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ORIGINAL ARTICLE

Incidence and prognostic factors of isolated para-aortic lymph node metastasis in endometrial cancer: a single-center study

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ABSTRACT

BACKGROUND: Para-aortic lymph node metastasis (PALNM) is a key prognostic factor in endometrial cancer (EC). This study aimed to determine the incidence and prognostic factors of lymph node metastasis (LNM) and isolated PALNM in endometrioid-type EC patients.
METHODS: EC patients treated surgically between 2000 and 2015, staged by FIGO 2009 criteria, were retrospectively analyzed. Included were patients with endometrioid histology grades I-III who underwent pelvic and PALN dissection. Excluded were those without lymph node dissection or with non-endometrioid histology.
RESULTS: A total of 417 patients met the criteria. Of these, 246 (59%) were grade I, 117 (28.1%) grade II, and 46 (11%) grade III. Pelvic LNM (PLNM) was found in 43 (10.3%), and PALNM in 22 (5.3%). Five patients (1.19%) had isolated PALNM. PALNM was more frequent in patients with stage III, tumors >2 cm, cervical glandular/stromal involvement, deep myometrial invasion, positive peritoneal cytology, adnexal involvement, PLNM, and LVSI. Isolated PALNM was notably higher with adnexal involvement. Independent predictors of PALNM were cervical glandular involvement and LVSI. Deep myometrial invasion, LNM, PLNM, LVSI, and adnexal involvement were linked to disease-free survival (DFS), while peritoneal cytology, PLNM, and LVSI were linked to recurrence. There was no significant difference in recurrence and DFS between PALNM and isolated PALNM.
CONCLUSIONS: Isolated PALNM without PLNM is rare in EC patients but should be assessed for optimal staging and treatment.

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Key words: Endometrial neoplasms; Lymphatic metastasis; Prognosis.

Endometrial cancer (EC) is one of the most common malignancies of the female reproductive system, the incidence of which is increasing. EC, the fourth most common cancer among women in the United States, was the sixth most common cause of cancer death in 2021.[1] The standard treatment, especially for early-stage EC, is total hysterectomy and bilateral salpingo-oophorectomy with systematic lymphadenectomy.[2] Tumor stage, tumor histological subtype, depth of myometrial invasion, lymphovascular invasion, and lymph node metastasis (LNM) are factors associated with the prognosis of EC.[3] LNM is one of the most important prognostic factors in EC and is used as an indicator of the need for pre/postoperative radiotherapy.[4, 5] In 2009, the International Federation of Gynecology and Obstetrics (FIGO) revised the staging criteria and classified pelvic LNM (PLNM) and para-aortic LNM (PALNM) as stage IIIC1 and stage IIIC2.[6] Histological subtype, grade and diameter of the tumor, cervical

infiltration, depth of myometrial invasion, lymphovascular space invasion (LVSI), and positive peritoneal cytology are prognostic factors associated with LNM.[7] In the presence of PLNM and PALNM, the 5-year disease-free survival (DFS) rates are 55-70% and 30-50%, respectively.[8] Although LN is helpful in staging, assessing the extent of disease, and deciding on adjuvant treatments, LN dissection (LND) has been reported to increase morbidity in low-risk patients.[9, 10] To prevent unnecessary LND, many centers perform lymphadenectomy based on intraoperative evaluation of LN.[11-13] However, some LNMs may be missed with this approach. A sentinel lymph node (SLN) algorithm was recently proposed by the National Comprehensive Cancer Network (NCCN).[14] The goal of SLN is to minimize collateral damage by avoiding unnecessary LND. SLN has demonstrated good sensitivity and low false positive rates without compromising the survival outcomes of EC.[15] EC spreads first to the pelvic lymph and then to the para-aortic lymph.[16] Approximately 57-73% of patients with PLNM have PALNM.[17-19] However, there is no absolute relationship between PLNM and PALNM, and PALNM can occur without PLNM. Studies have shown that the incidence of isolated PALNM varies greatly, ranging from 6% to 46.2%.[20-26] Debates continue in EC, especially regarding the scope of PALND. Moreover, the prognostic impact of isolated PALNM in patients with EC remains unclear. If isolated PALNM is present in patients who are PLNM negative and/or SLN negative, the patients are incorrectly considered to be low stage, their PALND is not performed, and the prognosis is negatively affected because adjuvant treatments are missing. Determining the frequency of isolated PALNM and risk factors is very important for the safety of conservative approaches. This study aimed to describe the incidence and characteristics of PALNM in patients with EC and to evaluate the prognostic impact of PALNM on recurrence and DFS.

Materials and methods

This retrospective study was conducted at Hacettepe University Faculty of Medicine, Department of Gynecology and Obstetrics. Ethical approval was received for the study from Hacettepe University Non-Interventional Clinical Research Ethics Committee. The files of 835 EC cases who underwent surgical treatment between 2000 and 2015 were retrospectively evaluated. The inclusion criteria for the study were cases with endometrioid histological type tumor, patient with histological grade I-III, and patients who underwent pelvic and para-aortic lymph node dissection. Exclusion criteria from the study were cases with non-endometrioid histology and cases without para-aortic lymph node dissection. A total of 417 patients who underwent pelvic and para-aortic lymphadenectomy were included in the study (Figure 1).

All surgical procedures were performed by gynecologic oncologists. All patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, PLND, and PALND. PLND involves the removal of lymphatic tissues on the external and common iliac vessels and in the obturator fossa. PALND includes the removal of all lymphatic tissues, starting from the aortic bifurcation, laterally to the paracaval and para-aortic lymphatic tissues, and superiorly to the left renal vessels. Patients with EC were staged using the revised 2009 FIGO staging system. Additional criteria such as peritoneal cytology and cervical glandular involvement were also evaluated in the patients. Clinical and pathological characteristics of the patients, patient's age, histological subtype, FIGO grade, depth of myometrial invasion, tumor size, LVSI, cervical and adnexal involvement, and presence of LND were evaluated.

This study was approved by the Non-Interventional Clinical Research Ethics Committee of Hacettepe University (decision number 835).

Statistical analysis

Statistical evaluation was performed using SPSS (Statistical Package for Social Sciences; IBM SPSS Inc., Chicago, IL, USA) 20 for Windows (Microsoft Corp., Redmond, WA, USA). Normal distribution of the data was evaluated with the Kolmogorov-Smirnov Test. Variables were expressed as mean ± standard deviation (SD), median, minimum, maximum, frequency, and percentage. Independent samples *t*-test and Mann-Whitney U Test were used to determine factors associated with two-category risk groups. Pearson χ^2 and Fisher's Exact χ^2 Tests were used to compare categorical data. Possible risk factors that may affect the presence of retroperitoneal LNM and PALNM were examined by univariate logistic regression analysis, and independent markers were determined by multivariate logistic regression analysis. Possible risk factors that may have an impact on recurrence and mortality were examined with univariate Cox regression analysis. Independent predictors predicting the risk of recurrence were determined by multivariable Cox regression. Independent markers predicting survival risk could not be determined due to the small number of patients with exitus. Survival times for risk factors were tested with Kaplan-Meier anal-

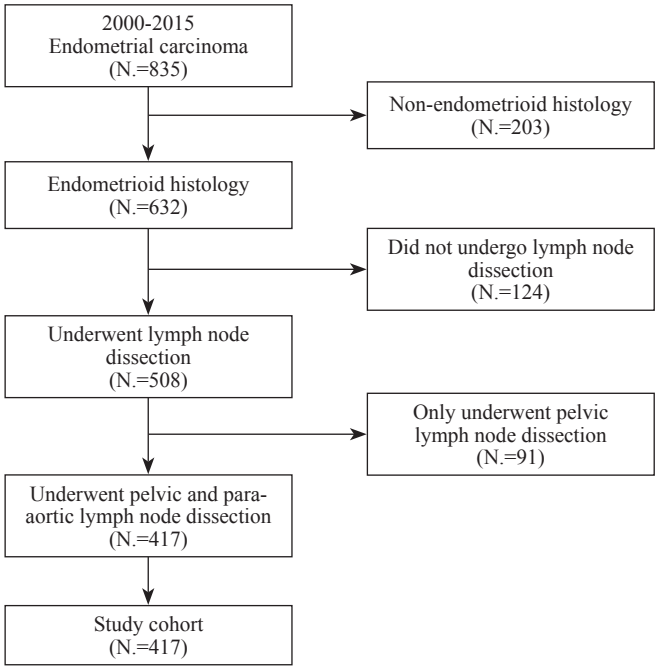

Figure 1.—Study cohort diagram.

ysis. For statistical analysis results, a P value of less than 0.05 was considered significant.

Results

Demographic and clinical data of the participants included in the study are given in Table I. The patients had a mean age of 58.8±10.1 (26-86) years; 82 (19.7%) were premenopausal and 335 (80.3%) were postmenopausal. Two hundred forty-six (59%) patients were grade I, 117 (28.1%) patients were grade II, and 46 (11%) patients were grade III, and the grades could not be evaluated in 1.9% (n:8) of the patients due to autolysis. The tumor was found to be limited to the endometrium in 50 patients (12%), <50% superficial invasion in 186 patients (44.6%), and deep invasion in 181 patients (43.4%). The tumor size was 2 cm or less in 30.5% (N.127) of the patients and over 2 cm in 69.5% (N.290). LVSI was positive in 96 (23%) of the patients, cervical glandular involvement was positive in 105 (25.2%), cervical stromal involvement was positive in 64 (15.3%), omentum involvement was positive in 10 (2.4%), and peritoneal cytology was positive in 24 (5.8%) patients. There were 43 (10.3%) patients who were PLNM positive and 22 (5.3%) who were PALNM positive. While 17 of the 22 patients with positive PALNM had PLNM, isolated PALNM was detected in five patients, and the frequency of isolated PALNM was 1.19%. The median number of removed PLN from the patients was 24 (3-90), the median number of removed PALN was 5 (1-50), and the median total number of removed LN was 30 (5-108).

The relationship between retroperitoneal LNM and other factors is given in Table II. The rate of retroperitoneal LNM was higher in patients with grade III (P=0.003), patients with primary tumor size over 2 cm (P=0.004), patients with cervical glandular involvement (P<0.001), patients with cervical stromal involvement (P<0.001), patients with deep myometrial invasion (P<0.001), patients with positive peritoneal cytology (P=0.013), patients with adnexal involvement (P<0.001), and patients with LVSI (P<0.001).

The relationship between PALNM and other parameters is given in Table III. The rate of PALNM was higher in patients with grade III (P=0.005), patients with primary tumor size over 2 cm (P=0.025), patients with cervical glandular involvement (P<0.001), patients with cervical stromal involvement (P=0.003), patients with deep myometrial invasion (P=0.001), patients with positive peritoneal cytology (P=0.030), patients with adnexal involvement (P=0.003), patients with LVSI (P<0.001), and patients with PLNM (P<0.001). Recurrence was detected in two of the patients with PALNM, and there were also two patients with exitus.

Isolated PALNM was detected in 22.7% (N.5) of patients with PALNM (Table IV). Although the rate of isolated PALNM was higher in Grade III patients compared to Grades I-II, there was no statistical significance (4.3% *vs*. 0.8%; P=0.099). Isolated PALNM was detected in 1.7% of the patients with a primary tumor diameter over two cm, and the primary tumor diameter in all patients with isolated PALNM was over two cm. Isolated PALNM was significantly higher in patients with adnexal involvement than in those without (6.5% *vs*. 0.8%; P=0.046). No statistically significant relationship was determined between isolated PALNM and other factors (P>0.05). No recurrence was detected in patients with isolated PALNM, and there was one patient with exitus.

The results of multivariate logistic regression analysis for independent predictors predicting retroperitoneal LNM and PALNM are given in Table V. Independent markers predicting retroperitoneal LNM were cervical glandular involvement (OR=2.25; P=0.024), presence of LVSI (OR=4.20; P<0.001), and adnexal involvement (OR=4.61; P=0.001). Independent markers predicting PALNM were cervical glandular involvement (OR=2.85; P=0.29) and the presence of LVSI (OR=5.83; P<0.001).

TABLE I.—*Demographic and pathological data of the patients.*

Variables	Statistics
Age, years	58.8±10.1
>60	178 (42.6%)
≤60	239 (57.4%)
Menopausal status	
Premenopausal	82 (19.7%)
Postmenopausal	335 (80.3%)
FIGO grade	
Grade I	246 (59.0%)
Grade II	117 (28.0%)
Grade III	46 (11.0%)
Autolysis	8 (2.0%)
LVSI	
Yes	96 (23.0%)
No	321 (77.0%)
Primary tumor size (cm)	
≤2 cm	127 (30.5%)
>2 cm	290 (69.5%)
Cervical glandular involvement	
No	312 (74.8%)
Yes	105 (25.2%)
Cervical stromal involvement	
No	353 (84.7%)
Yes	64 (15.3%)
MI	
No	50 (12.0%)
MI <1/2	186 (44.6%)
MI >1/2	181 (43.4%)
Lymph node involvement	
Positive	48 (11.5%)
Negative	369 (88.5%)
Pelvic lymph node involvement	
Positive	43 (10.3%)
Negative	374 (89.7%)
Para-aortic lymph node involvement	
Positive	22 (5.3%)
Negative	395 (94.7%)
Peritoneal cytology	
Positive	24 (5.8%)
Negative	393 (94.2%)
Omentum involvement	
Positive	10 (2.4%)
Negative	407 (97.6%)

MI: myometrial invasion.

TABLE II.—*Histological factors that are significantly associated with retroperitoneal LNM.*

Variables	Retroperitoneal LNM		P
	Yes N.=48	No N.=369	
FIGO grade*			
I-II	35 (9.6%)	328 (90.4%)	0.003
III	12 (26.1%)	34 (73.9%)	
Primary tumor size (cm)			
≤2 cm	6 (4.7%)	121 (95.3%)	0.004
>2 cm	42 (14.5%)	248 (85.5%)	
Cervical glandular involvement			
Yes	22 (7.1%)	290 (92.9%)	<0.001
No	26 (24.8%)	79 (75.2%)	
Cervical stromal involvement			
Yes	29 (8.2%)	324 (91.8%)	<0.001
No	19 (29.7%)	45 (70.3%)	
Depth MI			
Yes	35 (19.3%)	146 (80.7%)	<0.001
No	13 (5.5%)	223 (94.5%)	
Peritoneal cytology			
Positive	7 (29. 2%)	17 (70.8%)	0.013
Negative	41 (10.4%)	352 (89.6%)	
Adnexal involvement			
Yes	14 (45.2%)	17 (54.8%)	<0.001
No	34 (8.8%)	352 (91.2%)	
LVSI			
Yes	28 (29.2%)	68 (70.8%)	<0.001
No	20 (6.2%)	301 (93.8%)	

FIGO: International Federation of Gynecology and Obstetrics; MI: myometrial invasion; LNM: lymph node metastasi; LVSI: lymphovascular space invasion. *Grade was evaluated on 409 patients; 8 patients were not evaluated due to autolysis.

The median DFS time of the patients was 168.8 months, and recurrence was detected in 27 (6.5%) patients (Table VI). Median DFS time was shorter in patients with deep myometrial invasion (P=0.001), patients with LNM (P=0.001), patients with PLNM (P=0.001), patients with adnexal involvement (P=0.017), patients with the presence of LVSI (P=0.001), and patients with positive peritoneal cytology (P=0.001). No significant difference was detected in terms of recurrence and median DFS time with the presence of PALNM (P=0.314) and isolated PALNM (P=0.751). No significant relationship was found between age, menopausal status, FIGO stage, primary tumor size, cervical glandular involvement, cervical stromal involvement, total number of removed lymph nodes and omentum involvement, and median DFS time (P>0.05). In the multivariate Cox regression model, positive peritoneal cytology (HR: 4.03; P=0.003), PLNM (HR: 2.62; P=0.026), and LVSI (HR: 2.67; P=0.016) were detected as independent markers predicting the risk of recurrence (Table VII).

Discussion

This study aimed to investigate the effect of isolated PALNM on prognosis in patients with EC. Of the patients with EC, 22 (5.3%) were PALNM positive, and five of them (1.19%) had isolated PALNM. PALNM was more common in patients with grade III, patients with primary tumor size over 2 cm, patients with cervical glandular involvement, patients with cervical stromal involvement, patients with deep myometrial invasion, patients with positive peritoneal cytology, patients with adnexal involvement, patients with LVSI, and patients with PLNM. Isolated PALNM

TABLE III.—*Histological factors that are significantly associated with para-aortic LNM.*

Variables	Para-aortic LNM		P
	Yes	No	
	N.=22	N.=395	
FIGO grade*			
I-II	14 (3.9%)	349 (96.1%)	0.005
III	7 (15.2%)	39 (84.8%)	
Primary tumor size (cm)			
≤2 cm	2 (1.6%)	125 (98.4%)	0.025
>2 cm	20 (6.9%)	270 (93.1%)	
Cervical glandular involvement			
Yes	13 (12.4%)	92 (87.6%)	<0.001
No	9 (2.9%)	303 (97.1%)	
Cervical stromal involvement			
Yes	9 (14.1%)	55 (85.9%)	0.003
No	13 (3.7%)	340 (96. 3%)	
Depth MI			
Yes	17 (9.4%)	164 (90.6%)	0.001
No	5 (2.1%)	231 (97.9%)	
Peritoneal cytology			
Positive	4 (16.7%)	20 (83.3%)	0.030
Negative	18 (4.6%)	375 (95.4%)	
Adnexal involvement			
Yes	6 (19.4%)	25 (80.6%)	0.003
No	16 (4.1%)	370 (95.9%)	
LVSI			
Yes	15 (15.6%)	81 (84.4%)	<0.001
No	7 (2.2%)	314 (97.8%)	
Pelvic lymph node metastasis			
Yes	17 (39.5%)	26 (60.5%)	<0.001
No	5 (1.3%)	369 (98.7%)	

FIGO: International Federation of Gynecology and Obstetrics; MI: myometrial invasion; LNM: lymph node metastasi; LVSI: lymphovascular space invasion.
*Grade was evaluated on 409 patients; 8 patients were not evaluated due to autolysis.

TABLE IV.—*Histological factors that are significantly associated with isolated para-aortic LNM.*

Variables	Isolated para-aortic LNM		P
	Yes (N.=5)	No (N.=412)	
FIGO grade*			
I-II	3 (0.8)	360 (99.2)	0.099
III	2 (4.3)	44 (95.7)	
Primary tumor size (cm)			
≤2 cm	-	127 (100.0)	0.329
>2 cm	5 (1.7)	285 (98.3)	
Cervical glandular involvement			
Yes	2 (1.9)	103 (98.1)	0.604
No	3 (1.0)	309 (99.0)	
Cervical stromal involvement			
Yes	2 (3.1)	62 (96.9)	0.170
No	3 (0.8)	350 (99.2)	
Depth MI			
Yes	1 (0.4)	235 (99.6)	0.171
No	4 (2.2)	177 (97.8)	
Peritoneal cytology			
Positive	1 (4.2)	23 (95.8)	0.258
Negative	4 (1.0)	389 (99.0)	
Adnexal involvement			
Yes	2 (6.5)	29 (93.5)	0.046
No	3 (0.8)	383 (99.2)	
LVSI			
Yes	2 (2.1)	94 (97.9)	0.325
No	3 (0.9)	318 (99.1)	
Pelvic lymph node metastasis			
Yes	-	43 (100.0)	0.999
No	5 (1.3)	369 (98.7)	
Para-aortic lymph node metastasis			
Yes	5 (22.7)	17 (77.3)	<0.001
No	-	395 (100.0)	

FIGO: International Federation of Gynecology and Obstetrics; LNM: lymph node metastasi; LVSI: lymphovascular space invasion.
*Grade was evaluated on 409 patients; 8 patients were not evaluated due to autolysis.

TABLE V.—*Independent markers predicting the risk of retroperitoneal and para-aortic LNM.*

Variables	OR	95% CI		P
		Low	High	
Retroperitoneal LNM				
Cervical glandular involvement	2.25	1.11	4.54	0.024
LVSI	4.20	2.14	8.26	<0.001
Adnexal involvement	4.61	1.92	11.08	0.001
	Nagelkerke R^2=0.341; P<0.001			
Para-aortic LNM				
Cervical glandular involvement	2.85	1.12	7.32	0.029
LVSI	5.83	2.2	15.43	<0.001
	Nagelkerke R^2=0.297; P<0.001			

CI: confidence interval; LNM: lymph node metastasis; LVSI: lymphovascular space invasion; OR: odds ratio.

was more common in patients with adnexal involvement than in those without. Independent predictors of PALNM were cervical glandular involvement and LVSI. The presence of PALNM and isolated PALNM had no relationship with recurrence and median DFS time.

Predominantly affecting postmenopausal women approximately 60 years of age, EC is the most common gynecological malignancy and the fourth most common cancer in developed countries.[27] More than two-thirds of patients with EC are diagnosed at stage I, and the 5-year survival rate is between 74 and 95%.[28] However, metastatic EC is associated with a worse outcome, with 5-year survival rates ranging from 21% to 56%.[29] FIGO recommends complete surgical staging, including pelvic and para-aortic LND, in the treatment of EC. Clinically, LND aims to clarify the tumor stage, eliminate possible metastatic lesions, guide adjuvant therapy, and evaluate and improve the prognosis of patients.[30] Although LND has been shown to have therapeutic benefits, it has also been reported that it does not provide any survival benefit, especially in the early stages of the disease.[4, 31] Moreover, LND may be associated with complications that affect the patient's quality of life, such as vascular and nerve damage, lymphatic cyst formation, venous thrombosis, and

TABLE VI.—*DSF findings.*

Variables	DSF (months)	5-year DSF (%)	HR	95% CI	P
Age, years					
≤60	167.0	94%	Ref		
>60	169.0	91%	1.27	0.60-2.71	0.531
Menopausal status					
Premenopausal	166.2	91%	Ref		
Postmenopausal	169.2	93%	0.82	0.33-2.04	0.674
FIGO grade					
I-II	169.3	93%	Ref		
III	163.3	88%	1.50	0.52-4.35	0.453
Primary tumor size (cm)					
≤2 cm	172.3	96%	Ref		
>2 cm	166.4	90%	2.30	0.87-6.09	0.093
Cervical glandular involvement					
No	170.7	93%	Ref		
Yes	157.8	89%	1.86	0.85-4.06	0.120
Cervical stromal involvement					
No	169.8	93%	Ref		
Yes	148.7	91%	1.84	0.74-4.56	0.188
Deep myometrial invasion					
No	176.7	97%	Ref		
Yes	158.8	87%	4.90	1.98-12.15	0.001
Peritoneal cytology					
Negative	170.7	94%	Ref		
Positive	139.7	74%	4.98	2.01-12.35	0.001
Lymph node involvement					
Negative	171.2	94%	Ref		
Positive	145.6	78%	3.83	1.67-8.75	0.001
Pelvic LNM					
Negative	171.3	94%	Ref		
Positive	142.9	76%	4.21	1.841-9.62	0.001
Para-aortic LNM					
No	169.3	93%	Ref		
Yes	103.4	88%	2.10	0.49-8.92	0.314
Isolated para-aortic LNM					
No	172.8	92%	Ref		
Yes	79.0	100%	0.49	0.01-185.50	0.751
Removed total lymph node					
<10	135.0	91%	Ref		
≥ 10	168.0	94%	0.656	0.089-4.849	0.679
Omentum involvement					
Negative	169.5	93%	Ref		
Positive	102.9	76%	4.06	0.96-17.17	0.057
Adnexal involvement					
No	170.2	99%	Ref		
Yes	147.0	93%	3.25	1.23-8.60	0.017
LVSI					
No	172.6	95%	Ref		
Yes	154.6	83%	3.50	1.64-7.45	0.001

CI: confidence interval; DSF: Disease-free survival; FIGO: International Federation of Gynecology and Obstetrics; HR: hazard ratio; LNM: lymph node metastasis; LVSI: lymphovascular space invasion.

lymphedema in the lower extremities.[32] Therefore, a consensus on the effectiveness and scope of LND has not yet been reached.

LNM is an important prognostic factor in EC. Therefore, it is important to determine the factors related to LND in order to decide on effective LND. Mariani *et al*.[4] identified endometrioid histology, tumor size of 2 cm or less, depth of myometrial invasion less than or equal to 50%, and grade 1-2 tumor as low-risk criteria. They noted that these patients did not have LNM or die from the dis-

TABLE VII.—*Independent markers predicting the risk of recurrence.*

Variables	HR	95% CI	P
Peritoneal cytology			
Negative	Ref		
Positive	4.03	1.61-10.09	0.003
Pelvic LNM			
Negative	Ref		
Positive	2.62	1.12-6.12	0.026
LVSI			
No			
Yes	2.67	1.20-5.93	0.016
Regression R model significance: -2 log Likelihood: 249.2; P<0.001			

CI: confidence interval; HR: hazard ratio; LNM: lymph node metastasi; LVSI: Lymphovascular space invasion; HR: hazard ratio.

ease. Todo *et al*.[33] defined patients with grade 1-2 tumors, endometrioid histology, and low CA-125 levels as a low-risk group and reported that overall PLNM and PALNM in this group were 3.6% and 0.7%, respectively. Pollom *et al*.[34] determined that LVSI, deep myometrial infiltration, tumor size >4 cm, and cervical stroma infiltration were associated with LNM in 296 EC patients who underwent selective LND. Mandić *et al*.[35] demonstrated that non-endometrioid tumor, myometrial infiltration depth of more than 50%, cervical stroma involvement, and LVSI are associated with LNM. Rathod *et al*.[36] documented that the presence of grade 3 tumors, tumor size >2 cm, deep myometrial invasion, and uterine serosal invasion are associated with a high LNM rate. In our study, stage III disease, tumor size >2 cm, deep myometrial invasion, positive peritoneal cytology, presence of LVSI and cervical glandular involvement, and cervical stromal and adnexal involvement were determined to be associated with high LNM. These results of our study reaffirm the results of previous studies identifying factors associated with LNM. Myometrial invasion is an early molecular process and may be the initial impetus for the progression of cancer cells. LVSI is also one of the first steps in the metastatic spread of EC and initiates lymphatic spread.[37] Therefore, in our study, the fact that the depth of myometrial invasion and LVSI increased the rate of LNM is a clear reflection of the increased exposure to lymphatics as the tumor grows along the uterine wall.

Estimating the prevalence of isolated PALNM is currently of great interest. Rathod *et al*.[36] determined that 32.7% of patients who underwent LND had LNM, 52.9% of patients with LNM had both PLNM and PALNM, and 5.9% had isolated PALNM. Mariani *et al*.[4] reported that more than half of the patients who underwent PLND had PALNM and approximately 10% of LNM was isolated PALNM. In another study, the authors observed isolated PALNM in 5 (7.9%) of 63 cases.[24] Li *et al*.[16] determined that the rate of LNM was 10.8% and the rate of isolated PALNM was 2.8% in patients who underwent LND. Widschwendter *et al*.[8] noted isolated PALNM in 3 (10%) of 30 patients in whom they performed LND. In other studies, the rate of isolated PALNM was determined as 1.6%,[38] 1.2%,[20] and 3%.[39] In the systematic review by Todo *et al*., the rate of isolated PALNM was documented as 2.7% from data obtained from 25 studies.[40] In our study, LNM was detected in 48 (11.5%) patients and isolated PALNM in 5 (1.19%) patients. The LNM rate in our study was similar to the rates obtained in previous studies. If aortic lymphadenectomy had been performed only in cases with PLNM, LN metastasis would have been missed in 5 (46%) of a total of 48 cases with LNM. Thus, these patients would not have received optimal treatment. Therefore, determining factors that predict isolated PALNM is very important for optimal treatment. In our study, the rate of PALNM was higher in patients with grade III, patients with primary tumor size larger than 2 cm, patients with cervical glandular involvement, patients with cervical stromal involvement, patients with deep myometrial invasion, patients with positive peritoneal cytology, patients with cervical glandular involvement, patients with adnexal involvement, patients with LVSI, and patients with PLNM. Sautua *et al*.[24] determined that myometrial invasion was greater than 50% in all six patients with isolated PALNM and that three patients had LVSI. Similarly, Kumar *et al*.[39] documented a significant relationship between isolated PALNM and myometrial invasion. Nomura *et al*.[10] determined that the strongest association with isolated PALNM was PLNM. GOG data revealed that PALNM was significantly associated with myometrial invasion, PLNM, adnexal involvement, and grade 2 or 3 lesions.[41] Todo *et al*.[32] determined that high tumor volume, grade 3/non-endometrioid histology or high CA-125 levels were associated with PALNM; of all PALNs removed in patients, none of them were negative. In our study, we determined that cervical glandular involvement increased LNM by 2.25 times, LVSI increased LNM by 4.20 times, and adnexal involvement increased LNM by 4.61 times. Additionally, cervical glandular involvement increased PALNM by 2.85 times and LVSI increased PALNM by 5.83 times. Nasioudis *et al*.[42] documented that LVSI increases PALNM by 4.8 times. According to these results, it can be said that LVSI has a strong relationship with PALNM.

Kim *et al*.[43] determined that systemic LND in 786

patients with EC could improve the patients' prognosis. Alhilli *et al*.[11] noted that PLND may improve the prognosis of EC patients with intermediate- and high-risk endometrial carcinoma. However, it has been suggested that PALND may not significantly improve the prognosis in patients with EC.[31] Eggemann *et al*.[44] determined that LND did not improve overall survival (OS) in low-risk EC patients, but improved OS in intermediate-risk ECs. Papathemelis *et al*.[45] found that performing pelvic and para-aortic LND in high-grade endometrial carcinomas improved OS and 5-year survival rate compared to those without LND. In the SEPAL study, it was shown that combined PLND and PALND improved OS compared to PLND alone.[46] Therefore, pelvic and para-aortic LND is recommended in high-risk ECs.

Studies have reported that positive peritoneal cytology negatively affects both recurrence and survival.[41] Similarly, it was determined that the recurrence rate is higher in high-grade ECs and that high recurrence reduces the DFS time.[47] Creasman *et al*.[48] reported that pelvic or para-aortic lymph node involvement resulted in poor prognosis, with 5-year survival reduced to 44-52%. Researchers also documented that myometrial invasion affects LNM. However, Gadducci *et al*.[49] did not find a relationship between the initial stage of the disease, stage of disease and degree of myometrial invasion, and survival in cases of recurrent EC. Wang *et al*.[50] determined the recurrence rate in patients with PLNM and PLNM+PALNM as 9.1% and 20.0%, respectively. Researchers also determined that the recurrence rate in grade III patients with PLNM+PALNM was significantly higher than in those with PLNM. In our study, we observed that deep myometrial invasion, PLNM, adnexal involvement, LVSI, and positive peritoneal cytology negatively affected DFS. This study also determined that positive peritoneal cytology significantly increased the risk of recurrence of PLNM and LVSI. However, we observed that PALNM and isolated PALNM did not significantly change the recurrence and DFS time.

Limitations of the study

Our study has some limitations. The first limitation is that it is a retrospective study and consists of a heterogeneous population. Changes in surgical techniques over the 15-year study period may have affected results. The second limitation is the small sample size and the fact that it is a single-center study. Other limitations in terms of patient population are that there are incomplete records in the files scanned in the hospital registry system and patients who cannot be reached by phone are excluded from the study. Therefore, the results of this study should be confirmed by larger sample and multicenter, randomized controlled studies.

Conclusions

In this study, the incidence of PALNM and isolated PALNM in patients with EC and its associated factors were evaluated. Of the patients with EC, 5.3% had PALNM and 1.19% had isolated PALNM. Independent predictors of PALNM were cervical glandular invasion and LVSI. Although adnexal involvement showed a relationship with PALNM, it was not found to be an independent predictor. The presence of PALNM and isolated PALNM were not associated with recurrence and mean DFS time. Although it is important to confirm the results of our study with prospective randomized controlled studies, our results can be a valuable reference in clinical settings.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Akbar Ibrahimov and Gökhan Boyraz have given substantial contributions to the study conception and design, methodology and formal analysis; Akbar Ibrahimov contributed to the study supervision; Akbar Ibrahimov and Gökhan Boyraz contributed to the manuscript draft and revised it critically. Both authors read and approved the final version of the manuscript.

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