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Lymphovascular space invasion and positive peritoneal cytology are independent prognostic factors for lymph node metastasis and recurrence in endometrial cancer

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Summary

Aim: The aim is to identify the risk factors for recurrence and lymphatic metastasis of endometrial cancer. *Materials and Methods:* Patients who were operated primarily for endometrial cancer between 2010-2016 were included. Parameters such as stage, grade, histology, depth of invasion, cytology status, lymphovascular space invasion (LVSI), and tumor size were recorded. Univariate and multivariate logistic regression models were used to identify pathological predictors of lymphatic dissemination and recurrence. *Results:* A total of 278 patients were evaluated. Mean age was 60. 80% were Stage I, 10% were Stage III, and 4% were Stage IV, and 36.7% of patients had LVSI. Lymphadenectomy was performed in 56% of patients and lymphatic metastasis was observed in 7.1% of patients. In 13 patients, recurrence occurred; seven were loco-regional and six were distant. Three patients who had recurrence (3/13) were in early stage. With multivariate analysis, LVSI [OR = 8.826;1.874-41.576 (95%CI), $p = 0.006$] and positive cytology [OR = 9.503;1.811-49.876 (95%CI), $p = 0.008$] were independent factors for recurrence in endometrial cancer. Additionally, for lymphatic metastasis, LVSI [OR = 6.195;1.258-30.506 (95%CI), $p = 0.025$] and positive cytology [OR = 14.258; 2.330-87.247 (95%CI), $p = 0.004$] were found as significant risk factors. *Conclusion:* LVSI and positive cytology are significant risk factors for lymphatic metastasis and recurrence in endometrial cancer. Patients who had these risk factors should be followed-up more cautiously in terms of recurrence.

Key words: Endometrial cancer; Lymph node; Lymphovascular space invasion; Peritoneal cytology; Recurrence.

Introduction

Endometrial cancer is the most common gynecological cancer in developed countries [1]. Although there is no effective screening method for it, most of the patients are diagnosed at early stages because of early symptoms such as abnormal vaginal bleeding. Main treatment strategy depends on removal of uterus and adnexa. Lymphadenectomy is indicated as a part of staging procedure but in early stage patients, it is still controversial [2, 3]. Many strategies and algorithms regarding lymphadenectomy in apparently early stage patients have been implemented in the management of endometrial cancer. Radiotherapy is the main option for adjuvant therapy to obtain local control, where chemotherapy may be added in advanced stage patients. However the indication and/or route of radiotherapy are also controversial in patients with the disease confined to uterus.

Many prognostic parameters were discussed that some of them directly change the stage and some of them do not. Depth of myometrial invasion and cervical involvement are the main parameters for staging early endometrial adenocarcinomas (FIGO Stages I-II) [4]. Furthermore, some parameters such as age, histology, tumor size, grade, lymphovascular space invasion (LVSI), and peritoneal cytology were reported to have prognostic effects in endometrial cancer [5, 6].

One of the most challenging parts of endometrial cancer management is to identify the patient at risk of lymph node metastasis. Lymph node involvement, especially at early stages, is quite low, which is about 3.8% for pelvic lymph node and 0.8% for para-aortic lymph node metastasis in patients with FIGO Stage 1A, grade 1, endometrioid histology with tumor size less than 2 cm [7]. In this context, routine lymphadenectomy is not recommended and causes unnecessary intra/post-operative complications such as vascular injuries, lymphedema, and lymphocele [3].

The second problem is that the patient is placed at risk for recurrence. Adjuvant radiotherapy, especially for patients whose disease is confined to uterus is the cornerstone for obtaining local control. Patients who have indications for adjuvant radiotherapy are determined by some prognostic parameters such as age, stage, tumor grade, LVSI, and presence or absence of lymphadenectomy [8-10]. The other

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major point is that adjuvant radiotherapy does not improve overall survival in early stage patients [8-10]. Thus, identifying the high-risk patient for recurrence who is an optimal candidate for adjuvant therapy is crucial.

In this study, the authors aimed to investigate the risk factors for lymph node metastasis and recurrence in patients operated for endometrial carcinoma.

Materials and Methods

Patients who were operated for endometrial cancer between 2010-2016 in Ege University, Faculty of Medicine, Department of Obstetrics & Gynecology were reviewed retrospectively in this study. Ethical approval was obtained from local institutional committee. Demographic features such as age, body mass index, parity, and histopathological features like depth of myometrial invasion, histology, tumor grade, FIGO (2009) stage [4], LVSI, lymph node metastasis, and peritoneal cytology status were recorded. LVSI was defined as the presence of tumor cells in a vascular space lined by endothelium. Histology was evaluated according to World Health Organization (WHO) classification and architectural grade was defined as grade 1: 5% of a non-squamous or non-morular solid growth pattern; grade 2: 6%–50% of a non-squamous or non-morular solid growth pattern; grade 3: >50% of a non-squamous or non-morular solid growth pattern [11].

Decision for lymphadenectomy was taken according to frozen section. If myometrial invasion was less than 50% of the full myometrial thickness, tumor grade was 1 and the histology was endometrioid, then lymphadenectomy was omitted. In advanced stage patients, it was decided according to the medical performance of the patients. Adjuvant radiotherapy was administered according to age (> 60 years), LVSI status, deep myometrial invasion, cervical involvement, and presence of lymphadenectomy. Adjuvant chemotherapy was given to patients with the disease outside the uterus (≥ Stage 3) and/or poor histology.

Frozen sections and histopathological materials from specimens were evaluated by experienced gynecological pathologists. Patients who were treated for another primary cancer before and/or after had a synchronous malignancy detected during the surgery were excluded. Additionally, patients who had no follow up after surgery and had less than six months of follow-up were excluded.

Statistical analysis was performed using SPSS v15.0. The categorical variables were analyzed using Pearson Chi-square test or Fisher exact test, where appropriate. Mann-Whitney U test was used for non-categorical/non-parametric variables. Multivariate logistic regression analysis was performed to assess the impact of various risk factors on lymph node metastasis and recurrence in a backward stepwise fashion. Kaplan-Meier analysis was performed for disease-specific and overall survival analysis. *P* values < 0.05 were considered significant.

Results

Two hundred seventy-eight patients who were operated for endometrial carcinoma between 2010-2016 were included in this study and 240 (86.3%) were early stage (Stages I-II) and 38 (13.7%) were advanced stage (Stages III-IV). Demographic features, histopathological results, and the oncological outcomes are summarized in Table 1. One hundred two (36.7%) patients had lymphovascular space invasion (LVSI) and 20 (7.1%) patients had lymph node metastasis. Recurrence occurred in 13 (4.7%) patients. Three of the recurrences were seen in early stage patients. All of three recurrences seen in early stage patients were at the vaginal cuff. In advanced stage group, four recurrences were seen in pelvis and six were seen as distant metastasis. Mean follow-up period was 42 months.

Table 1. — *Demographic and clinic-pathologic features of the patients.*

	Total (n=278)	Early (n=240)	Advanced (n=38)
Age (years)	60.1 ± 9.8	59.7 ± 9.6	62.3 ± 10
Parity	2 (0-9)	2 (0-7)	2 (0-9)
BMI (kg/m^2)	34.3 ± 6.7	33.8 ± 5.2	34.3 ± 6.9
FIGO Stage			
I			
Ia	162 (58.2%)	162 (67.5%)	-
Ib	60 (21.5%)	60 (25%)	-
II	18 (6.4%)	18 (7.5%)	-
III	28 (10%)	-	28 (73.6%)
IV	10 (3.9%)	-	10 (26.4%)
Tumor Grade			
I	85 (30.5%)	85 (35.4%)	-
II	136 (48.9%)	117 (48.7%)	19 (50%)
III	57 (20.6%)	38 (15.9%)	19 (50%)
Histology			
Endometrioid	176 (63.3%)	162 (67.5%)	14 (36.8%)
Serous	11 (4%)	8 (3.3%)	3 (7.9%)
Clear-cell	7 (2.5%)	4 (1.7%)	3 (7.9%)
Mucinous	18 (6.5%)	13 (5.4%)	5 (13.2%)
Mixed	56 (20.1%)	47 (19.6%)	9 (23.7%)
Carcinosarcoma	10 (3.6%)	6 (2.5%)	4 (10.5%)
LVSI			
(+)	102 (36.7%)	69 (28.8%)	33 (86.8%)
(-)	176 (63.3%)	171 (71.3%)	5 (13.2%)
LN dissection			
(-)	121 (43.5%)	108 (45%)	13 (34.2%)
(+)	157 (56.5%)	132 (55%)	25 (65.8%)
Pelvic	*133 (84.7%)*	*115 (87.1%)*	*18 (72%)*
Pelvic + para-aortic	*24 (15.3%)*	*17 (12.9%)*	*7 (28%)*
LN metastasis	20 (7.1%)		20 (52.6%)
Pelvic	*17 (85%)*	-	*17 (85%)*
Pelvic + para-aortic	*3 (15%)*		*3 (15%)*
Adjuvant therapy	171 (50.7%)	134 (55.8%)	37 (97.3%)
Radiotherapy	163 (95.3%)	132 (98.5%)	31 (83.7%)
Chemotherapy	45 (26.3%)	11 (8.2%)	34 (91.8%)
Recurrence	13 (4.7%)	3 (1.3%)	10 (26.3)
Locoregional	7 (53.8%)	3 (100%)	4 (40%)
Distant	6 (46.2%)	-	6 (60%)

BMI: body-mass index, LVSI: lymphovascular space invasion, LN: lymph node.

In 102 patients with positive LVSI, age was significantly higher according to LVSI negative group ($p = 0.0001$) (Table 2). Additionally, tumor grade ($p = 0.0001$), FIGO Stage ($p = 0.0001$), non-endometrioid histology ($p = 0.0001$), depth of myometrial invasion ($p = 0.0001$), the rate of tumor size > 2 cm ($p = 0.008$), lymph node metastasis ($p = 0.0001$), and recurrence rate ($p = 0.0001$) were significantly higher according to LVSI negative group. Dis-

Table 2. — *Patient characteristics according to LVSI and peritoneal cytology status.*

	LVSI		*p**	Cytology		*p**
	- (n=176)	+ (n=102)		- (n=270)	+ (n=8)	
Age (years)	58.3 ± 10	63.1±8.5	**0.0001**	60 ± 9.4	65 ± 8.2	0.155
Parity	2 (0-9)	2 (0-8)	0.595	2 (0-6)	2 (0-9)	0.293
BMI (kg/m^2)	34.5±7.1	33.9±5.8	0.453	34.2 ± 6.7	35.2 ± 4.3	0.666
FIGO Stage			**0.0001**			**0.0001**
I					-	
Ia	147 (83.5%)	36 (35.3%)		188 (69.6%)		
Ib	15 (8.6%)	24 (23.5%)		33 (12.2%)		
II	9 (5.1%)	9 (8.8%)		18 (6.7%)	-	
III	3 (1.7%)	25 (24.5%)		24 (8.9%)	4 (50%)	
IV	2 (1.1%)	8 (7.8%)		7 (2.6%)	4 (50%)	
Tumor Grade			**0.0001**			**0.001**
I	76 (43.2%)	9 (8.8%)		85 (31.5%)	-	
II	80 (45.5%)	56 (54.9%)		134 (49.6%)	2 (25%)	
III	20 (11.3%)	37 (36.3%)		51 (18.9%)	6 (75%)	
Histology			**0.0001**			
Endometrioid	125 (71%)	51 (50%)		175 (64.8%)	1 (12.5%)	**0.0001**
Serous	3 (1.7%)	8 (7.8%)		10 (3.7%)	1 (12.5%)	
Clear-cell	3 (1.7%)	4 (3.9%)		5 (1.9%)	2 (25%)	
Mucinous	9 (5.1%)	9 (8.8%)		16 (5.9%)	2 (25%)	
Mixed	35 (19.9%)	21 (20.6%)		55 (20.4%)	1 (12.5%)	
Carcinosarcoma	1 (0.6%)	9 (8.8%)		9 (3.3%)	1 (12.5%)	
Depth of invasion			**0.0001**			0.127
< 50%	147(83.5%)	36 (35.3%)		180 (66.7%)	3 (37.5%)	
≥ 50%	29 (16.5%)	66 (64.7%)		90 (33.3%)	5 (62.5%)	
Tumor size			**0.008**			0.608
< 2 cm	37 (21%)	9 (8.8%)		45 (16.7%)	1 (12.5%)	
≥ 2 cm	139 (79%)	93 (91.2%)		225 (83.3%)	7 (87.5%)	
LN metastasis	2 (1.1%)	18 (17.6%)	**0.0001**	16 (5.9%)	4 (50%)	**0.0001**
Recurrence	2 (1.1%)	11 (10.8%)	**0.0001**	10 (3.7%)	3 (37.5%)	**0.004**
Death	1 (0.6%)	9 (8.8%)	**0.001**	7 (2.6%)	3 (37.5%)	**0.002**
Disease free survival (months)	106.2	81.2	**0.0001**	115.3	48.4	**0.0001**
Overall survival (months)	108.6	84	**0.0001**	116.6	50.6	**0.0001**

*LVSI: lymphovascular space invasion, BMI: body-mass index, LN: Lymph node. * Bold numbers indicate significance.*

ease-free survival (DFS) and overall survival (OS) were significantly shorter in LVSI positive group than LVSI negative group [DFS: 81.2 *vs*. 106.2 months ($p = 0.0001$) and OS: 84 *vs*. 108.6 months ($p = 0.0001$), respectively].

Positive peritoneal cytology was detected in eight patients (2.8%) (Table 2). FIGO Stage ($p = 0.0001$), tumor grade ($p = 0.001$), non-endometrioid histology ($p = 0.0001$), lymph node metastasis ($p = 0.0001$), and recurrence rate ($p = 0.004$) were significantly higher in patients with positive cytology. DFS and OS were significantly shorter in cytology positive group than cytology negative group [DFS: 48.4 *vs*. 115.3 months ($p = 0.0001$) and OS: 50.6 *vs*. 116.6 months ($p = 0.0001$), respectively].

Lymph node metastasis was detected in 20 patients. Tumor grade ($p = 0.0001$), non-endometrioid histology ($p = 0.003$), depth of invasion more than 50% ($p = 0.0001$), tumor size > 2 cm ($p = 0.023$), rate of LVSI ($p = 0.0001$), positive cytology rate ($p = 0.001$), cervical invasion ($p = 0.0001$), and recurrence rates ($p = 0.0001$) were significantly higher in patients with lymph node metastasis according to patients without lymph node metastasis (Table 3). DFS was 55.6 months and OS was 58.9 months in lymph node metastasis group and both of them were significantly shorter than the group without lymph node metastasis ($p = 0.0001$ and $p = 0.0001$, respectively).

Risk factors for recurrence are summarized in Table 4. After multivariate analysis, LVSI [OR: 8.826; (95% CI: 1.874-41.576), $p = 0.006$] and positive cytology [OR: 9.503; (95% CI: 1.811-49.876), $p = 0.008$] remained independent prognostic factors for recurrence in endometrial cancer.

Univariate and multivariate analysis were also performed for lymph node metastasis (Table 5). The authors found that myometrial invasion was more than 50% [OR: 21.156; (95% CI: 4.792-93.403), $p = 0.0001$], LVSI [OR: 6.195; (95% CI: 1.258-30.506), $p = 0.025$] and positive cytology [OR: 14.258; (95% CI: 2.330-87.247), $p = 0.004$] were independent prognostic factors for lymph node metastasis in endometrial cancer.

Table 3. — *Patient characteristics according to lymph node metastasis.*

	Lymph node metastasis		*p**
	- (n=258)	+ (n=20)	
Age (years)	60 ± 9.8	61.3 ± 10.1	0.565
Parity	2 (0-9)	2 (0-8)	0.235
BMI (kg/m^2)	34.3 ± 6.8	33.3 ± 4.9	0.489
FIGO Stage			**0.0001**
I			
Ia	162 (62.8%)	-	
Ib	60 (23.2%)	-	
II	18 (7%)	-	
III	10 (3.9%)	18 (90%)	
IV	8 (3.1%)	2 (10%)	
Tumor Grade			**0.0001**
I	85 (33%)	-	
II	127 (49.2%)	9 (45%)	
III	46 (17.8%)	11 (55%)	
Histology			**0.003**
Endometrioid	169 (65.5%)	7 (35%)	
Serous	11 (4.3%)	-	
Clear-cell	6 (2.3%)	1 (5%)	
Mucinous	14 (5.5%)	4 (20%)	
Mixed	51 (19.8%)	5 (25%)	
Carcinosarcoma	7 (2.7%)	3 (15%)	
Depth of invasion			**0.0001**
< 50%	181(70.2%)	2 (10%)	
≥ 50%	77 (29.8%)	18 (90%)	
Tumor size			**0.023**
< 2 cm	46 (17.8%)	-	
≥ 2 cm	212 (82.2%)	20 (100%)	
LVSI	84 (32.6%)	18 (90%)	**0.0001**
Positive cytology	4 (1.6%)	4 (20%)	**0.001**
Cervical invasion	27 (10.5%)	10 (50%)	**0.0001**
Recurrence	8 (3.1%)	5 (25%)	**0.0001**
Death	5 (1.9%)	5 (25%)	**0.0001**
Disease free survival (months)	115.6	55.6	**0.0001**
Overall survival (months)	117.5	58.9	**0.0001**

*LVSI: lymphovascular space invasion, BMI: body-mass index. * Bold numbers indicate significance.*

Discussion

Endometrial cancer can be delineated as the least dangerous among gynecological cancers, since more than 70% can be diagnosed at early stages [1]. The most common spread patterns are direct invasion to vagina/parametria and /or adnexa, or lymphatic spread to the pelvic and/or paraaortic lymph nodes. Peritoneal dissemination can be seen especially in poor histologic subtypes such as serous or clear-cell. Hematogenous spread is more common when mesenchymal component is malignant.

Lymph node metastasis is one of the most important prognostic parameters that directly change FIGO Stage [4] and hence survival of the patient. Since most of the patients are diagnosed at early stages and lymph node metastasis rates are very low in this group of patients, routine lymphadenectomy can be accepted as over-treatment [7]. In MRC ASTEC trial, efficacy of systemic pelvic lymphadenectomy was evaluated and they concluded that there was no evidence of benefit in terms of overall or recurrence-free survival for pelvic lymphadenectomy in women with early endometrial cancer [3]. Afterwards, many algorithms that stratified patients according to risk groups for nodal involvement became popular; one of the best known included depth of myometrial invasion, tumor grade, and histologic subtype [7-9].

LVSI that is defined as the presence of tumor cells in a vascular space, is another parameter evaluated in many studies regarding endometrial cancer [6, 12-15]. It might be hypothesized that LVSI can be a preliminary phase of lymphatic/hematogenous spread or may represent nodal disease before lymph node dissection. In the present study, LVSI was detected in 102 out of 278 patients (36.7%). LVSI positivity rate was similar with previous studies, which was reported between 25-37% [12, 14]. In early stage group it was detected in 28.8%, where it was 86.8% in advanced stage group. Lymph node metastasis was detected in only 1.1% of patients who had no LVSI, and it was 17.6% in LVSI positive group ($p = 0.0001$). According to multivariate analysis, LVSI was found to have independent prognostic factor for lymph node metastasis and recurrence. Previous studies reported conflicting results regarding LVSI in endometrial cancer. Hahn *et al.* [12] evaluated 438 patients retrospectively. They reported that although LVSI positive group showed more lymph node metastasis and recurrence, in multivariate analysis LVSI did not influence DFS and OS. Koskas *et al.* [16] reviewed 485 patients in a multicenter trial and reported that LVSI should be considered as an independent risk factor for lymph node metastasis. In a recent study by Jorge *et al.* [17], it was reported that the risk ratio of nodal disease in patients with LVSI was 9.29 (95% CI, 7.29–11.84) for T1A tumors and 4.64 (95% CI 3.99–5.39) for T1B tumors. In the present study, nodal disease risk was 6.195 times higher in patients with LVSI (95% CI: 1.258-30.506).

Recurrence is another challenging point in endometrial cancer. Even in early stage patients, the risk of relapse was reported between 4-19% [8, 14, 18]. In the present study, LVSI was found as a significant risk factor for recurrence in endometrial cancer. The odds ratio for recurrence in LVSI positive patients was 8.826 (95% CI: 1.874-41.576). Similarly, Briet *et al.* [14] reported that LVSI increased recurrence risk with OR: 2.34 (95% CI: 1.37-3.99, $p < 0.002$) and concluded that adjuvant pelvic radiotherapy should be intended in the Stage I "low risk" patients if LVSI is present. In another study by Weinberg *et al.*, they evaluated 388 patients with Stages I-II who had at least one of these three criteria: LVSI, outer-half myometrial invasion, and grade 2-3 tumor. They reported that LVSI was the only independent poor prognostic factor of overall and site-specific recurrences as well as PFS, OS, and disease specific sur-

Table 4. — *Univariate and multivariate analysis of possible prognostic factors on recurrence in endometrial cancer.*

	Univariate			Multivariate		
	No. of patients with recurrence	λ^2	*p**	OR	95% CI	*p**
Age (years)		0.896	0.829			
< 60	6/142 (4.2%)					
≥ 60	7/136 (5.1%)					
Parity		0.250	0.487			
≤ 2	8/149 (5.3%)					
> 2	5/129 (3.8%)					
BMI (kg/m^2)		1.164	0.316			
≤ 30	5/86 (5.8%)					
> 30	8/192 (4.1%)					
Grade		15.675	**0.001**			
1	0/85					
2-3	13/193 (6.7%)					
Histology		25.996	**0.0001**			
Endometrioid	2/176 (1.1%)					
Non-endometrioid	11/102 (10.7%)					
Myometrial invasion						
< 50%	3/183 (1.6%)	16.649	**0.003**			
≥ 50%	10/95 (10.5%)					
LVSI		13.485	**0.0001**	8.826	1.874-41.576	**0.006**
-	2/176 (1.1%)					
+	11/102 (10.7%)					
Cytology		19.909	**0.004**	9.503	1.811-49.876	**0.008**
-	10/270 (3.7%)					
+	3/8 (37.5%)					
LN metastasis		15.364	**0.001**			
-	8/258 (3.1%)					
+	5/20 (25%)					
Cervical invasion		1.128	0.242			
-	10/241 (4.1%)					
+	3/37 (8.1%)					
Infertility		1.606	0.448			
-	10/258 (3.9%)					
+	3/20 (15%)					
Tumor size		0.421	0.457			
< 2 cm	3/46 (6.5%)					
≥ 2 cm	10/232 (4.3%)					

*BMI: body-mass index, LVSI: lymphovascular space invasion, OR: odds ratio, LN: lymph node, CI: confidence interval. *Bold numbers indicate significance.*

vival [19]. According to the present results, LVSI status should be evaluated in order to make an adjuvant radiotherapy decision, especially for patients who were suboptimally staged since LVSI significantly increased the risk of nodal disease and recurrence.

Peritoneal cytology is a prognostic factor in endometrial cancer and should be noted separately without changing the stage [4]. The studies about peritoneal cytology are not as much as the studies about LVSI. Milgrom *et al.* [20] studied 196 FIGO Stage III endometrial cancer patients and found 23% peritoneal cytology positivity. Additionally they found that five-year DFS rate was 39% *vs*. 69% in patients with and without positive peritoneal cytology (PPC), respectively. In another study, Han *et al.* [21] performed a subgroup analysis in endometrioid and non-endometrioid endometrial carcinoma. In a group of 42 patients who had non-endometrioid histology, recurrence-free survival was significantly lower in PPC group than negative peritoneal cytology group (22 *vs*. 120 months, respectively; $p < 0.01$). In the present study, PPC was found in eight of 38 advanced stage patients (21%). It was significantly higher in high-grade tumors and non-endometrioid histology ($p = 0.001$ and $p = 0.0001$, respectively). PPC remained a significant prognostic factor for recurrence and lymph node metastasis after multivariate analysis. Garg *et al.* [22] reported a similar study regarding the relationship between lymph node metastasis and PPC in endometrial cancer. They showed that PPC is an independent predictor of lymph node metastasis after multivariate analysis in apparent Stages I-II patients with OR: 11 (95% CI: 9.13-13.26, $p < 0.0001$).

Table 5. — *Univariate and multivariate analysis of possible prognostic factors on lymph node metastasis in endometrial cancer*

	Univariate			Multivariate		
	Nb. of patients with LN metastasis	λ^2	*p**	OR	95% CI	*p**
Age (years)		0.934	0.642			
< 60	9/142 (6.3%)					
≥ 60	11/136 (8%)					
Parity		0.658	0.464			
≤ 2	12/149 (8%)					
> 2	8/129 (6.2%)					
BMI (kg/m^2)		0.886	0.268			
≤ 30	7/86 (8.1%)					
> 30	13/192 (6.7%)					
Grade		19.164	**0.0001**			
1	0/85					
2-3	20/193 (10.3%)					
Histology		18.239	**0.001**			
Endometrioid	7/176 (3.9%)					
Non-endometrioid	13/102 (12.7%)					
Myometrial invasion		29.858	**0.0001**	21.156	4.792-93.403	**0.0001**
< 50%	2/183 (1.1%)					
≥ 50%	18/95 (18.9%)					
LVSI		26.366	**0.0001**	6.195	1.258-30.506	**0.025**
-	2/176 (1.1%)					
+	18/102 (17.6%)					
Cytology		22.606 **0.001**		14.258	2.330-87.247	**0.004**
-	16/270 (5.9%)					
+	4/8 (50%)					
Cervical invasion		25.144	**0.0001**			
-	10/241 (4.1%)					
+	10/37 (27%)					
Tumor size		4.273	**0.023**			
< 2 cm	0/46					
≥ 2 cm	20/232 (8.6%)					

*BMI: body-mass index, LVSI: lymphovascular space invasion, OR: odds ratio, LN: lymph node, CI: confidence interval. *Bold numbers indicate significance.*

In this context, PPC may refer to advanced stage disease. Thus, especially in suboptimally staged patients, adjuvant therapy should be considered in patients with PPC. Additionally, although PPC does not change the stage according to current FIGO 2009 staging system, the surgeon should remember to take peritoneal cytology at the beginning of the operation and it should definitely be emphasized in pathology reports.

The present study has also some restrictions. First, it is clear that more problematic group in endometrial cancer that is difficult to decide for lymph node dissection or adjuvant radiotherapy is "apparent" Stage I-II group. In this study, the number of patients with lymph node metastasis or relapse in the aforementioned group is quite low to make optimal statistical assessment. Secondly, prognostic factors such as grade, histology, and myometrial invasion for recurrence, and grade, histology, cervical invasion, and tumor size for lymph node metastasis, which were significant after univariate analysis did not remain significant after multivariate analysis. Studies with larger volumes will better elucidate the significance of these factors. The other restriction is the retrospective design of this study.

Conclusion

As a result, LVSI and positive peritoneal cytology are independent prognostic factors for lymph node involvement and recurrence in endometrial cancer. LVSI reported in preoperative endometrial biopsy or frozen section should remind the surgeon about the risk of lymphatic metastasis. Patients who have LVSI and PPC in final pathology report should be evaluated carefully for adjuvant radiotherapy in order to minimalize the risk of recurrence.

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