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RESEARCH ARTICLE

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Evaluation of Inferior Mesenteric Superior Lymph Node Metastasis in Early-Stage Endometrium Cancer and Its Clinical Significance

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ABSTRACT

Endometrial cancer is the fourth most common type of cancer in women cancers. In the light of projections, approximately 11,000 deaths occur annually in the USA alone. Lymph node metastasis is the most important prognostic factor in endometrial cancer. The aim of this study is to investigate the clinical and histopathological risk factors affecting lymph node involvement.

The study included 30 randomly selected women from external centers who applied to our clinic with a preliminary diagnosis of endometrial cancer and were diagnosed with endometrial cancer in our clinic. The study group was divided into two groups as stage I (early stage) and stage II and above (advanced stage) according to the stages. Total abdominal hysterectomy (Type II), bilateral salpingo-oophorectomy, paraaortic lymph node dissection from the pelvic and IMA to the level of the left renal vein, omentectomy, and peritoneal cytology sampling were performed on each of the endometrial cancer participants.

The mean number of lymph node involvement in 30 patients in the study group was 45.9±15.1. The mean number of pelvic lymph nodes involved was 32.1±10.1, while the mean number of paraaortic lymph nodes involved was 13.9±6.9. As a result of the examinations, the highest number of Stage Ia was found. The frequency of endometrial adenocarcinoma was 80% and it was seen in 24 people. The mean tumor size, myometrial thickness, and depth of invasion of the patients were 2.97(±1.6), 1.57(±0.6), and 0.7(±0.6), respectively.

With positive sub-IMA lymph node involvement, lymph node positivity was also detected in the area extending from the IMA to the level of the renal vein. It has been shown that the non-endomethroid tumor type detected in this group, myometrial invasion of more than 50%, grade 3 tumor and the presence of lymphovascular invasion affect lymph node involvement above the IMA.

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Introduction

Endometrial cancer is the most common gynecological malignancy. It is the fourth most common type of cancer in women after breast, lung, and colorectal cancers. In the light of projections, approximately 60,000 cases and 11,000 deaths occur annually in the USA alone. The incidence of death from endometrial cancer has increased by more than 100% in the past 20 years. The mean age at diagnosis is 63 years and 90% of cases are older than 50 years. Only 20% of those diagnosed with endometrial cancer are in the premenopausal period [1].

The mainstay of treatment for endometrial cancer is total hysterectomy combined with bilateral salpingo-oophorectomy. Radiation and chemotherapy may also play a role in treatment. Low or intermediate-risk endometrial hyperplasia can be treated with nonsurgical options. Survival is often dependent on the stage and histology of the disease. Most patients in stages I and II have a good prognosis. Controlling risk factors such as obesity and diabetes may provide benefits in terms of disease prevention [2].

Lymph node metastasis is the most important prognostic factor in endometrial cancer. Approximately 10% of early-stage endometrial cancer patients progress to the next stage due to lymph node involvement. Although the role of pelvic lymphadenectomy in early-stage disease is controversial by some sources, analysis of retrospective data in high-risk patients has shown a survival benefit. Currently, the most accurate way to assess the status of retroperitoneal lymph nodes is their surgical removal and histopathological analysis. The result of this analysis is crucial for determining prognosis and tailoring the use of adjuvant oncological therapies. Pelvic and aortic lymphadenectomies remain standard staging procedures. Surgical intervention to detect the spread of the disease in patients diagnosed with endometrial cancer should be performed together with pelvic and paraaortic (up to the level of the renal vein) lymphadenectomy [3].

Pelvic lymphadenectomy involves removal of all fatty and lymphatic tissue above and below the internal and external

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iliac arteries and obturator nerve. Although isolated paraaortic involvement seems low, it is seen in approximately half of those with positive pelvic lymph nodes and has prognostic value. Therefore, the paraaortic area should be part of the lymph node dissection. Recent studies have shown that the rate of positive lymph nodes is high in lymphadenectomy performed above the inferior mesenteric artery (IMA). It has been determined that lymph node metastasis is above the level of IMA in approximately 80% of patients with paraaortic involvement [4].

The aim of this study is to investigate the clinical and histopathological risk factors affecting lymph node involvement in lymphadenectomy performed from the top of the IMA to the level of the left renal vein in early-stage endometrial cancer.

Materials and Methods

Study Design

This study was carried out in the gynecological oncology department of the obstetrics and gynecology department of a tertiary health center. Ethical approvals of the study were obtained from the relevant institution. Our study was planned as a retrospective study. The study included 30 randomly selected women from external centers who applied to our clinic with a preliminary diagnosis of endometrial cancer and were diagnosed with endometrial cancer in our clinic. Participation in the study is on a voluntary basis. There was no coercion in participation.

The study group was divided into two groups as stage I (early stage) and stage II and above (advanced stage) according to the stages. There were 16 people in the stage I group and 14 people in the other group. While the first group includes stages Ia and Ib, the other group included stage II, stage IIIc1, and stage IIIc2.

Treatments Performed

Total abdominal hysterectomy (Type II), bilateral salpingo-oophorectomy, paraaortic lymph node dissection from the pelvic and IMA to the level of the left renal vein, omentectomy, and peritoneal cytology sampling were performed on each of the endometrial cancer participants. The stages of the patients were determined by postoperative histopathological evaluation.

Statistical Analysis

Statistical analysis of the obtained data were made in SPSS statistical package program. As descriptive statistics, number and percentage in categorical variables, mean and standard deviation in continuous variables are given. Since no pathological lymph nodes were detected in the first group of stage I women, no statistical analysis was performed. In the other group consisting of stage II and above women, age, body mass index (BMI), grade, histopathological type, tumor size, lymphovascular invasion, metastatic pelvic lymph node, and lymph metastasis positivity variables were examined. The chi-square test was used to compare metastatic lymph node involvement below the IMA with the supra-arterial lymph node involvement. In all analyses, $p<0.05$ was accepted as the statistical significance level.

Results

The demographic characteristics of the participants are presented in Table 1.

The mean number of lymph node involvement in 30 patients in the study group was 45.9±15.1. The mean number of pelvic lymph nodes involved was 32.1±10.1, while the mean number of paraaortic lymph nodes involved was 13.9 ± 6.9. Other features related to lymph node involvement are given in Table 2.

As a result of the examinations, the highest number of Stage Ia was found. There are 16 women in stage Ia. At the end of the pathological examinations of the patients, the most common endometroid type adenocarcinoma was found. The frequency of endometrial adenocarcinoma was 80% and it was seen in 24 people. The mean tumor size, myometrial thickness, and depth of invasion of the patients were 2.97(±1.6), 1.57(±0.6), and 0.7(±0.6), respectively. The most common grade level was found to be grade 1, 16 women were grade 1. The histopathological features of the participants are presented in Table 3.

In the second group, which included stage II and above participants, the correlation between demographic data and lymph metastasis positivity in the region extending from the upper IMA to the level of the left renal vein was examined. No statistically significant correlation was found in terms of age, grade, histopathological type, mean BMI, tumor size, lymphovascular invasion, metastatic pelvic lymph node, and lymphatic metastasis positivity ($p>0.05$). However, a significant difference was found between the participants with negative and positive lymph node involvement under IMA in terms of lymph node positivity in the part extending over the IMA to the level of the renal vein ($p=0.018$) (Table 4).

As a result, while no pelvic and/or paraaortic metastases were detected in the first group, which is stage I, 3 participants with pelvic metastases (27.2%), 1 participant with pelvic and paraaortic metastases (9.1%), and 1 participant with paraaortic

Table 1: Demographic characteristics of the participant.

Age(±SD)		58.4 ± 7.6
BMI(±SD)		32.4 ± 6.9
Gravida		3.3 ± 3.0
Parity	At least one	28 (93.3)
	Negative	2 (6.7)
Hypertension	Negative	13 (43.3)
	Positive	17 (56.7)
Diabetes	Negative	25 (83.3)
	Positive	5 (16.7)
Smoke	Negative	23 (76.7)
	Positive	7 (23.3)

Table 2: Characteristics of lymph node involvement.

Characteristics	Number (±SD)
Number of total lymph nodes	45.9(±15.1)
Number of pelvic lymph nodes	32.1(±10.1)
Metastatic pelvic lymph node	0.4(±1.8)
Number of paraaortic lymph nodes	13.9(±6.9)
Number of lymph nodes below IMA	9.8(±6.4)
Number of lymph nodes above IMA	4.07(±2.9)
Number of metastatic lymph nodes below IMA	0.33(±1.6)
Number of metastatic lymph nodes above the IMA	0.13(±0.5)

Table 3: Histopathological characteristics of the participants.

Stage	Ia	16 (53.3)
	Ib	3 (10)
	II	7 (23.3)
	IIIc1	2 (6.7)
	IIIc2	2 (6.7)
Cell Type	Endometroid	24 (80)
	Serous	4 (13.3)
	Mixed type	1 (3.3)
	Transparent cell	1 (3.3)
Grade	1	16 (53.3)
	2	8 (26.7)
	3	6 (20)
Myometrial invasion depth	<1/2	23 (76.7)
	>1/2	7 (23.3)
Lymphovascular invasion	Negative	24 (80)
	Positive	6 (20)
Cervical stromal invasion	Negative	23 (76.7)
	Positive	7 (23.3)
Ovarian involvement	Negative	28 (93.3)
	Positive	2 (6.7)
Tubal involvement	Negative	29 (96.7)
	Positive	1 (3.3)
Omental involvement	Negative	30 (100.0)
	Positive	0 (0.0)
Peritoneal cytology	Negative	30 (100.0)
	Positive	0 (0.0)
Lymph node metastasis	Negative	26 (86.7)
	Positive	4 (13.3)
Pelvic lymph node metastasis	Negative	27 (90)
	Positive	3 (10)
Lymph node metastasis above IMA	Negative	28 (93.3)
	Positive	2 (6.7)
Lymph node metastasis below IMA	Negative	28 (93.3)
	Positive	2 (6.7)

Table 4: Comparison of Various Characteristics of Supra-IMA Lymph Node Positive and Negative Group 2 Participants*.

		LND metastasis above the Inferior Mesenteric Artery		**p**
		Positive n (%)	**Negative n (%)**	
Age	**<**57.9	0 (0.0)	6 (54.5)	0.182
	>57.9	2 (18.8)	3 (27.3)	
Grade	I	0 (0.0)	2 (18.2)	0.231
	II	0 (0.0)	4 (36.4)	
	III	2 (18.2)	3 (27.3)	
Histopathological Type	Endometroid	0 (0.0)	7 (63.6)	0.109
	Non-endometroid	2 (18.2)	2 (18.2)	
BMI	<32.7	1 (9.1)	5 (45.5)	0.984
	>32.7	1 (9.1)	4 (36.4)	
Tumor size	<3.3	0 (0.0)	5 (45.5)	0.455
	>3.3	2 (18.2)	4 (36.4)	
Lymphovascular Invasion	Negative	0 (0.0)	6 (54.5)	0.182
	Positive	2 (18.2)	3 (27.3)	
Metastatic Pelvic Lymph Node	Negative	1 (9.1)	7 (63.6)	0.491
	Positive	1 (9.1)	2 (18.2)	
Metastatic Sub-IMA Lymph Node	Negative	0 (0.0)	9 (81.8)	**<0.05**
	Positive	2 (18.2)	0 (0.0)	

*: Includes Stage II, IIIc1, IIIc2.

metastases (%9,1) were detected in the second group, which is stage II and above.

Discussion

Lymphadenectomy remains one of the most controversial issues in endometrial cancer. In many cases, the success of systemic pelvic and paraaortic lymphadenectomy depends on the personal experience of the surgeon. Particularly high body mass index and the intervention made in elderly patients complicate the surgeon's work. Paraaortic lymphadenectomy requires high surgical skill and experience, especially in the infrarenal region. For these reasons, incomplete lymphadenectomy is mostly limited to sub-IMA [5].

Lymphadenectomy has diagnostic and potential benefits as well as risks. The diagnostic role of this procedure is to understand the spread of the disease, and its therapeutic role is to reduce the recurrence rate in nodal areas. Lymphadenectomy ranges from lymph node sampling to systemic pelvic and paraaortic lymphadenectomy. Examination of the large area is safer in giving the number of pathological lymph nodes. A standardized surgical technique approach cannot be mentioned with the use of laparoscopic and robot-assisted techniques [5,6].

Studies emphasize that lymph node metastasis should be considered the most important prognostic factor in early stage endometrial cancer. One study examined the relationship between pathological risk factors in stages I and II and outcomes. In the light of the data obtained, survival was 90% in patients without lymph node metastases, 75% and 38% in patients with pelvic and paraaortic lymph node metastases, respectively. In a similar study, Lurain et al. calculated the survival rate as 54% in patients with lymph node metastases and 90% in patients without metastasis. In addition, disease recurrence was also examined and the frequency of recurrence increased from 8% in the case of negative lymph nodes to 48% in the case of positive lymph nodes [7-9].

Paraaortic lymph node metastasis indicates a poor prognosis. In a retrospective study, among 2559 stage IIIC endometrial cancer patients, the mortality rate of those presenting with paraaortic involvement was found to be significantly higher than those without involvement. With this determination, FIGO modified the staging of endometrial cancer. It divided stage IIIC into two subgroups according to paraaortic lymph node involvement. Therefore, precise staging of patients is meaningful for planning further treatment. Adjuvant chemotherapy is necessary for the treatment of stage III and IV endometrial cancer [10-13].

There are differences between different health centers and countries in the management of endometrial cancer, especially with regard to lymph node staging. In the light of the data obtained from some studies published recently, it has been claimed that pelvic lymphadenectomy does not improve overall survival rates, therefore it is not meaningful to recommend it as a routine practice. However, the results are questionable because there are some shortcomings in the design of these studies, such as the lack of randomization and the absence of systematic paraaortic lymphadenectomy [14].

Major criticisms of lymphadenectomy are based on the results of some studies evaluating the role of pelvic and limited para-aortic lymph node dissection in early-stage endometrial cancer. In these studies, the effects of bilateral salpingo-oophorectomy and the addition of pelvic and, in some cases, para-aortic lymphadenectomy to standard hysterectomy, on survival outcomes were investigated. According to the cumulative results of the studies, lymphadenectomy does not affect disease-free and overall survival [15,16].

Although there have been various assessments of its therapeutic value, today lymph node dissection is the only way to accurately stage endometrial cancer and identify patients likely to benefit from adjuvant therapy. Imaging procedures that determine the condition of the disease outside the uterus are missing in the treatment of endometrial cancer. With magnetic resonance imaging enhanced with ultrasmall superparamagnetic iron oxide, normal sized lymph node metastases can be detected, and preoperative staging can be improved. However, it is thought that more experience and experience is needed for this technique to be considered useful and reliable [11,14,17,18].

A retrospective study was conducted on a group of patients with endometrial cancer who underwent staging surgery. According to the data of the study, it has been shown that cervical invasion, myometrial invasion depth, adnexal spread, tumor size and pelvic lymph node status are determinants in the spread of the tumor to the paraaortic lymph node [19].

The results of a study in which patients with endometrial cancer in the intermediate – high risk group underwent systemic surgical staging, including pelvic and paraaortic lymph nodes, were reviewed. Accordingly, 54% of the group with lymph node metastases had metastases in the lymph nodes in the region up to the level of the renal vein over the IMA. It has been shown that lymphovascular invasion, serous cell type and grade level are determinants for the presence of any lymph node metastasis. While pelvic lymph node status and lymphovascular invasion involvement were significantly effective for paraaortic lymph node metastasis, grade level, age and cell type were found to be ineffective [20].

In this study, lymph node metastasis above the IMA was not detected in the stage I group. 73.8% of the group were found to be grade 1, 21% were grade 2, and the final pathology of 89.5% was found to be endometrioid type. Myometrial invasion is below 50% in 84.3% of the patient group. These findings support the argument expressed in studies in the literature that “performing lymphadenectomy over the IMA for patients in the low-risk group is not as beneficial as the renal vein” [19].

In our study, the relation of lymph node metastasis with some variables in the region from the top of the IMA to the level of the left renal vein was investigated in the stage II and above group. No statistically significant correlation was found between the aforementioned metastasis and age, grade, histopathological type, mean BMI, tumor size, lymphovascular invasion, and metastatic pelvic lymph node. However, in two patients with positive sub-IMA lymph node involvement, lymph node positivity was also detected in the area extending from the IMA to the level of the renal vein, which was statistically significant (p=0.018). It has been shown that the non-endomethroid tumor type detected in this group, myometrial invasion of more than 50%, grade 3 tumor and the presence of

lymphovascular invasion affect lymph node involvement above the IMA. These findings are also consistent with the data of studies in the literature [19,20].

In contemporary medical oncology, it is aimed to increase the efficacy of treatment through targeted therapies. This goal is briefly expressed as personalized medicine. In this context, sentinel lymph node mapping has begun to be used in the surgical staging of endometrial cancer in order to obtain prognostic information about lymph nodes. It seems possible to include the sentinel lymph node mapping algorithm in the staging of high-grade endometrial cancer. It has been put into use by some centers. The early results seem encouraging, but controversy remains regarding the safety and efficacy of sentinel lymph node biopsies. It is considered that studies should be planned to obtain more data on the safety and efficacy of sentinel lymph node biopsies [21,22].

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