.7%) with cervical cancer. Histology of CIN-I and higher was defined as positive. Comparison of the pathological co-incidence rate between high-risk HPV and cytology can be seen at Table 2.

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

Patients were divided into 3 groups for the Doppler (PI, RI) of uterine and cervical arteries. Group 1 consisted of 39 patients with positive Hr-HPV, group 2 had 28 patients with positive HPV other than type 16 and 18, group 3 consisted of 62 patients with negative HPV-DNA as a control group. Cervical artery RI was statistically significantly lower in group 1 when compared to 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 others (+) groups in Table 4. RI of the uterine artery and also cervical artery RI was significantly lower in HPV (+) group when compared to controls (p=0.02, p=0.03, respectively). In subsequent sub-analysis among patients with positive HPV-DNA (+), PI of uterine artery was significantly higher in HPV 16 (+) group when compared to HPV 18 (+) (p=0.04).

Cut-off values discriminating CIN-I or above from others by

Table 2. Distribution of pathology results based on cytology results and HrHPV positivity

Cytology (n=39)	Pathological results					
	Inflammation	CIN I	CIN II	CIN III	Ca	Pathological co-incidence 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.

using Receiver Operating Characteristics (ROC) curve analysis of cervical artery RI, uterine artery RI and uterine artery PI were 0.68 (AUC: 0.647), 0.84 (AUC: 0.545) and 2.40 (AUC: 0.534), respectively.

Table 5 represents sensitivity, specificity and the performance of the Doppler indices in assessing the diagnostic efficiency of alone and joint screening of the three indexes for discriminating CIN-I or above from below. Cytology showed a moderate sensitivity with 58.5% and specificity of 54.4% while testing Hr-HPV alone indicated a good sensitivity with 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 uterine artery pulsatility index with Hr-HPV slightly increased the positive predictivity when compared to testing Hr-HPV alone (36.1% vs. 33.3%).

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.

Discussion

As far as we know, this was the first study evaluating the diagnostic performance of measuring pulsatility and resistance indices of uterine and cervical arteries in colposcopically verified pre-invasive cervical cancer lesions and investigation the relation with the cytology and Hr-HPV. Assessing the angiogenesis of the pre-invasive lesions alone represented higher sensitivity when compared with cytology but lower than Hr-HPV testing in discriminating CIN-I or above in the present cohort study. Beside, 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 evaluation of cervical carcinoma vascularization and in showing the correlation with specific tumor characteristics and in predicting the therapeutic response to treatment.[9] Liberal use of transvaginal and transrectal ultrasound is getting frequently used to determine the extent and size of the cervical tumour since TVU is a non-invasive and easy to use method with almost no-cost.[12, 13] It has been proven that vascularity of the invasive tumour assessed by transvaginal colour Doppler ultrasound highly correlates with the tumour size, parametrial invasion, lymph node metastasis and response to neoadjuvant chemotherapy in histologically proven cervical carcinomas.[14, 15]

Assessing the velocimetric indexes of uterine and cervical arteries in the early period revealed some important changes in the present study. Cervical artery resistance index 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 think that assessing the CA-RI

may still warn clinicians since it was shown that increased vascularization and therefore the lower RI is related to the cervical cancer as a prognostic and response to treatment factor.[9, 16] Dalstein et al 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 7.5 months.[17] They found that the outcome was strongly related to the viral load at entry and the persistence. We speculate that the viral load or persistence may have been 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 which should be evaluated in future studies.

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

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

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

The small size of this cross-sectional study and unilateral measurements were the other limitations of this study. The inter and intra-observer reproducibility was not assessed prior to the study, however, we think that has irrelevant effect on the results since all the measurements were taken 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. 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, resistance index of uterine and cervical arteries differed regarding to the presence of HPV infection while cervical artery RI differed in also high-risk HPV cases. Initial findings of specific changes in blood flow indices depending on HPV infection may be used in future studies as markers to monitor persistance 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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