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Prediction of lymph node metastasis based on tumor size in stage 1A endometrioid endometrium cancer

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Abstract. – OBJECTIVE: Endometrium cancer (EC) is the most prevalent cancer affecting women in developed countries. There is debate about the need to perform lymphadenectomy in cases with a tumor diameter >2 cm. The aim of our study is to research the prediction of lymph node metastasis using tumor size in stage 1A endometrioid endometrium cancer (EEC).

PATIENTS AND METHODS: The study enrolled cases operated in the clinic due to stage 1A EEC (FIGO 2009) from December 2010-2021. The correlations of age, age interval, parity, type of operation, tumor diameter, myometrial invasion, histological grade, and lymph node metastasis were statistically analyzed. The cut-off point for tumor size was determined with the ROC curve and Youden index.

RESULTS: The study analyzed a total of 292 cases, and the mean age of cases was 62.3±10.0 years. Of the cases, 79.5% had histological grade 1, and 20.5% had grade 2. Myometrial invasion ≤50% was detected in 69.5%, and no myometrial invasion was detected in 30.5%. The mean tumor diameter was 34.0±18.0. Lymph node metastasis was identified in 6 cases (2.1%). Based on the tumor diameter cut-off value of 35 mm, sensitivity was 100%, and specificity was 50.3%. 116 cases with tumor diameter >35 mm and 176 with diameter ≤35 mm, and grade 2 histology and lymph node positivity were found statistically significant between these groups (respectively, *p*=0.012 and *p*=0.038). The lymph node metastasis risk was 0% in cases with tumor diameter ≤35 mm, while it was 5.2% in cases with tumor diameter >35 mm.

CONCLUSIONS: The general approach in stage 1A EEC is not to perform lymphadenectomy. However, when the tumor diameter is noted, lymphadenectomy may be considered as the lymph node metastasis risk increases in cases with a tumor diameter of 35 mm or more. There is a need for more clinical studies on this topic.

Key Words:
Endometrium cancer, Lymphadenectomy, Lymphatic metastasis.

Introduction

Endometrium cancer (EC) is the gynecological cancer most frequently observed in developed countries[1]. In traditional classification, EC is divided into two groups as type 1 and type 2[2]. Most EC comprise endometrioid endometrium cancer (EEC), especially in the early stage[3]. The treatment for EC is surgery[4]. The majority of EC are diagnosed at an early stage [International Federation of Gynecology and Obstetrics (FIGO), stage I and II], and the 5-year general survival for stage 1 EC is more than 90%[1,5]. According to FIGO staging, myometrial invasion of less than half is defined as stage 1A[6]. Magnetic Resonance Imaging is essential in evaluating myometrial invasion in early-stage EC[7,8]. In some studies[9-12], low-risk EC is defined as cancer limited to the uterine corpus, endometrioid type, histological grade 1 or 2, and less than 50% myometrial invasion.

One of the main metastasis routes for EC is lymph node metastasis[13]. In cases with lymph node metastasis, the 5-year survival rate is less than 50%[14,15]. A study by Creasman et al[16] identified that the size of the primary tumor was a risk factor for lymphatic metastasis. However, FIGO and the European Society of Medical Oncology (ESMO) define all cases with stage IA and grade 1 or 2 EEC as low-risk, without regard to tumor size, and do not recommend systematic lymphadenectomy for these cases[17,18]. The National Comprehensive Cancer Network (NCCN, 2016) and the Spanish Association of Medical Oncology (SEOM) assessed tumor size and defined cases with EEC, myometrial invasion ≤50%, grade 1 or 2, and primary tumor diameter ≤2 cm as low-risk. They did not recommend systematic lymphadenectomy in these cases[19,20].

There is a significant correlation between tumor size with lymphatic metastasis and progno-

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sis[21-23]. In 2013, the ESMO published significant parameters for recurrence of early-stage EC as >2 cm tumor diameter, myometrial invasion >50%, histological type, grade 2 and positive lymph node. Additionally, lymphadenectomy was important for assessment of prognosis and in terms of adjuvant treatment in the future[12]. Additionally, the most important risk factors for lymphatic metastasis were accepted to be tumor volume index, myometrial invasion and histological grade[24]. Wright et al[25] showed that lymphadenectomy affected survival in early-stage EC. As lymphadenectomy procedures are associated with severe postoperative complications like lymph edema[26], it is important to determine which cases require lymphadenectomy and the scope of lymph node dissection during the surgical procedure to reduce associated operative morbidity. Current guidelines state the consensus about lymphadenectomy not being required for cases with low-risk EEC diagnosis. However, the basic problem is research into the ability to perform lymphadenectomy by classifying cases with the cut-off point of >2 cm tumor diameter as low risk. Therefore, this study was planned to research the cut-off point of tumor diameter for prediction of lymph node metastasis in stage 1A endometrioid endometrium cancer.

Patients and Methods

This retrospective study received ethical approval from Selcuk University Faculty of Medicine Ethics Committee numbered 2023/23 and dated 03.01.2023. The study included 292 cases operated in the clinic from December 2010 to 2021 due to stage IA (FIGO 2009) endometrioid type endometrium cancer. Inclusion criteria for the study were histologic grade 1 and 2 endometrioid type, myometrial invasion ≤50%, absence of cervical involvement, negative LVSI and pelvic and/or para-aortic lymphadenectomy performed. Exclusion criteria were histologic grade 3 endometrioid type, non-endometrioid type, myometrial invasion >50%, cervical involvement and LVSI positivity. The cases were assessed statistically for correlations between age, age interval (≤60 years and >60 years), parity, type of operation (laparotomy and laparoscopy), degree of myometrial invasion (none and less than 50%), histopathological tumor diameter (mm), histological grade (1 and 2), and lymph node positivity. All patients underwent total abdominal hysterectomy, bilateral salpingo-oopherectomy and pelvic and para-aortic lymphadenectomy. Lymph node sampling was performed on bilateral external iliac, internal iliac, obturator, main iliac regions and para-aortic lymph nodes up to the level of renal vein. All operations were performed by a single gynecological oncologist. The type of operation was selected by the surgeon. Tumor diameter measurements were defined as the largest diameter of the tumor measured in paraffin blocks of pathological samples. All cases were staged according to the FIGO classification[6]. The cut-off point for tumor size was calculated using ROC curve and the Youden index.

Statistical Analysis

All statistical calculations used SPSS V21 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA). A range of descriptive features in the study (like mean, median, standard deviation and percentage) were analyzed with the aid of descriptive statistical tests. Mann-Whitney U test and The Student *t*-test were used for comparing non-parametric and parametric continuous variables, while the Chi-square test or Fisher's exact test were used for comparing categorical variables, respectively. ROC curve was used to calculate the cut-off point for tumor diameter using Youden index. The *p* less than 0.05 was accepted as statistically significant.

Results

A total of 292 cases with stage 1A EEC were evaluated in the present study (Table I). The mean age of cases was 62.3±10.0 years. Of cases, 57.5% were >60 years old and 42.5% were ≤65 years old. Median parity was calculated as 3.5 (0-11). Histological grade was grade 1 for 79.5% and grade 2 for 20.5%. Laparotomy was performed in 64.4%, and laparoscopy in 35.6%. Myometrial invasion ≤50% was detected in 69.5% and no myometrial invasion was detected in 30.5%. The mean tumor diameter was 34.0±18.0. Lymph node metastasis was identified in a total of 6 (2.1%) cases; 2 cases (0.7%) had isolated pelvic, 1 case (0.3%) had isolated para-aortic and 3 cases (1.0%) had both pelvic and para-aortic lymph node metastasis. Based on cut-off points of tumor diameter of 35 mm, specificity was 50.3%, and sensitivity was 100%. With the cut-off point of this tumor diameter, 176 cases were ≤35 mm and 116 cases were >35 mm and no significant differences were found in terms of age, age interval, parity and type of operation

Table I. Characteristic features of stage 1a endometrioid endometrium cancer cases.

Variable		(n=292)	%
Age		62.3±10.0 (36-95)	
Age interval			
	≤60 years	124	42.5
	>60 years	168	57.5
Parity		3.5 (0-11)	
Grade			
	1	232	79.5
	2	60	20.5
Type of operation			
	Laparotomy	188	64.4
	Laparoscopy	104	35.6
Myometrial invasion			
	≤50%	203	69.5
	No	89	30.5
Tumor diameter, mm		34.0±18.0	
Tumor diameter			
	≤35 mm	176	60.3
	>35 mm	116	39.7
Lymph node positivity			
	Yes	6	2.1
	No	286	97.9
Isolated pelvic lymph node positivity			
	Yes	2	0.7
	No	290	99.3
Isolated para-aortic lymph node positivity			
	Yes	1	0.3
	No	291	99.7
Pelvic and para-aortic lymph node positivity			
	Yes	3	1.0
	No	290	99.0

(Table II). Based on the cut-off point of tumor diameter of 35 mm, significant differences were identified between cases in terms of histological grade 2 and lymph node metastasis (p=0.012 and p=0.038, respectively, Figure 1). The lymph node metastasis risk was 0% for cases with tumor diameter ≤35 mm and 5.2% for cases with tumor diameter >35 mm.

Discussion

Due to low lymphatic metastasis risk in cases with a diagnosis of low-risk EEC, studies[11,17,27] show that routine systematic lymphadenectomy does not need to be performed, and total hysterectomy and bilateral salpingo-oophorectomy are adequate for optimal treatment. Additionally, tumor diameter is not assessed in the FIGO staging system[28]. However, in cases with EEC diagnosis, studies show a significant correlation between tumor diameter and lymph node metastasis[12,19,29]. Different results are reported related to the cut-

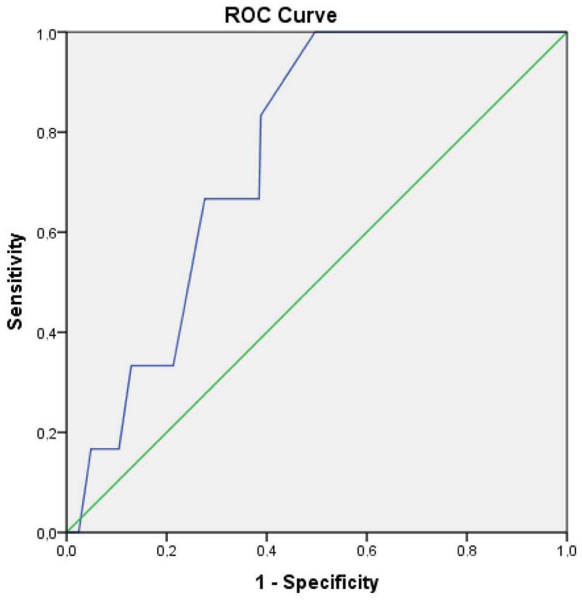

Figure 1. ROC analysis for tumor diameter in stage 1A endometrioid endometrium cancer.

Table II. Analysis of cases according to tumor diameter for stage 1A endometrioid endometrium cancer.

Variable		Tumor diameter ≤35 mm (n=176)	%	Tumor diameter >35 mm (n=116)	%	p
Age		62.5±9.7		62.2±10.4		0.808
Age interval						0.524
	≤60 years	75	42.6	49	42.2	
	>60 years	101	57.4	67	57.8	
Parity		3.7±1.7		3.7±1.7		0.940
Grade						0.012*
	1	148	84.1	84	72.4	
	2	28	15.9	32	27.6	
Type of operation						0.241
	Laparotomy	110	62.5	78	67.2	
	Laparoscopy	66	37.5	38	32.8	
Myometrial invasion						0.103
	≤50%	117	66.5	86	74.1	
	No	59	33.5	30	25.9	
Lymph node positivity						0.038*
	Yes	0	0.6	6	5.2	
	No	176	99.4	110	94.8	

•$p<0.05$ is statistically significant.

off point of tumor diameter for the prediction of lymphatic metastasis in EEC. This situation may be due to the heterogeneous groups in the study designs.

Tumor size was first shown to be a prognostic factor in EC in 1960 by Gusberg et al[30]. They associated uterus size larger than 10 cm with poor prognosis. After this study, tumor size was defined as a prognostic factor again by Schink et al[21] who assessed mean tumor diameter as tumor size. A study[21] including 142 cases divided cases into 2 groups as those with tumor diameter ≤2 cm (group 1) and >2 cm (group 2). With this definition, independent of tumor diameter, the lymph node metastasis risk was 4% in group 1 and 15% in group 2. A study including a total of 328 cases with low-risk EEC using 2 cm cut-off point for tumor diameter found that lymphatic metastasis was not identified in 59 cases with primary tumor diameter ≤2 cm, while 8 out of 107 cases (7%) with tumor diameter >2 cm were identified to have lymph node metastasis. Additionally, in 8 out of 107 cases, myometrial invasion >50% was identified. Additionally, a prospective study comprising 422 low-risk EEC cases with tumor diameter ≤2 cm reported no benefit from lymphadenectomy[11,22]. A multi-center study[19] in 2012 used the modified Mayo criteria (histological grade 1 or 2, tumor diameter <2 cm, and myometrial invasion <50%) to define low-risk EEC. In this study, the metastasis rate was reported to be 0.8% (3/389) in the low-risk group. Low-risk criteria in EEC hysterectomy samples were associated with a reduced risk of lymph node metastasis. After accepting the cut-off point for tumor diameter as 2 cm according to Mayo criteria, among studies assessing tumor diameter cut-off with EEC myometrial invasion ≤50% and grade 1 or 2, there are studies not identifying lymphatic metastasis in cases with primary tumor diameter ≤2 cm[11,22,31] and studies identifying lymph node metastasis with minimal risk rates like 0.3%[29] and 0.8%[19]. Additionally, some studies found that cases with tumor diameter >2 cm had lymph node metastasis of 7%[11], 1.9%[29] and 6.28%[31]. Contrarily, this study only comprised stage 1A low-risk EEC cases. Cases with a tumor diameter ≤35 mm had a lymphatic metastasis risk of 0%, while cases with a >35 mm tumor diameter had a lymphatic metastasis risk of 5.2%.

There is a correlation between the growth in tumor diameter with histological grade, degree of myometrial invasion, and presence of LVSI. Zhu et al[29] identified significantly higher degrees of histological grade, myometrial invasion and LVSI positivity in cases with >2 cm tumor diameter. The study by Ali et al[15] identified cut-off point for tumor diameter >8 cm as significant for the prediction of lymph node metastasis. Additionally, the tumor diameter cut-off point of 8 cm was significant for the degree of myometrial invasion and histological grade. Oz et al[32] did not identify lymph node me-

tastasis in any case with stage 1A grade 1 EEC. While no correlation was identified between the increase in tumor size and lymphatic metastasis, an increase in the degree of surficial myometrial invasion was detected. Canlorbe et al[33] identified a tumor diameter of 35 mm as significant in terms of lymph node metastasis in a low-risk EC study. When the tumor diameter was <35 mm, the lymph node metastasis rate was 3.2%, while for a tumor diameter ≥35 mm, this was calculated as 10.5%. Similarly, in the present study, the cut-off point for a tumor diameter of 35 mm was identified to be significant for predicting lymph node metastasis. Histological grade 2 and degree of myometrial surface invasion were identified to be higher in cases with tumor diameter >35 mm. However, the low lymph node metastasis risk is due to the inclusion of only low-risk EEC cases.

This retrospective study only assessed histopathological tumor diameter, which can be considered limitations. Strong aspects are the excess number of cases and calculation of a threshold value with ROC analysis of tumor diameter in only low-risk EEC cases. As a result, it is considered the study will contribute to the literature in terms of researching the effect of tumor diameter and the need to perform lymphadenectomy without including factors that may affect lymph node metastasis apart from tumor diameter, like type 2 EC, histological grade 3, presence of LVSI, >50% degree of myometrial invasion, and cervical invasion.

Conclusions

The general approach in stage 1A endometrioid type endometrium cancer is not to perform lymphadenectomy. However, considering the cut-off point for a tumor diameter of 35 mm, lymphadenectomy may be considered due to the increased risk of lymphatic metastasis in cases with a tumor diameter of 35 mm or more. There is a need for more clinical studies on this topic.

Conflict of Interest
The authors declare that they have no conflict of interests.

Ethics Approval
This retrospective study received ethical approval from the Selcuk University Faculty of Medicine Ethics Committee numbered 2023/23 and dated 03.01.2023.

Informed Consent
Informed consent was waived due to the retrospective design of the study.

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Authors' Contribution
Fazıl Avcı, Bayram Can, Betul Dik, Ayse Gulmez and Mehmet Kulhan contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article; validation and final approval of the version of the article to be published. Cetin Celik and Ahmet Bilgi contributed to the conception and design of the study, reviewing and editing the article; supervision; validation and final approval of the version of the article to be published.

Data Availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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