Research Report

The Correlation of Decreased E-Cadherin and β1-Integrin Expression with the Depth of Myometrial Invasion and Pelvic Lymph Node Metastasis in Resectable Endometrial Cancer

Hubungan antara penurunan E-Cadherin dan Ekspresi β1-Integrin dengan Kedalaman Invasi Miometrial dan Metastasis Kelenjar Getah Bening pada Kanker Endometrial yang Masih Dapat Direseksi

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Abstract

Objective: The purpose of this study was to determine the correlation between decreased E-Cadherin and β1-integrin expression in resectable endometrial cancer with the depth of myometrial invasion and pelvic lymph node metastasis.

Method: This was a cross sectional study, we used immunohistochemistry examination on E-Cadherin and β1-integrin expression in resectable endometrial cancer patients who had surgery in 1997 to 2006 in Dr. Cipto Mangunkusumo Hospital and searched the correlation with the depth of myometrial invasion and pelvic lymph node metastasis.

Result: The prevalence of endometrial cancer from 1997 to 2006 in Dr. Cipto Mangunkusumo Hospital was 7.0 in a year. Out of 64 patients with endometrial cancer only 36 paraffin block could be found and immunostaining on E-Cadherin and β1-integrin was done in 30 samples. Decreased E-Cadherin and β1-integrin expression was associated with the depth of myometrial invasion, pelvic lymph node metastasis, lymph ovascular space involvement and degree of differentiation in resectable endometrial cancer patients.

Conclusion: Decreased E-Cadherin and β1-integrin expression was associated with the depth of myometrial invasion and pelvic lymph nodes metastasis.

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Keywords: E-Cadherin, β1-integrin, the depth of myometrial invasion, pelvic lymph node metastasis

Abstrak

***Tujuan**: Penelitian ini dibuat untuk membuktikan apakah penurunan ekspresi E-Cadherin dan β1-integrin pada penderita kanker endometrium berhubungan dengan kejadian kedalaman invasi miometrium dan metastasis kelenjar getah bening pelvis.*

***Metode**: Ini adalah penelitian retrospektif. Dilakukan pemeriksaan ekspresi E-Cadherin dan β1-integrin secara imunohistokimia pada penderita kanker endometrium yang telah dioperasi tahun 1997 - 2006 di Rumah Sakit Dr. Cipto Mangunkusumo dan mencari hubungan dengan kejadian invasi miometrium dan metastasis kelenjar getah bening.*

***Hasil**: Kejadian kanker endometrium tahun 1997 - 2006 di Rumah Sakit Dr. Cipto Mangunkusumo adalah 7,0 pertahun. Dari 64 penderita kanker endometrium hanya 36 yang ditemukan blok parafinnya dan hanya 30 sampel yang dapat diperiksa ekspresi E-Cadherin dan β1-integrin secara imunohistokimia. Diperoleh hasil bahwa penurunan ekspresi E-Cadherin dan β1-integrin berhubungan dengan kejadian invasi miometrium, metastasis KGB pelvis, LVSI dan derajat diferensiasi sel penderita kanker endometrium.*

***Kesimpulan**: Ekspresi E-Cadherin dan β1-integrin yang menurun berhubungan dengan kedalaman invasi miometrium dan metastasis kelenjar getah bening pelvis.*

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***Kata kunci**: E-Cadherin, β1-integrin, invasi miometrium, metastasis kelenjar getah bening pelvis*

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INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy known worldwide. Its occurrence is increasing in the developed countries. According to the American Cancer Society, there were an estimated 40,100 new cases and 7,470 deaths due to endometrial cancer in 2008.[1,2]

Endometrial cancer is the fourth common cancer in woman after breast, lung and colorectal cancer. The risk for women to be diagnosed with endometrial cancer is approximately 2.45%.[3,4]

In Indonesia, according to the previous research of endometrial cancer in Dr. Cipto Mangunkusumo Hospital Jakarta, was found the prevalence of endometrial cancer were 7.2 cases in a year. The age of patients

tend to be younger than the age of patients in Europe and Western countries.[3,5]

Epidemiological, clinical, and experimental data indicated that the incidence of endometrial cancers were highly dependent on age, most of patient at 60 years of age. Approximately 75 percent of endometrial cancers occur red in postmenopausal women and the rest appeared among the premenopausal women. One of the mayor issues for young women with endometrial cancers are to maintain reproductive function and conservative treatment may be considered. But conservative treatment can only be done for endometrial cancer without invasion.

Hence the first incidence of endometrial cancer, there were no specific and accurate tools to detect endometrial cancer invasion and metastasis yet. To detect the depth of myometrial invasion pelvic ultrasonography, computerized tomography imaging and magnetic resonance imaging were used. However the accuracy of pelvic ultrasonography was only 69% and the accuracy of magnetic resonance imaging (MRI) was 74% in endometrial cancer stage I.[6]

Since we try to find another modality to detect the depth of myometrial invasion and metastasis in the reproductive women who suffer from endometrial cancer. The expression of cell adhesion molecules such as integrin and cadherin can be used to predict the invasion and metastasis of endometrial cancer. The cases of endometrial cancer without invasion and metastasis to myometrial may be considered to maintain the reproductive function in woman who still wants to get children.

One of the most characteristic features of cancer cell is invasion and metastasis. The invasion and metastasis themselves consist of sequential steps involving host-tumor interaction.[7]

Many gene play a significant role in the invasion and metastasis, such as E-Cadherin and β1-integrin as cell adhesion molecules. The decreased cell adhesion molecules such as E-Cadherin and β1-integrin allows cancer cells to leave the primary cancer nest. Detachment of cancer cells from the primary tumor mass may involved decreased expression of adhesion molecule such as E-Cadherin and β1-integrin.[7,8]

The roles of E-Cadherin in the invasion and metastatic processes had been shown in the research of breast and prostate cancer. There was a strong correlation between the lost of E-Cadherin expression with the invasion and metastatic processes.[8]

Moreover, invasion and metastatic processes, which are the most life-threatening properties of malignant tumors consist of sequential steps involving host-tumor interactions. The cancer cells first leave the primary cancer nest then invade the surrounding host tissue, enter the circulation, lodge in a distant vascular bed, extravasate into target organ and proliferate. The cancer cells can interact with collagen, fibronectin and laminin through the binding of these extracellular matrix (ECM) components to integrin.[7]

The integrins are a family of cell-surface glycoproteins that act as receptors for extracellular matrix protein, or as membrane bound counter-receptors on others cells. Integrin-mediated cell-ECM adhesion sites are complex specialized structures term focal contacts or focal adhesions. Each integrin is a heterodimer that contains an α and a β subunit with each subunit having a large extracellular domain, a single membrane-spanning region. The integrins receptors play a central role in cell migration through their roles as adhesive receptors for both other cells. While the extracellular matrix components play a significant role in the control of tumor cell invasion and metastasis.[7-9]

The present study demonstrated statistically significant that β1-integrin plays a critical role in the invasion and metastatic process. These results are in agreement with previous report on the mice that was injected by β1-integrin. The β1-integrin was believed to have block the melanoma progression into lymph nodes and blood vascular system, and also blocked the spread of the tumor to distant metastasis.[10]

METHOD

The design of this study was cross sectional study. We enrolled fifty six patients with endometrial carcinoma and were treated between June 1997 and November 2006. None of the patients received chemotherapy or radiotherapy before surgery. All patients were treated by total hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, and pelvic and para-aortic lymph node sampling as indicated.

The study was conducted for 6 months in the Subdivision of Oncology-Gynecology, Department of Obstetrics and Gynecology and Department of Pathology, Medical Faculty of Indonesia University/Dr. Cipto Mangunkusumo Hospital, Jakarta.

From 56 patients, only 36 paraffin blocks could be found at the Department of Pathology, Medical Faculty of Indonesia University/Dr. Cipto Mangunkusumo Hospital, Jakarta. However, only 30 paraffin blocks were capable for immunostaining on E-Cadherin and β1-integrin expression. Prior to E-Cadherin and β1-integrin staining, two experienced pathologists were blinded to the clinical data collected. The histologic grade, the depth of myometrial invasion, and the clinical stage were classified as recommended by the International Federation of Gynecology and Obstetrics (FIGO) of 1995. The staining results were compared to histologic and clinical data. The histologic features of the 30 endometrial cancer's patients are shown in Table 1.

The samples size calculation formula using two tailed unpaired proportion with the number of samples were at least 12 samples, to determine the correlation of decreased E-Cadherin and β1-integrin expression in resectable endometrial cancer with the depth of myometrial invasion and pelvic lymph node metastasis.

There were inclusion and exclusion criteria in this study. The inclusion criterias were patients who had undergone surgery at Subdivision of Oncology-Gynecology, Department of Obstetrics and Gynecology, Medical Faculty of Indonesia University/Dr. Cipto Mangunkusumo Hospital, Jakarta. The medical record of patients with endometrial cancer were obtained at the polyclinic of Oncology-Gynecology, Department of Obstetrics and Gynecology, while the paraffin blocks and pathological records were available at Department of Pathology.

The exclusion criterias were damaged paraffin blocks, stocks fall during staining, necrotic cells. Incomplete data from the Subdivision of Oncology-Gynecology of Obstetrics and Gynecology Department, Department of Obstetrics and Gynecology and Department of Pathology, Medical Faculty of Indonesia University/Dr. Cipto Mangunkusumo Hospital, Jakarta.

There were independent and dependent criterias in this study. Independent criterias were E-Cadherin and β1-integrin. Whereas dependent criterias were lymp nodes metastasis, myometrial invasion, LVSI (lymphovascular space involvement), and degree of differentiation.

The expression of E-Cadherin and β1-integrin were examined by immunohistochemical technique from endometrial tissue in paraffin blocks. The paraffin blocks section were cut at 4 μm, and were placed in stock that had been coated with poly lysine, then were leaved for around 60 minutes with temperatures of 56.5° – 60° Celsius. Then the 4 μm thick section of paraffin blocks were deparaffinized in xylen I for around 5 minutes and xylen II for around 5 minutes, and rehydrated through a graded series of etanol, after which they were rinsed shortly tribuffered saline. The samples section for E-Cadherin staining were incubated with primary antibody of CDH1, Ig I: 200 (DAKO) with solvent 3% NHS for one night and the samples section for β1-integrin staining were incubated with anti-Human CD29, Ig: 100 (BioGenex) for one night.

All data were tabulated into the parent table, then the frequency distribution, median (range), mean, and standard deviation were calculated. Calculation were made using Stata, version 7.0. We also performed univariate and bivariate analysis and statistical tests using simple logistic regression to look for Odd's ratio, $p < 0.05$ was considered to be significant. We performed Spearman and Fisher's exact test to determine the correlation of decreased E-Cadherins and β1-integrins expression with the depth of myometrial invasion, degree of differentiation, lymphovascular space involvement, lymph node metastasis.

Positive immunostaining of E-Cadherin and β1-integrin expression from endometrial tissue in paraffin blocks were scored semiquantitatively by two independent observers. For semiquantitative analysis of tumor cells staining, the percentage of positive cell was noted for approximately 500 cells per slide, subdivided into five selected fields at x 400 magnification. We used scoring system to assess the staining intensity of expression E-Cadherin and β1-integrin on tumor cells. Intensity scores of 0 (no staining) - 3 (maximal staining intensity) were assigned.[21]

Score 0 : No staining
Skor +1 : the intensity of stained is weak.
Skor +2 : the intensity of stained is moderate.
Skor +3 : the intensity of stained is strong.

A score was calculated as followed;

Score = Σ (i + 1) pi.

i = the intensity of the stained tumor cells.

pi = the percentage of the stained tumor cells for each intensity varying from 0% to 100%.

The intensity score was multiplied by the percentage of positive cells yielding a total staining score of 0 (minimum) - 400 (maximum). Variations between the observers were below 5%.

Score 00 - 10 : negative expression
Score 11 - 200 : weak expression
Score 201 - 300 : moderate expression
Score 301 - 400 : strong expression

RESULT

A total of 36 patients diagnosed as having endometrial carcinomas were enrolled in this study, but only 30 paraffin-embedded specimens were used to study the expression E-Cadherin and β1-integrin using immunohistochemical technique. The median age at diagnosis was 52.41 years (range, 30 - 72 years). The distribution of histological type, tumor stage, histological grade, and pelvic lymph node metastasis was in accordance with previously published clinical trials. (Table 1)

The staining pattern of tumor cells in paraffin blocks was diffuse and widespread, and almost all of tumor cells were stained for E-Cadherin and β1-integrin. However, there was clear differences in staining intensity. Fourteen (46.66%) of tumor cells showed weak expression of E-Cadherin and β1-integrin, while eleven (36.67%) of tumor cells showed moderate expression of E-Cadherin and β1-integrin and five (16.67%) of tumor cells showed negative expression of E-Cadherin and β1-integrin. But none of tumor cells showed strong expression of E-Cadherin and β1-integrin in this study.

Table 1. Histologic characteristics of the 36 patients with endometrial cancer.

Histopathology Characteristics	n = 36	
	N	(%)
Adenocarcinoma	33	91.67%
Adenoskuamosa	3	8.33%
Well differentiated	9	25%
Moderately differentiated	17	47.22%
Poorly differentiated	10	27.78%
Invasion < ½ myometrium	13	36.11%
Invasion ≥ ½ myometrium	23	63.89%
Negative LVSI	17	47.22%
Positive LVSI	19	52.78%
None peritoneal cytology	6	16.67%
Negative peritoneal cytology	21	58.33%
Positive peritoneal cytology	9	25%
Lymp nodes metastasis (-)	25	69.44%
Lymp nodes metastasis (+)	11	30.56%
Cervical stromal invasion	9	25%
Metastasis to abdominal	10	27.78%
None metastasis	17	47.22%

Table 2. Odds ratio of cells differentiation with myometrial invasion, LVSI, lymph node metastasis. n = 36 (p = 0.05).

	Grade 1	Grade 1,2	OR (95% CI) p value
Invasion :			
< myometrial	7	6	12.25 (1.99 - 75.19)
≥ myometrial	2	21	p = 0.007*
LVSI (–)	8	9	16 (1.72 - 148.41)
LVSI (+)	1	18	p = 0.015*
Lymp nodes (–)	7	18	1.75 (0.30 - 10.20)
Lymp nodes (+)	2	9	p = 0.534

Table 3. The correlation of E-Cadherin expression with myometrial invasion, LVSI, degree of differentiation, lymph nodes metastasis. n = 30 (p = 0.05).

	E-Cadherin			
	Negative	Weak positive	Moderate positive	p value (0.05)
Invasion < ½ myometrium	0	0	11	0.001*
Invasion ≥ ½ myometrium	5	14	0	
Negative LVSI	0	4	11	0.001*
Positive LVSI	5	10	0	
Well differentiated	0	2	6	0.045*
Moderately-poorly differentiated	5	12	5	
Lymp nodes metastasis (-)	0	8	11	0.001*
Lymp nodes metastasis (+)	5	6	0	

Table 4. The correlation of β1-integrin expression with myometrial invasion, LVSI, degree of differentiation, lymph nodes metastasis. n = 30 (p = 0.05).

	β1-integrin			
	Negative	Weak positive	Moderate positive	p value (0.05)
Invasion < ½ myometrium	0	0	11	0.001*
Invasion ≥ ½ myometrium	5	14	0	
Negative LVSI	0	4	11	0.001*
Positive LVSI	5	10	0	
Well differentiated	0	2	6	0.045*
Moderately-poorly differentiated	5	12	5	
Lymp nodes metastasis (-)	0	8	11	0.001*
Lymp nodes metastasis (+)	5	6	0	

DISCUSSIONS

A total of 30 paraffin-embedded specimens were used to study the expression E-Cadherin and β1-integrin using immunohistochemical analysis. Two experienced pathologists blinded to the clinical data reviewed all the tumors to confirm the diagnosis and to determine histologic characteristics. The histologic grade, the depth of myometrial invasion, and the clinical stage were classified as recommended by the International Federation of Gynecology and Obstetrics (FIGO) of 1995. The staining results were compared to histologic and clinical data (Table 1).

Endometrial cancer occurs in premenopausal and postmenopausal women. In this study we found that the median age at diagnosis was 52.41 years (range, 30 - 72 years). Fifteen (41.67%) patients were premenopausal. The highest incidence occurs between the ages of 50 - 59 years was 14 (38.89%). The patients aged over 50 years were 23 (63.89%), the result of this study was lower than previous study by Creasman who reached 90%.[28]

The number of pascamenopausal women was 21 (58.33%), the result of this study was lower then previous study in Europe who reached 75%, This is because the higher life expectancy in developed coun-

tries and the use of hormone replacement therapy (HRT). While the number of premenopausal women was 15 (41.67%), the result of this study was higher than the study by Hernandes who only reached 25%.[22] These results support the theory that the incidence of endometrial cancer had shifted to younger age. This becomes a concern because for young patients still need to maintain their reproductive function.

The mean age of menopausal women was 50.14 years, the result of this study was lower than the study by Sofian A, but this was in accordance with the study by Baziad A, which was 50 years old. Further more these results did not support the theory of late menopause.[5]

The mean menarche was 13.83 years with a range between 12 - 15 years. The early menarche was associated with the high risk of endometrial cancer incidence. This may be attributed to the faster arise menarch would be longer exposure to estrogen.[29]

Theoretically, the use of estrogen increase the incidence of endometrial cancer. However none of the samples used HRT in the study. This is probably because the patients of endometrial cancer who came to the RSUPN Dr. Cipto Mangunkusumo-Jakarta came from the low socio-economic level which was reflected in the low education level. The mean educational level of endometrial cancer patients was only 6 years (77.78%).

The histopathologic characteristics was shown in Table 1. The most frequently was endometrioid adenocarcinoma type (91.67%). The result of this study showed that most endometrial cancer patients were type I (estrogen dependent) with a better prognosis than type II (nonestrogen dependent).[13]

We sometimes found that the histopathology results of paraffin blocks were different with the histopathology results of curettage specimen, especially the cells type and degree of differentiation. But suitability analysis for histopathology results of paraffin blocks with histopathology results of curettage specimen using a correlation test showed cell type were 0.485 ($p = 0.003$), meaning that the diagnosis of cell type from histopathology results of curettage specimen were in accordance with the cell type from histopathology results of operation specimen, regardless of the number of specimen that had been sent to the laboratory. However, the results of correlation test for degree of differentiation we found was 0.505 ($p = 0.201$) for curettage specimen < 1cc, 0.378 ($p = 0.460$) for curettage specimen 1 - 3cc and 0.887 ($p = 0.008$) for curettage specimen > 3cc. These results showed that the degree of differentiation from histopathology results of operation specimen only in accordance with histopathology results of curettage specimen for curettage specimen more than 3cc. Hence ideally for degree of differentiation and cells type examination we need curettage specimen more than 3cc which should be sent to the Department of Pathology.

We also looked for odds ratio or predictive value from degree of differentiation to several variables with logistic regression test (Table 2). The tumor with moderately-poorly differentiated, the possibility of myometrial invasion > 50% was 12.25 times ($p = 0.007$), the possibility of positive LVSI 16 times ($p = 0.015$). In this study, the possibility of positive pelvic lymph node in moderately-poorly differentiated was only 1.7 times ($p = 0.534$). According to statistical calculation which received significant for moderately-poorly differentiated was associated with the positive myometrial invasion > 50% was 12.25 times compared to well differentiated and was associated with the possibility of positive LVSI (lymphovascular space involvement) was 16 times compared to well differentiated. But this was not significant for moderately-poorly differentiated associated with the possibility positive pelvic lymph node metastasis when we compared to well differentiated.

In Table 3 showed the correlation of E-Cadherin expression with myometrial invasion, LVSI, degree of differentiation, lymph node metastasis. The myometrial invasion < 50% were found 11 cases were moderate positive E-Cadherin expression, in contrast to myometrial invasion > 50% were found 14 cases were weak positive E-Cadherin expression and were found 5 cases were negative E-Cadherin expression, none of moderate positive E-Cadherin expression. So the deeper of myometrial invasion would decreased E-Cadherin expression. In this study we found that the decreased E-Cadherin expression was associated with the depth of myometrial invasion > 50% ($p = 0.001$). In Table 3 showed that all E-Cadherins expression were negative at the depth of myometrial invasion > 50%. In this study we concluded that E-Cadherin expression can be used as a predictor of the depth of myometrial invasion.

We found 4 cases were weak positive E-Cadherin expression, 11 cases were moderate positive E-Cadherin expression in negative LVSI. In contrast to positive LVSI, we found 5 cases were negative E-Cadherin expression, 10 cases were weak positive E-Cadherin expression and none of moderate positive E-Cadherin expression. The decreased E-Cadherin expression was associated with positive LVSI ($p = 0.001$). In Table 3 showed that all E-Cadherin expression were negative in positive LVSI. In this study, we concluded that E-Cadherin expression can be used as a predictor of lymphovascular space involvement (LVSI).

We found 2 cases were weak positive E-Cadherin expression, 6 cases were moderate positive E-Cadherin in well differentiated. In contrast to moderately-poorly differentiated, we found 5 cases were negative E-Cadherin expression, 12 cases were weak positive E-Cadherin expression and 5 cases were moderate positive E-Cadherin expression. The decreased E-Cadherin expression was associated with moderately-poorly differentiated ($p = 0.001$). In Table 3 showed that all E-Cadherin expression were negative in moderately-poorly differentiated. In this study, we concluded that E-Cadherin expresion can be used as a predictor of degree of differentiation

In negative lymph node metastasis, we found 8 cases were weak positive E-Cadherin expression and 11 cases were moderate positive E-Cadherin expression. In contrast to positive lymph node metastasis, we found 6 cases were weak positive E-Cadherin expression and 5 cases were negative E-Cadherin expression. The decreased E-Cadherin expression was associated with positive lymph node metastasis ($p = 0.001$). In Table 3 showed that all E-Cadherin expres-

sion were negative in positive lymph node metastasis. We concluded in this study that E-Cadherin expression can be used as a predictor of the depth of lymph node metastasis.

In Table 4 showed the correlation of β1-integrin expression with myometrial invasion, lymphovascular space involvement (LVSI), degree of differentiation, lymph node metastasis. We found 11 cases were moderate positive β1-integrin expression in the myometrial invasion < 50%. In contrast to the myometrial invasion > 50%, we found 14 cases were weak positive β1-integrin expression, 5 cases were negative β1-integrin expression and none of moderate positived β1-integrin expression. So the deeper of myometrial invasion would decreased β1-integrin expression. In this study we found that the decreased β1-integrin expression was associated with the depth of myometrial invasion > 50% (p = 0.001). In this study, we concluded that β1-integrin expression can be used as a predictor of the depth of myometrial invasion.

We found 4 cases were weak positive β1-integrin expression, 11 cases were moderate positive β1-integrin expression in negative LVSI. In contrast to positive LVSI, we found 5 cases were negative β1-integrin expression, 10 cases were weak positive β1-integrin expression and none of moderate positive β1-integrin expression. The decreased β1-integrin expression was associated with positive LVSI (p = 0.001). In Table 4 showed that all β1-integrin expression were negative in positive LVSI. We can concluded that β1-integrin E-Cadherin expression can be used as a predictor of the depth of lymphovascular space involvement.

We found 2 cases were weak positive β1-integrin expression, 6 cases were moderate positive β1-integrin in well differentiated. In contrast moderately-poorly differentiated, we found 5 cases were negative β1-integrin expression, 12 cases were weak positive β1-integrin expression and 5 cases were moderate positive β1-integrin expression. The decreased β1-integrin expression was associated with moderately-poorly differentiated (p = 0.001). In Table 4 showed that all β1-integrin expression were negative in moderately-poorly differentiated. We concluded that β1-integrin expression can be used as a predictor of degree of differentiation.

In negative lymph node metastasis, we found 8 cases were weak positive β1-integrin expression and 11 cases were moderate positive β1-integrin expression. In contrast to positive lymph nodes metastasis, we found 6 cases were weak positive β1-integrin expression and 5 cases were negative β1-integrin expression. The decreased β1-integrin expression was associated with positive lymph node metastasis (p = 0.001). In Table 4 showed that all β1-integrin expression were negative in positive lymph node metastasis. In this study, we concluded that β1-integrin expression can be used as a predictor of the depth of lymph node metastasis.

CONCLUSION

In conclusion, our study support the decreased E-Cadherin and β1-integrin expression in resectable endometrial cancer patients were associated with the depht of myometrial invasion, pelvic lymph node metastasis, lymphovascular space involvement, and degree of differentiation.

SUGGESTIONS

The mayor limitation of our study was the small sample size. A large number of endometrial cancer samples is needed for further research on other cell adhesion molecules. However, this study would be important because these finding clarified the relationship between cell adhesion molecules with the invasion and metastatic processes of endometrial cancer.

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