

Original Research Article

Comparison of clinicopathological characteristics of endogenous and exogenous cervical cancer with its clinical significance

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ABSTRACT

Background: Cervical cancer is the third leading cause of cancer death in women of less developed countries due to poor screening and decreased diagnostic approaches. We aimed to investigate and differentiate the distinct clinicopathological characteristics and prevalence of endogenous and exogenous cervical in hospitalized patients.

Methods: A study was performed contained 663 patients that were enrolled and underwent for screening of endogenous and exogenous cervical cancer in Qilu Hospital of Shandong University, from January 2010 to March 2015.

Results: Our results indicated that combined examination of thin-prep liquid-based cytology test and human papillomavirus (HPV)-DNA are effective for diagnosis of endogenous and exogenous cervical cancer. The clinicopathological characteristics based on tumor growth pattern, and high risk HPV-DNA incidence had no significant difference ($p > 0.05$) in endogenous and exogenous cervical cancer patients. The higher ratio of lymph node metastasis in endogenous cervical cancer and exogenous cervical cancer during IB1-stage (24.3% vs 12.9%), and in IIA2-stage (36.4% vs 25%) was observed respectively. In addition, our data provide compelling evidence that the level of deep interstitial infiltration, and lymphatic vascular infiltration in endogenous cervical cancer was collectively higher (82.7% and 33%) compared to exogenous cervical cancer (62.4% and 18.3%) respectively during all stages.

Conclusions: The higher percentage of lymph node metastasis, deep interstitial infiltration, and lymphatic vascular infiltration was observed in endogenous cervical cancer which might be the biomarker and differential key points for the diagnosis of endogenous cervical cancer. Taken together, our study provides clinicopathological features to diagnose, and differentiate the endogenous and exogenous type cervical cancer with its prevalence.

Keywords: Cervical cancer, Endogenous cervical cancer, Exogenous cervical cancer, Lymph node metastasis

INTRODUCTION

Cancer is fetal disease and leading cause of death worldwide by affecting more than 17 million people.¹ Different survey reports have shown that around 8.5 million deaths occur per year related to cancer and 9.5 million deaths occur in 2018, while the number of death due to cancer are exceeding compared with death from other leading disorders including human immune

deficiency virus, malaria and tuberculosis combined.² Globally, the rate of cancer suffering patients increasing dramatically and estimated to be more than 23.6 million new cases by 2030.³ Another report have determined that more than 50% of all cancer cases are reported in low and middle-income countries and the ageing population and also western life style adaptations potentially increasing the case prevalence.^{4,5}

Cervical cancer is the fourth most commonly diagnosed female malignancy affecting the reproductive system and is third leading cause of death among women in developing countries.⁶ Previous reports have shown that the cases of cervical cancer increasing rapidly with 50% death rate.⁷ Based on statistical survey analyses, the morbidity of cervical cancer in China is high with one-third of total worldwide cervical cancer cases.⁸ According to epidemiological reports, recently the cases of cervical cancer in young age women are increasing rapidly compared with aged women.⁹⁻¹² Few reports showed that young women with cervical carcinoma had low prognosis and survival rate compared with elder women.^{13,14} Conversely, different researchers have found no relationship of cervical cancer with aging.^{15,16}

Based on tumor growth, cervical cancer is divided into four types including, exogenous, endogenous, ulcerative and cervical canal type. Exogenous and endogenous cervical cancer is the most common type with typical symptoms and clinicopathological features. Exogenous cervical cancer has papillary or cauliflower-like brittles, and highly affecting the vaginal part of reproductive tract compared to other reproductive structure. Endogenous cervical carcinoma is deep infiltration into the cervix with no obvious abnormalities on the surface. Ulcerative is exogenous and endogenous type cervical cancer continues to develop and causes infection necrosis by forming a crater-like ulcer or cavity inside the cervix. Cervical canal type also affects the lower segment of the cervix and uterus of female reproductive tract.

The persistent infection of high-risk human papilloma virus (HPV) is the leading cause of cervical oncogenesis.^{17,18} HPV is most commonly sexually transmitted infection worldwide and more than 80% women and men effected with this disease at some stage of life. The reliable screening test availability and techniques for diagnosis of cervical cancer including, HPV detection, liquid based cytology, and biopsy technique could make feasible to detect precancerous lesion and intervene during early stage of disease.¹⁹ Recently, cervical cytological based screening proved effective tool to improve the cervical cancer diagnosis.²⁰ Although, cervical cancer is curable at early stage by the applications of different medical therapies but still morbidity and mortality is high due to poor diagnosis of different clinicopathological features of cervical cancer. Hence, there is an urgent need for further study for systematic and retrospective analyses to diagnose and differentiate different types of cervical cancer based on lab experimental examination with relevant clinical data.

In this study we performed detailed comparative systematic analyses of 663 patients suffering in endogenous and exogenous cervical cancer by using different diagnostic techniques including thin-prep liquid-based cytology test (TCT) and HPV-DNA, CT examination, and ultrasonography. We observed that combined examinations of TCT and HPV-DNA for

cervical cancer patients diagnosis has more efficacy compared to performed separately. Based on tumor growth pattern and high risk HPV-DNA examination, no difference was observed in endogenous and exogenous cervical cancer. However, endogenous cervical cancer indicated more ratios of pathological features including, lymph node metastasis, deep interstitial infiltration, and lymph vascular infiltration compared to exogenous cervical cancer.

METHODS

Cervical cytology examination

Cervical cytology was performed by TCT. Samples were taken according to the instructions of the US New Berthner TCT detector. By following instructions, cervical cells were collected from the cervical canal of all participants with plastic brushes and placed into vials of ThinPrep® PreservCyt® solution for cytology. Thin layer slices with a diameter of 2 cm were prepared by the program treatment of ThinPrep 2000 system, and then fixed by 95% ethanol and stained by pap staining to observe heterotypes in cervical epithelial cells. Cytological diagnosis was performed by the 2001 TBS classification system (the Bethesda system).

The TBS diagnosis report is as follows: negative for intraepithelial lesion or malignancy, including normal and inflammation; squamous cell abnormalities, including atypical squamous cells (ASC), squamous intraepithelial lesions (SIL) and squamous cell carcinoma (SCC); glandular cell abnormalities, including atypical glandular cells (AGC) and adenocarcinoma. ASC includes atypical squamous cells undetermined significance (ASC-US), atypical squamous cells, and high-grade squamous intraepithelial lesion (ASC-H). SIL including, low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL).

HR-HPV detection

The hybrid capture 2 (HC2) technology provided by Digene is used to detect the HPV-DNA content in cervical secretion samples. The 96-well plate method is adopted for HC2, which can detect 13 high-risk HPV at one time (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). Using a HPV sampler (digene), inserted into the outer cervix, turned 5 times clockwise or counterclockwise, and slowly take out the sampler and then put into the vial containing the preservative solution. The sample was stored -20 °C before deliver to the laboratory for examination.

The test results were analyzed by the ratio (RIUs/CO) obtained by dividing the RIUs value of the tested cervical secretion sample by the positive control value (CO). RIUs represents the measurement unit of light (i.e. relative light units), and CO represents the positive

control value (i.e., RIUs value at the concentration of hr-HPV DNA in the solution at 1.0 pg/ml). The RIUs/CO value of specimens' ≥ 1.0 is positive; RIUs/CO value less than 1 is negative.

Statistical analysis

SPSS 20 software was used for the analysis of the composition ratio and non-parametric test. The chi-squared test and RxC chi-squared test served to compare the composition ratio, and rank sum test was adopted for the non-parametric test, $p < 0.05$ was considered statistically significant. Binary logistic regression analysis was conducted by SPSS 17 software.

RESULTS

Clinicopathological features of study groups

From January 2010 to March 2015, 1034 cases of cervical cancer were hospitalized and surgically treated in the Department of Obstetrics and Gynecology, Qilu Hospital of Shandong University, China. However, our study included endogenous and exogenous cervical cancer cases. The characteristics of patients and case parameters are presented in Table 1. This study included

a total of 663 cases with 188 endogenous type cervical cancer of different stages including, 111 cases in IB1 stage, 39 cases in IB2 stage, 27 cases in stage IIA1, and 11 cases in stage IIAII (Table 1). In exogenous cervical cancer type, there were 475 cases, including 278 cases of IB1-stage, 113 cases of IB2-stage, 56 cases of stage IIA1, and 28 cases of stage IIA2. The mean age of endogenous cervical cancer cases and exogenous cervical cancer cases is 47.7 ± 9.0 years old and 45.7 ± 9.6 years old, respectively. No significant difference in the distribution of staging was observed between endogenous and exogenous cervical cancer cases ($p > 0.05$).

The cases were identified and treated based on symptoms including, irregular vaginal bleeding,

irregular vaginal fluid, and contact bleeding. In endogenous cervical cancer, 95 out of 188 (50.5%) cases of irregular vaginal bleeding, 90 out of 188 (48%) cases of irregular vaginal fluid, and 70 out of 188 (37.2%) cases of contact bleeding were included respectively. The endogenous cervical cancer cases included, 230 out of 475 (48.4%) irregular vaginal bleeding, 208 out of 475 (43.8%) irregular vaginal fluid, and 208 out of 475 (43.8%) contact bleeding (Table 1).

Table 1: Clinicopathological features of study groups.

Growth pattern	Age (years) Mean±SD	Cases					Case symptoms		
		IB1	IB2	IIA1	IIA11	Total	Irregular vaginal bleeding	Irregular vaginal fluid	Contact bleeding
Endogenous cervical cancer	47.7±9.0	111	39	27	11	188	95/188 (50.5%)	90/188 (48%)	70/188 (37.2%)
Exogenous cervical cancer	45.7±9.6	278	113	56	28	475	230/475 (48.4%)	208/475 (43.8%)	208/475 (43.8%)

Table 2: Comparison of clinicopathological features of endogenous cervical cancer and exogenous cervical cancer.

Growth pattern	Endogenous cervical cancer		Exogenous cervical cancer	
	Number	Percentage (%)	Number	Percentage (%)
TCT results				
Inflammation	15	16.5	37	18.7
ASCUS	23	25.3	45	22.7
ASCUS-H	14	15.4	24	12.1
LSIL	6	6.6	20	10.1
HSIL	26	28.6	53	26.8
CA	7	7.7	19	9.6
Total	91	100	198	100

Pathological risk factors percentage in endogenous and exogenous cervical cancer patients

The difference between endogenous and exogenous cervical cancer patients were observed on the basis of growth pattern by new Bai's liquid-based TCT. The results indicated no significant difference ($p > 0.05$) in clinicopathological features including, inflammation

(16.5% vs 18.7%), atypical squamous cells undetermined significance (ASCUS) (25.3% vs 22.7%), atypical squamous cells of undetermined significance of high grade (15.4% vs 12.1%), LSIL (6.6% vs 10.1%) or HSIL (28.6% vs 26.8%) and cancer cells (7.7% vs 9.6%) in endogenous and exogenous cervical cancer respectively (Table 2). In comparison of high-risk HPV infection between two groups by HPV DNA testing, no significant difference was detected in accumulation of HPV

infection in both endogenous and exogenous cervical cancer patients (Table 3). These results suggest that the chance of different pathological risk factors and HPV

infection percentage probability is same in both exogenous and endogenous type cervical cancer.

Table 3: Comparison of high-risk HPV-DNA between endogenous and exogenous cervical cancer.

Growth pattern	Positive	Negative	16/18 positive	16/18 negative
	N (%)	N (%)	N (%)	N (%)
Endogenous cervical cancer	67 (88.2)	09 (11.8)	21 (80.8)	5 (19.2)
Exogenous cervical cancer	154 (89.3)	19 (10.7)	51 (78.5)	14 (21.5)

Table 4: Imaging comparison between endogenous and exogenous cervical cancer.

Type	Imaging	Cervical enlargement	Normal	Uterine cavity	Total abnormalities
		N (%)	N (%)	N (%)	
Endogenous cervical cancer	Gynecological ultrasound	106 (62.0)	61 (35.7)	4 (2.3)	171
	CT of pelvic	58 (86.6)	08 (11.9)	1 (1.5)	67
Exogenous cervical cancer	Gynecological ultrasound	243 (58.6)	167 (40.2)	5 (1.2)	415
	CT of pelvic	165 (91.7)	14 (7.8)	1 (0.6)	180

Table 5: Comparison of staged lymph node metastasis of endogenous and exogenous cervical cancer.

Type staging	Endogenous cervical cancer			Exogenous cervical cancer		
	Positive	Negative	Positive rate (%)	Positive	Negative	Positive rate (%)
I B1	27	84	24.3	36	242	12.9
I B2	14	25	35.9	33	80	28.0
II A1	7	20	25.9	13	43	23.2
II A2	4	7	36.4	7	21	25.0
Total	52	136	27.7	89	386	18.7

The endogenous and exogenous cervical cancer abnormalities were estimated on imaging-based analysis. The ultrasonography and CT examination of pelvic region showed no significant difference in cervical enlargement among both endogenous and exogenous cervical cancer (106/171=62%, 243/415=58.6%; 58/67=86.6%, 165/180=91.7%) respectively (Table 4). In addition, the cervical enlargement and uterine cavity abnormalities were also determined by ultrasound imaging and CT of pelvic, and data revealed higher percentage of uterine cavity abnormalities in endogenous cervical cancer compared with exogenous cervical cancer (2.3% vs 1.2% by ultrasonography; 1.5% vs 0.6% by CT of pelvic) (Table 4) respectively.

Comparison of staged lymph node metastasis of endogenous and exogenous cervical cancer

Lymph node metastasis is divided into different stages from earlier to later stage including IB1, IB2, IIA1, and IIA2. We performed detailed lymph node metastasis comparison of both endogenous and exogenous cervical cancer at different stages. The results indicated higher positive rate of IB1 stage lymph node metastasis during endogenous cervical cancer 27 out of 111 (24.3%) compared to exogenous cervical cancer 36/278 (12.9%) (Table 5). A significant difference ($p < 0.001$) in positive

rate at IB1 stage was observed during endogenous cervical cancer. The percentage of lymph node metastasis during endogenous cervical cancer cases were also detected higher at different stages but no significant difference was noted compared to exogenous cervical cancer (Table 5). Collectively, higher percentage of lymph node metastasis cases were observed during endogenous cervical cancer 52 out of 188 (27.7%) compared to exogenous cervical cancer 89 out of 475 (18.7%) and a statistical difference was noted during all cases examination ($p < 0.05$).

Comparison of cervical interstitial infiltration and lymphatic vascular infiltration in endogenous and exogenous cervical cancer

Next, we observed and compared the depth of cervical interstitial infiltration among endogenous and exogenous cervical cancer patients. The results had shown that all stages including IB1, IB2, IIA1 and IIA2 revealed higher positive rate of cervical interstitial infiltration during endogenous cervical cancer cases compared with exogenous cervical cancer, however the IB1 stage showed significant difference ($p < 0.001$) in positive cases 82 out of 108 (75.9%) of cervical interstitial infiltration during endogenous cervical cancer compared to exogenous cervical cancer cases 126 out of 253 (49.8%)

(Table 6). The higher interstitial infiltrations ratio was also detected in IIA1 and IIA2-stages of endogenous cervical cancer compared with exogenous cervical cancer (Table 6). Taken together, the percentage of cervical interstitial infiltration regarding cases of all stages was significantly higher in ($p < 0.001$) endogenous cervical

cancer 153 out of 185 (82.7%) in comparison with endogenous cervical cancer 279 out of 447 (49.8%) (Table 6). These results suggest cervical interstitial infiltration at IB1 stage might be the biomarker for patients suffering in endogenous cervical cancer which might be valuable for screening.

Table 6: Comparison of depth of cervical interstitial infiltration between endogenous and exogenous cervical cancer.

Type staging	Endogenous cervical cancer			Exogenous cervical cancer		
	≥1/2	<1/2	Positive rate (%)	≥1/2	<1/2	Positive rate (%)
I B1	82	26	75.9	126	127	49.8
I B2	37	2	94.9	93	18	83.8
II A1	23	4	85.2	37	18	67.3
II A2	11	0	100	23	5	82.1
Total	153	32	82.7	279	168	62.4

Table 7: Comparison of lymphatic vascular infiltration in endogenous and exogenous cervical cancer.

Type staging	Endogenous cervical cancer			Exogenous cervical cancer		
	Positive	Negative	Positive rate (%)	Positive	Negative	Positive rate (%)
I B1	36	75	32.4	50	228	18.0
I B2	14	25	35.9	24	89	21.2
II A1	9	18	33.3	9	47	16.1
II A2	3	8	27.3	4	24	14.3
Total	62	126	33.0	87	388	18.3

We also determined the lymphatic vascular infiltration in both types of cervical cancer during different staging. The results revealed that endogenous cervical cancer during all staging IB1, IB2, IIA1 and IIA2 showed higher lymphatic vascular infiltration compared with exogenous cervical cancer patients and statistically significant difference ($p < 0.001$) was observed in positive cases (Table 7). Collectively, higher lymphatic vascular infiltration in endogenous cervical cancer cases 62 out of 188 (33%) were detected compared to exogenous cervical cancer 87 out of 475 (18.3%) (Table 7). Taken together, these results suggest that lymph node metastasis, cervical interstitial infiltration and lymphatic vascular infiltration might be the possible screening tools to diagnose and differentiation among endogenous and exogenous cervical cancer patients.

DISCUSSION

Previous studies have shown that the rate of cervical cancer is decreasing in different regions of the world, however the incidence of cervical cancer is still high in Asian countries.^{21,22} According to epidemiological survey reports more than 78% cervical cancer cases occurred in developing countries, where second most death cause in women is due to cervical cancer.²³ In China the morbidity of cervical cancer is high which is estimated one-third of the worldwide cases, and is considered major health issue.¹⁶ The main reason of high prevalence in that region is due to lack of proper screening and diagnosis of patients suffering in cervical cancer.

In our study, we have shown that liquid based TCT and high risk HPV-DNA combined examination is effective tools to diagnose and differentiate in endogenous and exogenous cervical cancer on the basis of growth pattern. The prevalence of endogenous and exogenous cervical cancer was similar by TCT and high risk HPV-DNA detection analysis. HPV infection is considered the major cause of cervical cancer in women age more than 35 year. In some region of China the prevalence of HPV was estimated 15-22% which is comparable with our study.²⁴⁻²⁶ Conversely, a report indicated the prevalence of HPV infection in Shandong region was found to be 11% in women enrolled in the hospital.²⁷

We also examined the cervical enlargement and uterine cavity abnormalities in both type of cervical cancer based on imaging methods, and data revealed more percentage of uterine cavity abnormalities in endogenous cervical cancer. In addition, our data indicated that the percentage of lymph node metastasis was higher in endogenous cervical cancer compared to exogenous cervical cancer. Initial evaluation of cervical cancer based on staging is essential for prognosis and treatment in less developing countries rather than surgical staging.²⁸ Previous report also indicated the higher lymph node metastasis in cervical cancer patients and identified a significant prognostic factor.¹⁶ It was determined that instability in HPV caused by transforming growth factor influence the accumulation of lymph node metastasis which is estimated cervical cancer predictor.²⁹ Recent report indicated the percentage of lymph node metastasis

involvement in cervical cancer (25.8%), which is comparable with our study results.³⁰ Another study have shown the significance relevance of lymph node metastasis with clinicopathological features of cervical cancer.³¹

Finally, our study also has shown the higher deep cervical interstitial infiltration and lymphatic vascular infiltration in endogenous cervical cancer, which is essential determinant for cervical cancer prognosis, and also to differentiate endogenous cervical cancer from exogenous cervical cancer. Cervical interstitial infiltration refers to cervical tissue involvement with interstitial infiltrations in measured with depth and width. According to recent report, the depth of interstitial infiltration during stage 1A1 should not exceed from 3mm. In our data the depth of interstitial infiltration in women with endogenous cervical cancer was high with increased percentage of positive cases in all stages compared with exogenous cervical cancer. In addition, the lymphatic vascular infiltration, the high risk factor for cervical cancer was found to be in higher percentage during all stages of endogenous cervical cancer which might be the effective biomarker for diagnosis.

CONCLUSION

In conclusion, our study provides distinct pathological features to diagnose and differentiate endogenous cervical cancer patients from exogenous cervical cancer patients based on uterine abnormalities, lymph node metastasis, cervical interstitial infiltration, and lymphatic vascular infiltration.

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