The Predictability of Lymph Node Metastasis in Patients with Endometrial Cancer

Endometrium Kanserli Hastalarda Lenf Nodu Metastazının Öngörülebilirliği

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ABSTRACT Objective: The aim of this study was to predict lymphatic involvement in endometrial cancer patients using clinicopathological variables in patients treated with surgical staging. **Material and Methods:** A retrospective chart review was performed in 147 women with pathologically proven endometrial carcinoma (EC) who were treated between January 2006 and January 2011. Surgically staged 125 patients were included in this study. We choose the patients who underwent surgical staging including washing cytology, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node (PLN) and para-aortic lymph node (PALN) dissection. The depth of tumor invasion, cervical extension and the tumor diameter were intraoperatively assessed via fresh frozen sections of the removed uterus. Demographic data, preoperative and postoperative variables were evaluated for association with any lymph node (LN) metastasis. **Results:** The medical records of 125 patients were eligible for analysis. The presence of LN metastasis was significantly associated with the patient's age (p=0.016) and but not with body mass index (p=0.288). Preoperative findings such as atypical cells in smear (p=0.001), computed tomography (CT) features of malignancy (p=0.014), ultrasonographic findings related with malignancy (p=0.011), presence of myometrial invasion on CT (p=0.011), preoperative serum CA125 level (p<0.001), preoperative serum CA15-3 level (p<0.001), clinical stage (p<0.001), and histologic grade (p=0.001) were significantly associated with LN metastasis. Postoperative findings which were significantly associated with LN metastasis were grade of differentiation, lymphovascular invasion, depth of myometrial invasion, dissemination to omentum or appendix, and positive peritoneal cytology. The mean number of all lymph nodes removed during operation was 38.9±14.194 (range 9- 81), PLN number was 32±11.747 (range 9-75) and PALN number was 7±5.123 (range 0-20). Nodal metastasis was shown in 24 patients (19.2%). Isolated PLN metastasis was shown in 9 patients (37%), isolated PALN metastasis in one (4%); both PLN and PALN metastasis was shown in 14 patients (59%). The most frequently affected LN area was the region of the left external iliac artery, with a ratio of 14%.The p value was set at <0.05 for statistical significance. **Conclusion:** Lymphatic involvement in EC should be carefully evaluated using clinicopathologic variables of patients. Demographic characteristics, preoperative and postoperative surgical-pathologic factors determine the lymph node metastasis of the tumor.

Key Words: Endometrial neoplasms; lymph node excision; lymph nodes

ÖZET Amaç: Bu çalışmanın amacı, cerrahi evreleme uygulanan endometrial kanserli hastalarda klinik ve patolojik değişkenleri kullanarak lenf nodu (LN) tutulumunun öngörülebilmesidir. **Gereç ve Yöntemler:** Ocak 2006 ile Ocak 2011 tarihleri arasında, endometrial kanser tanısı alan ve tedavisi yapılan 147 hasta retrospektif olarak incelendi. Cerrahi olarak evrelenmiş 125 hasta çalışmaya alındı. Peritoneal sitoloji, total abdominal histerektomi, bilateral salpingo-oophorektomi ve pelvik ve/veya para-aortik LN diseksiyonunu kapsayan cerrahi evrelemeye maruz kalan hastaları seçtik. Tümör invazyon derinliği, servikal yayılım ve tümör çapı, frozen section ile intraoperatif olarak değerlendirildi. Demografik veriler, preoperatif ve postoperatif değişkenler herhangi bir LN metastazı ile ilişki açısından değerlendirildiler. **Bulgular:** Araştırmaya alınan hastaların 125'inin kayıtları analiz edildi. Demografik değişkenlerden, hasta yaşı (p=0,016) LN metastazı ile anlamlı ilişkili iken, beden kitle indeksi anlamlı ilişkili değildi (p=0,288). Preoperatif bulgulardan, smearde atipik hücre anormalikleri (p=0,001), bilgisayarlı tomografide (BT) malignite bulguları (p=0,014), malignite ile ilişkili ultrsonografik bulgular (p=0,011), BT'de myometrial invazyon varlığı (p=0,011), preoperatif serum CA125 düzeyleri (p<0,001), preoperatif serum CA15-3 düzeyleri (p<0,001), klinik evre (p<0,001) ve histolojik grade (p=0,001) LN metastazı ile anlamlı derecede ilişkili idi. Postoperatif bulgulardan diferansiyasyon derecesi, lenfovasküler invazyon, myometrial invazyon derinliği, omentum veya apendiks tutulumu ve pozitif peritoneal sitoloji LN metastazı ile anlamlı ilişkili bulundu. Operasyonda çıkarılan total LN sayısı ortalama 38,9±14,194 (9-81) idi. Çıkarılan pelvik lenf nod (PLN) sayısı ortalama 32±11,747 (9-5) iken para-aortik lenf nod (PALN) sayısı ortalama 7±5,123 idi (0-20). Nodal metastaz 24 (%19,2) hastada gösterildi. İzole PLN metastazı, 9 (%37) hastada; izole PALN metastazı ise, bir (%4) hastada ortaya konuldu. Hem PLN ve hem de PALN metastazı 14 (%59) hastada mevcuttu. En çok etkilenen LN sahası, %14'lük bir oranla sol external iliak arter bölgesi idi. İstatistiksel anlamlılık için p değeri <0,05 olarak belirlendi. **Sonuç:** Endometrial kanserli olgularda lenf nodu tutulumu, hastanın klinik ve patolojik değişkenleri kullanılarak dikkatli bir şekilde değerlendirilmelidir. Demografik özellikler, preoperatif ve postoperatif cerrahi-patolojik faktörler tümörün lenf noduna yayılımını belirlemektedir.

Anahtar Kelimeler: Endometriyal tümörler; lenf düğümü çıkartma; lenf nodları

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Endometrial cancer (EC) is the most common malignant tumor of the female genital tract. Before 1988, the staging system used for EC was based on the clinical findings. After the poor prognostic nature of lymphatic involvement was recognized, Federation of Gynecology and Obstetrics (FIGO) announced the currently available surgical staging system that is based on histopathologic characteristics of tumors identified by a surgical staging procedure including complete pelvic lymph node (PLN) and para-aortic lymph node (PALN) dissection.

Some authors questioned the routine use of complete lymphadenectomy and proposed the use of high-risk histopathologic variables to predict the risk of lymphatic involvement. Among factors that can be evaluated before and during an operation, myometrial invasion and tumor grade are well recognized prognostic factors in EC and predictors of extrauterine spread.[1,2] Many different prognostic factors were reported to be related to lymphatic involvement.[3,4] Although the main purpose of these series was to formulate lymphatic dissection by using prognostic factors, the results and conclusions of the mentioned studies have been rather inconsistent.

The aim of the present study was to predict the lymphatic involvement in EC using clinicopathological variables in patients treated with surgical staging.

MATERIAL AND METHODS

STUDY DESIGN

We retrospectively reviewed the medical records of 147 women with pathologically proven endometrial carcinoma and were treated between January 2006 and January 2011. Surgically staged 125 patients were included in this study. Institutional review board approval was obtained. Demographic data, preoperative and postoperative variables were evaluated for their association with any lymph node (LN) metastasis.

Demographic data including age at diagnosis, body mass index (BMI) (obesity= BMI>30 kg/m^2), parity, presenting symptoms, personal background, and family history were obtained from the archive records. Examinations such as transvaginal ultrasonography (TVS), cystoscopy, rectosigmoidoscopy, colon X-ray in the presence of fecal occult blood, and computerized tomography (CT) or magnetic resonance imaging (MRI) were performed in all cases. Findings suggesting advanced disease on CT or MRI (the deep of myometrial invasion, the presence of cervical involvement, the presence/suspicion of parametrial invasion, the presence/suspicion of LN metastasis) were recorded to determine the value of these metods in the prediction of the spread of the disease, besides routine preoperative examinations. On TVS, we also recorded the total diameter of the endometrial cavity as well as its irregularity (total diameter of the endometrial cavity ≥1 cm was investigated whether to be an important parameter or not).

All operations were performed by gynecologic oncologists. All patients underwent surgical staging including washing cytology, total abdominal histerectomy, bilateral salpingo-oophorectomy, and PLN and PALN dissection. The depth of tumor invasion, cervical extension and the tumor diameter were intraoperatively assessed via fresh frozen sections of the removed uterus. Bilateral pelvic lymphadenectomy included complete skeletonization of the common, external and internal iliac vessels and harvesting all lymphatic tissue in the upper and lower parts of obturator fossa after visualization of the obturator nerve and lumbosacral trunk. The superior surgical margin of the dissection for the pelvic nodes was where the ureters cross the common iliac arteries. The anterior distal surgical margin of the pelvic lymphadenectomy was the circumflex iliac vein. The para-aortic lymphadenectomy was performed by mobilizing the paracolic peritoneum along the lateral border of the ascending and descending colon, permitting identification of the proximal ureters and high division of the ovarian vessels. This allowed visualization of the whole retroperitoneum up to the superior borders of the renal veins. All lymphatic tissue was then harvested from the lateral, anterior, and medial aspects of the vena cava and aorta, up to the renal veins. Postoperative pathologic specimens

were evaluated for tumor stage, degree of myometrial invasion, lymphovascular invasion (LVI), histologic type, histologic grade (three grades according to the FIGO surgical staging system adopted in 1988), and LN metastasis (present or absent).

STATISTICAL ANALYSIS

Data were analysed using the Statistical Package for Social Sciences 11.0 for Windows (SPSS INC, Chicago, IL). Statistical significance was analysed using Chi-square tests and Fisher's exact test for categorical variables. Independent samples t-test was used to compare continuous variables. A p-value <0.05 was considered significant.

RESULTS

The medical records for 125 patients (mean age 61.49±11.02 years; range 36-85) were eligible for analysis. Of all, 21.4% of the cases were in reproductive stage and 88.6% were postmenopausal. The mean ages of the patients with EC, and those with LN metastasis were found to be 61.49, and 66.33 years, respectively.

Demographic variables like BMI, parity, symptoms, personal background and family history are shown in Table 1. Mean BMI was 30.5 kg/m^2. The impacts of demographic variables such as age, BMI, and parity on the presence of LN metastasis were studied. As for demographic variables, patient's age (p=0.016) was significantly associated with the presence of lymph node metastasis, but not BMI (Table 2).

Among preoperative findings, presence of atypical cells on smear (p=0.001), findings suggesting malignancy on CT (p=0.014), ultrasonographic findings suggesting malignancy (p=0.011), presence of myometrial invasion on CT (p=0.011), preoperative levels of CA 125 (p<0.001), preoperative levels of CA 15-3 (p<0.001), clinical stage (p<0.001) and histological grade (p=0.001) were significantly associated with LN metastasis (Table 3). Glandular cell abnormality was associated with lymph node involvement in 50% of the cases. We detected lymph node metastases in 83.3% of 6 patients with increased CA- 15-3 values (>37 IU/ml).

TABLE 1: The demographic and clinical variables of the patients.

Variable		n (%)
Body mass index	Underweight (<18.5 kg/m^2)	4 (3.2%)
	Normal (18.5-24.9 kg/m^2)	29 (23.4%)
	Overweight (25-29.9 kg/m^2)	82 (66.1%)
	Obese (>30 kg/m^2)	10 (8.1%)
Parity	Nulliparity	4 (3.2%)
	Primiparity	15 (12%)
	Multiparity	106 (84.8%)
Presenting symptoms	Postmenopausal bleeding	81 (64.8%)
	Menometrorrhagia	20 (16%)
	Inguinal pain	15 (12%)
	Vaginal discharge	4 (3.2%)
	Abdominal distension	5 (4%)
Personal background	Diabetes mellitus	17 (13.7%)
	Hypertension	26 (21%)
	Coronary artery disease	3 (2.4%)
	Chronic obstructive pulmonary disease	3 (2.4%)
	Diabetes mellitus+Hypertension	17 (13.7%)
Family history	Carcinoma	5 (4%)
	Endometrium carcinoma	4 (3.2%)
	Breast carcinoma	1 (0.8%)
	Negative	120 (96%)

TABLE 2: The impact of demographic variables on lymph node metastas.

	N-stage	n	Mean±SD	p Value
Age	N0	101	60.33±10.732	0.016
	N1	24	66.33±11.146	
Weight	N0	101	82.69±9.524	0.004
	N1	24	76.46±9.193	
Body mass index	N0	101	0.31±0.041	0.288
	N1	24	0.30±0.033	
Parity	N0	101	2.72±1.311	0.194
	N1	24	3.13±1.569	

SD: Standard deviation.

Preoperative serum CA 19-9 level was not significantly associated with LN metastasis (p=0.511). LN metastases were not seen in patients with EC with a regular endometrium having a wall thickness of ≤1 cm. The risk of LN metastases increased in patients with irregular endometrium with a wall thickness of >1 cm.

There was a statistically significant difference between the groups in postoperative findings in-

TABLE 3: The impact of preoperative findings on lymph node metastasis.

		Negative n (%)	Positive n (%)	p Value
Atypical cells in smear	Absent	90 (85.7%)	15 (14.3%)	0.002
	Present	10 (52.6%)	9 (47.4%)	
	Total	100 (80.6%)	24 (19.4%)	
CT findings	Benign	65 (87.8%)	9 (12.2%)	0.014
	Malignant	35 (70%)	15 (30%)	
	Total	100 (80.6%)	24 (19.4%)	
Sonographic findings	Benign	40 (93.0%)	3 (7.0%)	0.011
	Malignant	60 (74.1%)	21 (25.9%)	
	Total	100 (80.6%)	24 (19.4%)	
Myometrial invasion on CT	Absent	62 (88.6%)	8 (11.4%)	0.011
	Present	38 (70.4%)	16 (29.6%)	
	Total	100 (80.6%)	24 (19.4%)	
CA 125	≤35 IU/ml	91 (86.7%)	14 (13.3%)	0.001
	>35 IU/ml	9 (47.4%)	10 (52.6%)	
	Total	100 (80.6%)	24 (19.4%)	
CA 19-9	≤37 IU/ml	88 (81.5%)	20 (18.5%)	0.511
	>37 IU/ml	12 (75%)	4 (25%)	
	Total	100 (80.6%)	24 (19.4%)	
CA 15-3	≤31 IU/ml	99 (83.9%)	19 (16.1%)	0.001
	>31 IU/ml	1 (16.7%)	5 (83.3%)	
	Total	100 (80.6%)	24 (19.4%)	
Clinical stage	Early stage (Ia-Ib)	93(93.9%)	6(6.1%)	0.001
	Advanced stage (II-III-IV)	8(30.8%)	18(69.2%)	
	Total	101(80.8%)	24(19.2%)	
Histologic grade	Grade 1	70 (90.9%)	7 (9.1%)	**G1-G2:0.001**
	Grade 2	23 (63.9%)	13 (36.1%)	**0.001 G1-G3:0.020**
	Grade 3	6 (60%)	4 (40%)	**G2-G3:1.000**
	Total	99 (80.5%)	24 (19.5%)	

CT: Computerized tomography.

cluding grade of differentiation, histological type, LVI, depth of myometrial invasion, involvement of omentum or appendix and positive peritoneal cytology ($p<0.001$) (Table 4). LN metastasis was detected in 41.9% of patients with deep myometrial invasion (≥1/2), while detected in 7.3% of the patients with myometrial invasion <50%. When myometrial invasion was investigated, a cut-off value of 15.5 mm was revealed. No LN metastasis was detected in 94% of 50 patients with myometrial invasion ≤15.5 mm. On the other hand, five of seven patients with myometrial invasion >15.5 mm showed LN metastasis.

When the comparisons were done between preoperative histological grades in terms of LN metastasis, there was no statistically significant difference between grade 2 and grade 3 ($p>0.05$), whereas statistically significant differences were seen between grade 1 and grade 2 ($p<0.001$), grade 1 and grade 3 ($p<0.020$), in favor of grade 1 (Table 3). When the comparisons were done between postoperative histological grades, there were statistically significant differences between the groups (grade 1 vs. grade 2, grade 2 vs. grade 3 and grade 1 vs. grade 3) ($p<0.038$, $p<0.001$, $p<0.034$, respectively) (Table 4).

TABLE 4: The impact of postoperative findings on lymph node metastasis.

		Negative n (%)	Positive n (%)	p Value
Postoperative Grade	Grade 1	71 (92.2%)	6 (7.8%)	**G1-G2:0.038**
	Grade 2	21 (75%)	7 (25%)	**<0.001 G1-G3:0.001**
	Grade 3	9 (45%)	11 (55%)	**G2-G3:0.034**
	Total	101 (80.8%)	24 (19.2%)	
Histological type	Adenocarcinoma	96 (85%)	17 (15%)	**Adenoc.-PS: 0.001**
	Papillary serous	1 (14.3%)	6 (85.7%)	**Adenoc.-CC: 0.400**
	Clear cell	2 (66.7%)	1 (33.3%)	**Adenoc.-Adenos.:1.000**
	Adenosquamous	2 (100%)	-	**PS-CC: 0.183**
	Total	101 (80.8%)	24 (19.2%)	**PS-Adenos: 0.083**
				CC-Adenos: 1.000
Lymphovascular invasion	Absent	87 (100%)	-	
	Present	14 (36.8%)	24 (63.2%)	<0.001
	Total	101 (80.8%)	24 (19.2%)	
Depth of myometrial invasion	<1/2	76 (92.7%)	6 (7.3%)	
	≥1/2	25 (58.1%)	18 (41.9%)	<0.001
	Total	101 (80.8%)	24 (19.2%)	
Dissemination to omentum	Absent	94 (94%)	6 (6%)	
	Present	-	16 (100%)	<0.001
	Total	94 (81%)	22 (19%)	
Dissemination to appendix	Absent	68 (88.3%)	9 (11.7%)	
	Present	1 (14.3%)	6 (85.7%)	<0.001
	Total	69 (82.1%)	15 (17.9%)	
Positive peritoneal cytology	Absent	98 (83.8%)	19 (16.2%)	
	Present	-	5 (100%)	<0.001
	Total	98 (80.3%)	24 (19.7%)	

Adenoc.: Adenocarcinoma; PS: Papillary serous; Adenos.: Adenosquamous; CC: Clear cell.

Frequency of metastatic LNs detected in cases with preoperatively determined tumor grades were as follows: Grade I, 9.1%; Grade II 36%; Grade 3, 40%. However the frequency of metastatic LNs as determined postoperatively were as follows: Grade I, 7.8%; Grade II, 25.0%; Grade III, 55.0%.The histological type was endometrioid adenocarcinoma in 113 (90%) patients, papillary serous carcinoma in 7 (5.6%) patients and clear cell adenocarcinoma in 3 (2.4%) patients. Eighty five percent of patients with endometrial adenocarcinoma did not have LN metastasis while 15% of patients had positive lymph nodes. Only one of 7 patients diagnosed with papillary serous carcinoma did not have LN metastasis, compared with six of seven patients who had positive lymph nodes. Although the number of cases is small, we detected lymph node metastases in 33.3% of the cases with clear cell endometrial carcinoma (Table 4).

When the dual evaluation results of histological types were scrutinized according to LN metastasis; it has been found that there was statistically significant differences between adenocarcinoma and papillary serous carcinoma ($p<0.05$). There was no statistically significant differences between the rest of the groups ($p>0,05$) (Table 4).

Presence of LN metastasis was significantly associated with depth of myometrial invasion (cut-off value, 15.5 mm). LN metastasis was not found in 94 % of 50 patients with demonstrated depth of tumoral invasion of ≤15.5 mm. In 71.4% of 7 patients with detected depth of tumoral invasion of >15.5 mm, metastatic lymph nodes were found.

Detailed description of the extirpated and affected lymph nodes divided by area in the 125 patients with EC was shown in Table 5 (Detailed description for 24 patients with nodal metastasis is shown in Table 6). The mean number of all lymph nodes removed intraoperatively was 38.9±14.194 (range 9-81), the number of PLN was 32±11.747 (range 9 -75) and the number of was PALN 7±5.123 (range 0-20). Nodal metastasis was shown in 24 patients (19.2%). Isolated PLN metastasis was shown in 9 patients (37%), isolated PALN metastasis in one (4%); both PLN and PALN metastasis was shown in 14 patients (59%). The most frequently affected LN area was the region of the left external iliac artery, with a ratio of 14%.

DISCUSSION

Calculating the probability of LN metastasis is important for the proper management of EC. The largest study was published by Creasman et al. in which the relationship between prognostic variables and LN metastasis was investigated by evaluating 621 EC patients after a surgical staging procedure including selective pelvic and paraaortic lymphadenectomy.[1] Clinical stage, grade, deep myometrial invasion, peritoneal cytology, isthmus-cervix location, adnexal involvement, capillary-like space involvement, and extrauterine tumoral metastasis were found to be related to LN metastases. Additionally, papillary and clear cell carcinomas were correlated with LN metastasis.

Some investigators ascertained advanced age as an independent risk factor correlated with endometrial neoplasia.[5,6] In our study, the presence of LN metastasis was associated significantly with the patient's age.

TABLE 5: Detailed description of the extirpated and affected lymph nodes divided by area in 125 patients with endometrial cancer.

		Lymph node number	
Lymph-node areas	**N-status**	**Mean±SD**	**%**
All region LN	N0	38.9±14.194	100%
	N+	1.34±4.084	
Total pelvic LN	N0	31.97±11.747	82.19%
	N+	1.03±3.365	
Para-aortic LN	N0	6.93±5.123	17.81%
	N+	0.31±1.066	
Right external iliac LN	N0	5.12±3.007	13.16%
	N+	0.14±0.605	
Left external iliac LN	N0	5.01±2.85	12.88%
	N+	0.18±0.53	
Right internal iliac LN	N0	2.91±2.403	7.49%
	N+	0.08±0.413	
Left internal iliac LN	N0	1.90±2.291	4.90%
	N+	0.07±0.363	
Right common iliac LN	N0	4.15±3.583	10.67%
	N+	0.09±0.492	
Left common iliac LN	N0	4.42±3.283	11.37%
	N+	0.14±0.564	
Right obturator LN	N0	4.49±3.207	11.54%
	N+	0.19±0.859	
Left obturator LN	N0	3.96±3.196	10.18%
	N+	0.13±0.718	

LN: Lymph node.

TABLE 6: Detailed description of the extirpated and affected lymph nodes divided by area in 24 patients with nodal metastasis.

		Lymph node number	
Lymph-node areas	**N-status**	**Mean±SD**	**%**
All region LN	N0	37.88±17.501	100%
	N+	7.00±6.972	
Total pelvic LN	N0	30.71±14.79	81.08%
	N+	5.38±6.056	
Para-aortic LN	N0	7.17±4.198	18.92%
	N+	1.63±1.974	
Right external iliac LN	N0	5.04±2.774	13.31%
	N+	0.75±1.225	
Left external iliac LN	N0	5.29±3.544	13.97%
	N+	0.96±0.859	
Right internal iliac LN	N0	2.38±2.499	6.27%
	N+	0.42±0.881	
Left internal iliac LN	N0	1.79±1.719	4.73%
	N+	0.38±0.77	
Right common iliac LN	N0	3.46±3.563	9.13%
	N+	0.46±1.062	
Left common iliac LN	N0	4.25±2.908	11.22%
	N+	0.75±1.113	
Right obturator LN	N0	4.54±3.563	11.99%
	N+	1.00±1.769	
Left obturator LN	N0	3.96±3.196	10.45%
	N+	0.67±1.551	

LN: Lymph node.

Savelli et al. reported that ultrasonographies performed in experienced hands have higher degrees of accuracy comparable to MRI in the detection of myometrial invasion in cases with EC.[7] In our study, presence of LN metastasis significantly correlated with ultrasonographic findings related with malignancy. We think that systematic lymphadenectomy should be targeted irrespective of preoperative histologic grade of the neoplasia, in cases with irregular endometria with wall thickness of >1 cm.

Glandular cell abnormalities detected on cervical smear (CVS) is a sufficient reason to perform endometrial biopsy in asymptomatic women.[8] In our study, presence of LN metastasis significantly correlated with atypical cells in smear. Interestingly, this phenomenon is encountered in advanced stage cancers. Probably, malignant cells begin to shed from the endocervical canal after they reach a certain number, and become visible on Pap smear.

It has been reported that the elevation of preoperative serum CA-125 levels is associated with an increase in the incidence of extrauterine disease, and that high CA-125 values are related strongly with advanced surgical stage, LN metastasis, and poor prognosis.[9] Hoon Chung et al. evaluated the predictive value of preoperative serum CA-125 levels in the assessment of disease extent and clinical outcome in 92 women with pathologically proven endometrial carcinoma.[10] Elevated serum CA-125 levels were associated significantly with advanced-stage disease, LN metastases, increased depth of myometrial invasion, and positive peritoneal cytology. In our study, LN metastasis was not detected in 86.7% of 105 cases whose CA-125 values were below 35 IU/ml. However LN metastasis was found in 52.6% of 19 patients whose CA-125 values were above 25 IU/ml. In our study, presence of LN metastasis was associated significantly with the preoperative serum CA125 level. Our results suggest that serum CA-125 levels may be useful for prediction of LN metastasis. Systematic lymphadenectomy should be planned for cases with higher CA-125 values. Larger scale studies should be performed in postmenopausal female populations.

Scambia et al., in their study including 148 patients with EC, evaluated CA-125 and CA 15-3 and stated that increased levels of CA-125 and CA-15-3 are indicators of worse prognosis which are important in the assessment of extrauterine invasion, LN metastasis, and response to chemotherapy.[11] In our study, presence of LN metastasis was associated significantly with preoperative serum CA15-3 level.

It has been indicated that the impact of histologic type on LN metastasis is minimal in EC, and maximal in serous papillary and clear cell types.[12,13] In a Gynecology-Oncology Group (GOG) study, Stock et al. compared histologic types in 819 cases with EC, and they did not detect any difference between endometrial adenocarcinomas as for the prevalence of mean age, myometrial invasion, or lymph nodes.[14]

There are many studies indicating LVI as a prognostic factor for recurrence, survival, and LN metastases. LVI is not a component of staging EC; it is mostly seen in patients diagnosed as advanced stage cancer. LVI is rather found in cases with deeper myometrial penetration or cervical invasion, and it is a strong predisposing factor for regional and intraabdominal metastases.[15] Briet et al. revealed that LVI was an independent prognostic factor for recurrences in LN negative cases subjected to surgical grading.[16] In our study, the presence of LN metastasis was associated significantly with LVI. Metastatic lymph nodes were observed in 24 (63.2%) out of 38 patients with LVI.

The histologic grade of the tumor and depth of myometrial invasion are important prognostic factors in EC.[14] There are reports on the relationship between tumor size and PLN metastasis in EC, however, they still remain sparse. Schink et al. showed the rate of PLN metastasis to be 4% for <2 cm, 15% for >2 cm, and 35% for lesions occupying the entire uterine cavity, but no PLN metastasis was documented in low-risk EC patients with primary tumor diameter 2 cm or smaller.[17] Kamura et al. showed that EC with PLN metastasis had a significantly greater diameter than those without PLN metastasis, and a logistic regression analysis re-

vealed deep myometrial invasion (>1/2) and primary tumor diameter more than 50 mm to be independently correlated with pelvic lymph node metastasis.[3] On the other hand, Takeshima et al. reported that PLN metastasis was observed in four of 100 EC patients with no myometrial invasion, in which tumor size for all four patients was less than 2 cm.[18] In our study, a significant correlation was found between the depth of myometrial invasion and the presence of metastatic lymph nodes. The presence of LN metastasis was also significantly associated with both preoperative and postoperative grade of differentiation. A strong correlation existed between the tumor grade and lymph node involvement, in accordance with the literature.

Kadar et al. indicated that positive peritoneal cytology had no effect on survival in disease states confined in uterus, however invasion into adnexes, lymph nodes or peritoneum were associated with decreased survival.[19] Heath et al. evaluated 243 patients in different stages of EC, and reported 3-year disease-free survival rates as 91% in stage 1 with negative, and 56% with positive peritoneal cytologies.[20] In a review, McLellan et al. reported the incidence of LN involvement as 8.7% and 35% in patients with negative and positive cytology, respectively.[21] It has been stated that the presence of intraperitoneal metastasis affected survival adversely.[22] In our study, presence of LN metastasis was significantly associated with dissemination to omentum or appendix, and a positive peritoneal cytology. Metastatic lymph nodes were detected in all patients with peritoneal malignant cytology, omental and appendical involvement.

CONCLUSION

It can be concluded that, demographic characteristics such as advanced age, findings suggesting advanced disease on transvaginal ultrasonography, presence of abnormal glandular cells on CVS, predetermined histologic grade, and type of the tumor are all important as predictors determining metastatic LN involvement. Postoperative histologic grade, myometrial invasion, depth of tumoral invasion, LVI, positive peritoneal cytology and the presence of intraperitoneal metastases appear also to be predictive factors for metastatic LN involvement.

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