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Evaluation of risk factors for pelvic and paraaortic lymph node metastasis in endometrioid type endometrial cancer

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ABSTRACT

Aim: Determining the relationship between clinical and pathological features in endometrial cancer is essential for both prognostic and potential therapeutic benefits. In this study, we aimed to investigate the relationship between pelvic and paraaortic lymph node (PLN and PALN) metastasis and prognostic factors in patients with endometrial cancer (EC).

Material and Method: Medical records of patients who underwent primary surgery for EC in our gynecological oncology center between the 2016 and 2018 were reviewed retrospectively. The relationship between pelvic and paraaortic lymph node metastasis was evaluated with data such as patient age, body mass index, serum CA 125 level, macroscopic tumor diameter, and patients' risk groups.

Results: Fifty-seven patients with EC were evaluated. Lymph node involvement was detected in 10 patients (17.5%). Acording to Modiffied Mayo criterias ; the patients with grade 3 EC had a higher risk of metastasis compared to other grades (p=0.025). Patients with lymph node metastases had a greater depth of invasion (p=0.001). There was no relationship between tumor size and lymph node metastasis (p=0.494). In the logistic regression analysis, the depth of invasion was found to be an independent risk factor for lymph node metastasis. There was no significant relationship between the presence of PLN and PALN metastases in patients with high-risk endometrial cancer, but the presence of PALN metastasis was significant in patients with low-risk endometrial cancer with PLN metastasis (p=0.002).

Conclusion: These findings support the idea that routine evaluation of tumor invasion depth during endometrial cancer surgery may be useful in predicting lymph node metastasis and guiding the operation.

Keywords: Endometrial cancer, metastasis, lymph node

INTRODUCTION

Endometrial cancer is the fourth most common type of cancer in women after breast, lung and colorectal cancers, and is the most common gynecological malignancy in our country (1,2). Age, obesity, parity, caucasian race, endocrine diseases, early menarche-late menopause, tamoxifen use and family history are risk factors for endometrial cancer (1). The most common pathogenetic type is associated with exposure to endogenous or exogenous unopposed estrogen, and the tumor starts as a hyperplastic endometrium and progresses to cancer. The other endometrial cancer is the type that develops spontaneously without an estrogen source and generally has a worse prognosis than estrogen-dependent cancer. The mainstay of surgical treatment is bilateral salpingo-oophorectomy, paraaortic and pelvic lymphadenectomy, and total hysterectomy, including examination of the abdominal cavity fluid. Laparoscopy has been associated with fewer postoperative complications than laparotomy.

In addition to the surgical staging recommended by the International Federation of Gynecology and Obstetrics, histological features, size, degree of myometrial invasion, serum tumor marker levels, lymphovascular area invasion, peritoneal cytology and lymph node (LN) involvement are also of prognostic importance (1,3-5).

LN involvement is important in terms of initiating postoperative adjuvant therapy and determining the area of radiotherapy. There is still no definitive method used to detect the presence of perioperative LN metastases. Routine pelvic and paraaortic lymph dissection (lymphadenectomy) is controversial in patients with early stage endometrial cancer. Although there are studies in

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the literature reporting that survival is associated with improvement, there are also research results suggesting that it is not necessary (6-9).

In this study, it was aimed to determine the risk factors for pelvic and paraaortic lymph node metastasis by examining the clinical and surgical characteristics of endometrial cancer patients who underwent surgical staging and to compare them with the literature data.

MATERIAL AND METHOD

In this study, 57 endometrioid-type endometrial cancer patients who had complete medical records (excluding non-endometrioid cancer and/or extrauterine involvement) and underwent endometrial cancer surgery in the Gynecology Clinic of the University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital between January 2016 and December 2018 were evaluated retrospectively. Written consent was obtained from all patients for treatment and analysis of scientific data. The study was carried out with the permission of Prof. Dr. Cemil Taşçıoğlu City Hospital Clinical Researches Ethics Committee (Date: 06.12.2021 Decision No: 06.12.2021/421). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Information about age, body mass index (BMI), International Federation of Gynecology and Obstetrics (FIGO) stage, myometrial invasion, menopause status, tumor size, type of surgery (laparoscopy/laparotomy) and serum CA 125 level were collected by examining the relevant medical records. Lymph node regions were classified as pelvic (PLN) and paraaortic lymph node (PALN). All patients underwent lymphadenectomy according to total hysterectomy, bilateral salpingo-oophorectomy and perioperative frozen result. Lymphadenectomy was performed in the presence of grade 3 and/or more than 50% myometrial invasion and/or cervical invasion and in the presence of tumors larger than 2 cm. The FIGO 2009 staging system was used. Prognostic factors determining lymph node metastasis distribution and metastasis were determined. The data and statistical results obtained from the literature regarding the prognostic factors determining lymph node metastasis were taken into consideration. In the study conducted by Mariani et al. (10) in Mayo clinic in 2000, they determined the low and high risk groups of patients with endometrial cancer. Accordingly, patients with tumor size ≤ 2 cm, stage 1 or 2 tumors and invasion depth <50% are considered low-risk. Therefore, in our study, patients with low risk characteristics were defined as "endometrioid type endometrial cancer, FIGO grade 1 or 2 histology, myometrial invasion < 50%" and other patients were classified as high-risk.

The inclusion criteria are listed below:

1. Patients with pathologically proven endometrial cancer.
2. Patients over 18 years of age.
3. Patients whose detailed medical records can be accessed, including the patient's history, clinical findings, laboratory and pathology test results, treatment results, etc.

The exclusion criteria are as follows:

1. Patients with no definitive pathological diagnosis.
2. Patients with secondary cancer.
3. Patients with conservatively treated endometrial cancer.

Statistical Analysis

In this study, Statistical Package for Social Science (SPSS) version 23.0 was used. The normal distribution of the data was evaluated with the Shapiro-Wilk-W test, and the continuous variables were evaluated with the Student-t test or Mann-Whitney U test. Categorical variables were evaluated by chi-squared test or Fisher's exact tests. Logistic regression and ROC curve analysis were used to evaluate lymph node metastasis and associated clinical conditions. A value of $p<0.05$ was considered statistically significant.

RESULTS

In the three-year period, 57 female patients were operated with laparotomy or laparoscopy methods applied in the gynecological oncology unit of our hospital due to endometrial cancer. The mean age of the patients was 60.72±9.12 years. In-hospital mortality rate was 0%. The clinical and surgical characteristics of patients with and without pelvic and paraaortic nodal metastasis are given in **Table 1**. Nodal metastasis was not seen in 47 (82.5%) patients, while it was present in 10 (17.5%) patients. There was no significant relationship between age, weight, height, body mass index (BMI), preCA125 level, menopause status and nodal metastasis ($p>0.05$). More PALNs were excised in patients with nodal metastasis ($p=0.006$). The presence of nodal metastasis does not have a significant effect on the duration of the operation ($p=0.643$).

The characteristics of the risk groups in the presence of nodal metastasis are shown in **Table 2**. According to the modified Mayo criteria, nodal lymph metastasis was found to be significantly lower in patients with lower risk than those with higher risk, that is, patients with grade 3 had a higher risk of metastasis than other grades ($p=0.025$), patients with lymph node metastasis had a higher depth of invasion ($p=0.001$), and there was no relationship between tumor size and lymph node metastasis ($p=0.494$).

Table 1. Clinical characteristics of patients with and without nodal metastasis

Presence of nodal metastasis	Not available n=47 (82.5%)	Available n=10 (17.5%)	p-value
Age	59.08±11.33	61.30±8.11	0.561 *
Weight (kg)	73.34±5.45	74.90±6.70	0.433 *
Height (cm)	165.70±4.13	166.30±4.40	0.683 *
Body mass index (BMI) (kg/m2)	31.20±31.16	26.84±1.76	0.663 *
Serum CA125 level	16.60±13.26	47.60±64.42	0.071 **
Menopause Status			0.671 ****
Menopause	36 (%76.6)	9 (%90.0)	
Premenopausal	11 (%23.3)	1 (%10.0)	
Surgical technique			0.034 ***
Laparoscopy	23 (%48.9)	1 (%10.0)	
Laparotomy	24 (%51.1)	9 (%90.0)	
Number of excised pelvic lymph nodes	22.72±10.92	23.30±10.67	0.880 *
Number of excised paraaortic lymph nodes	5.62±11.33	11.10±7.50	0.006 **
Operation_duration (minutes)	162.98±41.69	151.50±17.96	0.643 **

* t-test, **Mann-Whitney U test, *** Chi-Square test, **** Fisher's Exact test

Table 2. Characteristics of risk groups in the presence of nodal metastasis

Presence of nodal metastasis	Not available n=47 (82.5%)	Available n=10 (17.5%)	p-value
Grade			0.025 *
1 & 2	43 (91.5%)	6 (60.0%)	
3	4 (8.5%)	5 (40.0%)	
Invasion			0.001 *
<50	36 (76.6%)	2 (20.0%)	
≥50%	11 (23.3%)	8 (80.0%)	
Tumor Size			0.494 **
<2 cm	21 (44.7%)	3 (30.0%)	
≥2 cm	26 (55.3%)	7 (70.0%)	

* Fisher's Exact test, ** Chi-Square test

The characteristics of the patients according to the low and high risk patient groups are given in **Table 3**. The number of low-risk patients was 20 (35.1%) and the number of patients with high-risk endometrial cancer was 37 (64.9%). There was no statistically significant relationship between age, weight, height, BMI, serum CA125 level, menopause status and duration of surgery and risk groups (p>0.05). When the surgical technique was examined, it was found that laparotomy technique was used more in high-risk patients (p=0.044). PLN and PALN were excised more frequently in high-risk patients (p=0.022; p=0.06).

Table 4 shows the surgical characteristics of the low and high-risk patient groups. Grade 3 cancer was significantly higher in the high-risk group (p=0.000). The higher invasion depth of 50% in the high-risk group was significantly higher (p=0.001). There was no significant relationship between the high-risk group and lymph node metastasis (p=0.467). There was no significant relationship between the presence of pelvic and paraaortic lymph node metastasis and patient risk groups (p>0.05) (**Table 5**).

Table 3. Characteristics of patients by risk groups

	Low, n=20 (35.1%)	High,n=37 (64.9%)	p-value
Age	58.45±11.36	60.03±10.61	0.603 *
Weight (kg)	74.00±6.55	73.41±5.19	0.708 *
Height (cm)	166.40±4.12	165.49±4.18	0.432 *
Body mass index (BMI) (kg/m2)	37.27±47.75	26.74±1.82	0.182 *
Serum CA125 level	15.95±15.09	25.32±36.48	0.186 **
Menopause Status			1.000 ****
Menopause	16 (%80.0)	29 (%78.4)	
Premenopausal	4 (%20.0)	8 (%21.6)	
Surgical technique			0.044 ***
Laparoscopy	12 (%60.0)	12 (%32.4)	
Laparotomy	8 (%40.0)	25 (%67.6)	
Number of excised pelvic lymph nodes	18.25±8.11	25.30±11.33	0.022 **
Number of excised paraaortic lymph nodes	2.00±5.42	9.05±12.32	0.006 **
Operation_duration (minutes)	167.25±47.75	157.57±33.10	0.449 **

* t-test, **Mann-Whitney U test, *** Chi-Square test, **** Fisher's Exact test

Tablo 4. Tumoral characteristics of risk groups

	Low n=20 (35.1%)	High n=37 (64.9%)	p-value
Stage			0.000 *
1	16 (80.0%)	3 (8.1%)	
2	4 (20.0%)	26 (70.3%)	
3	0 (0.0%)	8 (21.6%)	
Invasion			0.001 *
<50	19 (95.0%)	19 (51.4%)	
≥%50	1 (5.0%)	18 (48.6%)	
Tumor Size			0.000 *
< 2 cm	19 (95.0%)	5 (13.5%)	
≥ 2 cm	1 (5.0%)	32 (86.5%)	
Nodal Metastasis			0.467 **
Available	2 (10.0%)	8 (21.6%)	
No	18 (90.0%)	29 (78.4%)	

* Chi-Square test * * Fisher's Exact test

Table 5. Evaluation of the risk of pelvic and paraaortic nodal metastasis according to risk groups

	Low, n=20 (35.1%)	High, n=37 (64.9%)	p-value
Pelvic lymph node metastasis			0.699 *
Not available	18 (90.0%)	31 (83.8%)	
Yes	2 (10.0%)	6 (16.2%)	
Paraortic lymph node metastasis			0.697 *
Not available	19 (95.0%)	33 (89.2%)	
Yes	1 (5.0%)	4 (10.8%)	

* Fisher's Exact test

When high-risk patients were examined in two groups as those with and without PLN metastasis, no relationship was found between them and PALN metastasis. However, in patients with low-risk a patient with PLN metastasis (n=1), PALN metastasis was also present and this finding was statistically significant (p=0.002) (**Table 6**).

Table 6. The relationship between pelvic and paraaortic nodal metastases

Risk Group	Pelvic lymph node metastasis	Paraaortic lymph node metastasis		p value
		Not available	Available	
High-risk patients*				0.052 *
	Not available	29 (87.9%)	2 (50.0%)	
	Available	4 (12.1%)	2 (50.0%)	
Low-risk patients				0.002 **
	Not available	18 (94.7%)	0 (0.0%)	
	Available	1 (5.3%)	1 (100.0%)	

* Chi-Square test, ** Fisher's Exact test

In the logistic regression evaluation, the depth of invasion was found to be significantly correlated with the presence of PALN and PLN metastases (p=0.02) (**Table 7**). **Figure** shows the ROC curve, according to which the cut-off value was 0.526 and the area under the curve was 0.809.

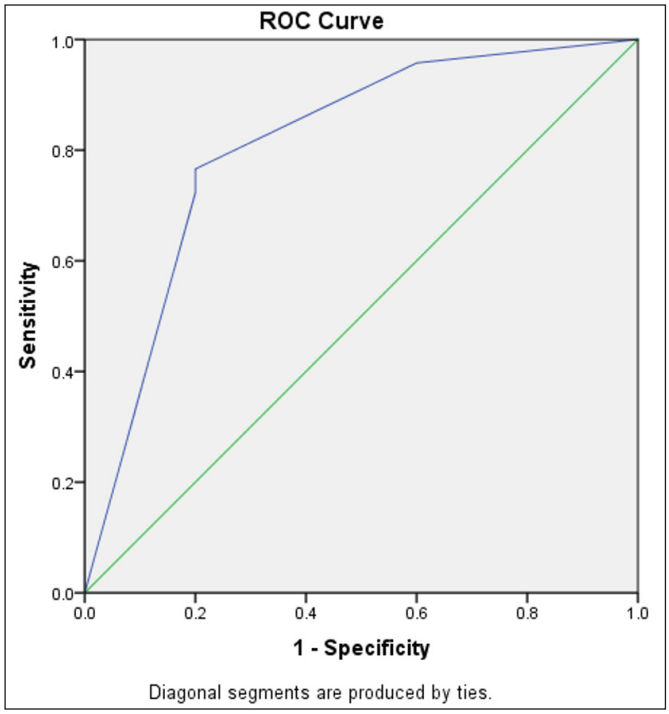

Figure. Cutoff Value: 0.526, Roc Curve and Area Below Curve (Auc): 0.809

Table 7. Logistic regression assessment

	Odds Ratio	P value
Invasion	2.218	0.020
Grade	0.908	0.184

DISCUSSION

In this study, it was aimed to determine the clinical and pathological risk factors for pelvic and paraaortic lymph node metastases in patients with endometrial cancer. In addition to determining important risk factors for LN metastases, the effect of nodal involvement was also evaluated. According to the results of our study, laparotomy procedure was performed more in patients with nodal metastasis. The presence of nodal metastasis did not affect the duration of the operation. Tumoral invasion depth was higher in patients with lymph node metastasis. There was no relationship between tumor diameter and the presence of lymph node metastasis. Clinical features such as age, weight, height, BMI, serum CA125 level, menopause status and duration of surgery were not statistically significantly correlated with patient risk groups. PLN and PALN were excised more in high-risk patients. There was no significant relationship between the presence of lymph node metastasis and patient risk groups. However, the depth of invasion is associated with the presence of PALN and PLN metastasis, and the depth of invasion may be useful in predicting lymph node metastasis.

The need for paraaortic (PA) lymphadenectomy in terms of survival in the treatment of endometrial cancer is controversial. In addition, the incidence of finding metastatic lymph nodes in the PA region is not very high in patients undergoing systematic pelvic and PA lymphadenectomy. In a study conducted by Fotopoulou et al. (11) on 62 patients with moderate and high-risk endometrial cancer and aimed to determine the predictive factors for pelvic and aortic lymphadenectomy, pelvic node involvement was reported in 21% of patients and both pelvic and PA lymph nodes were affected in 12% of this patient group. In our sample, lymph node involvement was present in 17.5% of the patients. Since low stage patients were also evaluated in our study, different results may have been obtained. According to the results of their study using logistic regression analysis to determine independent prognostic factors for PALN metastasis, Karube et al. (12) revealed that PLN and ovarian metastasis were associated with PALN metastasis. In this study, no significant relationship was found between lymph node metastasis and high-risk endometrial cancer. According to the results of a large patient population retrospective study comparing the relationships between paraaortic lymph node metastasis and various clinicopathological factors to evaluate whether paraaortic lymph node dissection is necessary in the treatment of endometrial cancer, the researchers emphasized that pelvic lymph node status should be taken into consideration when deciding whether to perform PALN dissection in patients with endometrial

cancer and that PALN dissection is not required if PLN metastasis is not present (13). In our study, the presence of PALN metastasis was also found to be statistically significant in patients with PLN metastasis, even in low-risk patients. In this study, which we set out to identify high-risk patients who will benefit from paraaortic lymphadenectomy and to create risk groups, we showed the importance of invasion depth. As a result, with the help of risk models, the status of PALN can be determined more clearly and unnecessary dissection of the PA region and related morbidity can be prevented. However, these models should be usable in routine practice. For this reason in our study, it was aimed to divide the patients into endometrial cancer risk groups and evaluate the presence of nodal metastasis. However, prospective studies with a larger number of cases are needed to define the risk groups more clearly and to standardize the treatment. In this study, involvement in the PA region was detected in 8.7% of patients who underwent systematic lymphadenectomy up to the level of the renal vein. It is possible to prevent procedure-related morbidity by evaluating independent risk factors such as depth of invasion.

Unlike cervical cancer, lymphatic spread in endometrial carcinoma does not occur in regional order. This is due to the variability of tumor localization and the apparent incidence of adnexal metastasis in endometrial carcinoma. Therefore, the lymphatic chain pattern is not associated with predictable lymphatic spread in endometrial carcinoma (14). Turan et al. (14) aimed to define a high-risk group for PALN metastasis in patients with endometrial cancer and showed that PALN involvement significantly increased in patients with high-risk endometrial cancer. Although PLN and PALN were excised more in high-risk cases evaluated in this study, no significant relationship was found between the presence of lymph node metastasis and patient risk groups. This can be explained by the low number of patients.

In their study evaluating the risk factors for lymph node metastasis in patients with endometrial cancer, Taş et al. (15) found lymph node metastasis in 9.1% of the patients participating in the study [pelvic only in 3.5%, paraaortic only in 2.1%, both pelvic and paraaortic lymph node involvement in 3.5%] and a significant relationship between lymph node metastasis and deep myometrial invasion (≥50% invasion depth), lymphovascular space invasion, positive peritoneal cytology and tumor size. According to the results of this study, there was a positive correlation between tumor size and lymph node metastasis. Similarly, our results show that paraaortic lymph node involvement is less than pelvic node involvement. Similarly, we found a relationship between lymph node metastasis and deep myometrial invasion.

In a study by Yokoyama et al. (16) in 1997 investigating the importance of pelvic and paraaortic lymphadenectomy in endometrial cancers, they found that both PLN and PALN metastases in 10% of patients with Stage I disease according to the FIGO 1988 classification, and reported that there was no significant relationship between the location or number of PLN and PALN metastases. In multivariate analysis, it was reported that low-grade and deep myometrial invasion had an independent relationship with PALN metastases, whereas vascular cavity invasion and cervical invasion were independently associated with PLN metastases. According to the advanced statistical evaluation of our data, it was observed that the depth of invasion was independently correlated with nodal lymph involvement. Furthermore, the survival of patients with PALN metastasis was significantly worse compared to patients with PLN metastasis alone (44.4% and 80.0%, respectively, $p< 0.05$). These results reveal that PLN and PALN metastases occur frequently even in early stage endometrial cancer, and PLN metastases, especially PALN metastases, have a serious effect on patient survival. In our study, survival was not evaluated because it was not the main purpose of the study.

In a study evaluating the effects of PALN in endometrial cancer patients without pelvic lymph node metastasis, it was reported that those without PLN involvement and those with PALN involvement constituted only 2.4% of all cases included in the study (9). We only had 5%. The probability of isolated PALN metastasis is considered low enough. The effects of a PLN-PALN lymphatic propagation model should therefore be considered by gynecological oncologists when determining patient management strategies in endometrial cancer.

Our study has some limitations such as being single-center and retrospective. However, our results are important in terms of showing that the depth of invasion is an important risk factor in the risk of increased LN metastasis in patients with endometrial cancer. Therefore, considering the depth of invasion before the operation when making the PALN decision may affect the lymph node sampling decision and the degree of LN sampling in high-risk patients.

CONCLUSION

According to our study, the only independent risk factor for lymph node metastasis in endometrial cancer cases is the depth of invasion. There was no linear relationship between tumor size and lymph node metastasis. Systemically concurrent pelvic and paraaortic lymphadenectomy may be useful for providing prognostic information, selecting appropriate postoperative treatment, and performing accurate figo staging in all patients with low and high endometrial cancer, except

those with stage Ia stage 1 and stage IV. Further studies are needed to determine other risk factors for lymph node metastasis. Randomized prospective publications evaluating systemic lymphadenectomy over disease-free survival times are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Prof. Dr. Cemil Taşçıoğlu City Hospital Clinical Researches Ethics Committee (Date: 06.12.2021 Decision No: 06.12.2021/421).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: The author declares that he has participated in the design, execution, and analysis of the paper, and he has approved the final version.

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