

The Results of Surgico-Pathologic Factors in Patients with Non-Endometrioid Type Endometrial Cancer: Is Tumor Type Important for Lymph Node Metastasis?

Non-Endometrioid Tip Endometrium Kanseri Cerrahi-Patolojik Faktörlerin Sonuçları: Lenf Nodu Metastazında Tümör Tipi Önemli mi?

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ABSTRACT

Aim: To determine the factors identifying lymph node metastasis and the association between tumor types and surgico-pathologic factors in patients with non-endometrioid type endometrial cancer.

Materials and Methods: This study included 150 patients with non-endometrioid type endometrial cancer whose staging surgeries had already been performed in our clinic.

Results: Tumor types were serous in 65 patients, clear cell in 55, undifferentiated in 23 and mucinous in 8. Sixty-one patients had stage I, 6 patients had stage II, 47 patients had stage III and 36 of them had stage IV disease. Median removed lymph node number was 52 (range; 2-118). Number of the removed lymph node did not change according to tumor type. Lymph node metastasis and non-nodal extra-uterine disease were detected in 47% and 36% of patients, respectively. The type of tumor predicted the lymphatic spread, deep myometrial invasion, serosal involvement, adnexal spread, cervical invasion and omental metastasis ($p < 0.05$). The lymphatic spread rate was 65% for undifferentiated tumor type and 12.5% for mucinous tumor type. The rate of non-nodal extra-uterine disease was 60.9%, 43.8%, 21.8% and none in patients with undifferentiated, serous, clear cell tumor and mucinous type tumor, respectively ($p = 0.001$). In multivariate analysis, it was determined that tumor type (undifferentiated vs. others), cervical invasion and omental metastasis were independent prognostic factors for lymph node metastasis.

Conclusion: Whereas the surgical-pathologic factors were significantly worse in the undifferentiated type than other tumor types, the opposite was true in the mucinous type. Mucinous type tumor is different from other non-endometrioid types in terms of nodal/non-nodal spread. Lymphatic spread was observed in slightly more than 10% of patients with mucinous tumor and non-nodal extra-uterine disease did not exist in those.

Key Words: Endometrial Cancer, Serous type, Mucinous type, Undifferentiated type, Clear Cell type, Lymph node metastasis

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ÖZET

Amaç: Non-endometrioid tip endometrium kanserli hastalarda lenf nodu metastazını belirleyen faktörlerin ve tümör tipi ile cerrahi ve patolojik faktörlerin arasındaki ilişkinin araştırılması.

Yöntemler: Bu çalışmada, evreleme cerrahisi kliniğimizde yapılmış 150 non-endometrioid tip endometrium kanserli hasta değerlendirilmiştir.

Bulgular: Tümör tipi 65 hastada seröz, 55 hastada berrak hücreli, 23 hastada andifferansiye ve 8 hastada müsinöz tipti. Altmış bir hasta evre I, altı hasta evre II, 47 hasta evre III ve 36 hasta evre IV hastalığa sahipti. Çıkarılan lenf nodu sayısının ortanca değeri 52'di (aralık 2-118). Çıkarılan lenf nodu sayısının tümör tipine göre değişmediği tespit edildi. Lenf nodu metastazı ve non-nodal ektrauterin hastalık sırasıyla %47 ve %36 hastada mevcuttu. Tümör tipinin; lenf nodu metastazını, derin myometrial invazyonu, serozal tutulumu, adneksal metastazı, servikal invazyonu ve omental metastazı öngörmede etkili olduğu bulundu ($p < 0.05$). Andifferansiye tipte lenfatik yayılım oranının 65% ve müsinöz tipte lenfatik yayılım oranının %12.5 olduğu belirlendi. Andifferansiye tip, seröz tip, berrak hücreli tip ve müsinöz tip tümörlerde non-nodal ektrauterin yayılım oranının sırasıyla %60.9, %43.8, %21.8 ve %0 olduğu tespit edildi ($p = 0.001$). Yapılan multivaryant analizde; tümör tipi (andifferansiye vs. diğerleri), servikal invazyon ve omental metastaz lenf nodu metastazı için bağımsız prognostik faktörler olarak belirlendi.

Sonuç: Andifferansiye tip tümörlerde cerrahi ve patolojik faktörler diğer tümör tiplerine oranla belirgin ölçüde daha kötü olmakla birlikte müsinöz tip tümörlerde bu durum tam tersiydi. Müsinöz tip tümörler nodal ve non-nodal yayılım açısından diğer non-endometrioid tümör tiplerinden farklı bulundu. Lenfatik yayılım müsinöz tip tümörlerin yaklaşık %10'unda tespit edilirken; non-nodal ektrauterin yayılım bu hastalarda izlenemedi.

Anahtar Sözcükler: Endometrium kanseri, seröz tip, müsinöz tip, andifferansiye tip, berrak hücreli tip, lenf nodu metastazı

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INTRODUCTION

With 300,000 new diagnosis every year, endometrium cancer (EC) is the most frequent cancer of female genital tract and the fourth cancer among all cancer types (1). EC is mostly diagnosed at early stage and the main treatment is surgery. However, extra-uterine spread could be determined in 20% of the cases (2). Five-year overall survival is over 80% for low grade tumors in early stage of EC (3).

EC has been staged surgically according to the International Federation Obstetricians and Gynecologists (FIGO) since 1988 (4). According to this staging system, the disease had been staged as IIIC according to presence of the metastatic lymph nodes without occurrence of abdominal or extra-abdominal spread. However, in 2009, FIGO revised the staging system and stage IIIC was split into two groups according to occurrence of paraaortic lymph node metastasis (5). Occurrence of pelvic lymph node metastasis only has been accepted as stage IIIC1 and existence of paraaortic lymph node metastasis has been staged as IIIC2.

Bookman defined the dual model in endometrial carcinogenesis for the first time in 1983 according to histo-pathologic, clinic, epidemiologic and genetic characteristics (6). According to this definition, endometrioid type tumor which is accepted as Type I EC is determined in 80% of the patients and is estrogen dependent. On the other hand, Type II EC, which is estrogen independent, is used to define the some non-endometrioid type tumors. Non-endometrioid tumors include serous, clear cell, undifferentiated and mucinous types. It is known that Type II EC; specifically serous, clear cell and undifferentiated types, is more aggressive than endometrioid type tumor with respect to clinic and surgico-pathologic factors. Serous type is the most common tumor in this group. Serous type tumor is the cause in 10%, clear cell type is in 3% (7), undifferentiated type is in 1-9% (8-11) and mucinous type is in 1-5% (12) of the EC. In spite of that, serous and clear type tumors are responsible from nearly half of the mortality in endometrium cancer (7, 13). Although the evidence is not sufficient because of the lack of data, it has been accepted that whereas undifferentiated tumor is accepted as an aggressive type tumor, mucinous tumor type can have almost similar aggressiveness level with endometrioid type. 5-year overall survival has been reported as 65-71% for serous tumor, 77-85% for clear cell and 40-70% for undifferentiated tumor type (14-18).

The objective of this study is to evaluate factors identifying lymph node metastasis and the association between tumor type and surgico-pathologic factors in patients with non-endometrioid type EC.

MATERIALS and METHODS

This study included 150 patients whose staging surgeries had been performed in our oncology clinic between January 1993 and October 2016 and who had non-endometrioid tip (65 patients with serous type, 55 patients with clear cell type, 8 patients with mucinous type and 23 patients with undifferentiated type) type EC according to final pathology results. Data of the patients were obtained from electronic database and patients' files, retrospectively. Patients whose surgeries had not been performed in our clinic, with endometrioid type or mixed type adenocancer, whose tumors had sarcoma component, with secondary primary tumor, who didn't have lymphadenectomy performed and the ones having neo-adjuvant treatment were excluded. The institutional review board approval was obtained. Staging were performed according to FIGO 2009 criteria. During the statistical analysis, cervical stromal and glandular spread was both defined as cervical invasion in order to evaluate the effect on lymphatic spread. Tumor size was measured as the longest tumor diameter.

Adnexal spread, uterine serosal involvement, peritoneal involvement, positive peritoneal cytology and solid organ metastasis were all defined as extrauterine non-nodal disease.

Lymphovascular space invasion (LVSI) was defined as the tumoral cells or cell clusters holding on vessels' wall that were stained with hematoxylin and eosin (H&E) in the pathologic sections containing both tumor and the surrounding healthy tissue. Omentum was pathologically examined through 2-3 sections taken from macroscopic tumor and suspicious areas, or through 3-5 sections taken from healthy looking omentum tissue. Pathologic examination of the hysterectomy material was performed with at least 4 cutout sections. Lymph node examination was performed as follows: the material was taken into paraffin block (i) directly, if the size was less than 1 cm; (ii) with cutting into horizontally at least two pieces changing according to size, if it was more than 1 cm. In the presence of the macroscopic tumor, only that part was directly taken into paraffin block. The sections has been evaluated through hematoxylin and eosin stain.

Frozen-section is utilized routinely for the patients with EC in our clinic and staging surgery is performed for the patients whose preoperative pathologic diagnosis or frozen-section revealed non-endometrioid adenocarcinoma. The standard staging surgery included cytological sampling, total abdominal hysterectomy, bilateral salpingo-oophorectomy, systematic pelvic and paraaortic lymphadenectomy and omentectomy. During the intra-operative observation, cytoreductive surgery techniques have been applied in addition to staging surgery in the presence of macroscopic tumor.

Lymphadenectomy was performed in most of the patients by skeletonizing pelvic and paraaortic regions. Nevertheless, there were patients treated by sampling of the suspicious lymph nodes at the discretion of the surgeon. Since patients with positive lymph nodes were evaluated, patients who had lymph node sampling were also included in the study. Bilateral pelvic lymphadenectomy was performed to complete skeletonization, with all lymphatic tissue of the common, external and internal iliac vessels and the obturator fossa that was removed after visualization of the obturator nerve. The superior surgical dissection margin for the pelvic nodes was the aortic bifurcation, and the anterior distal surgical dissection margin was the circumflex iliac vein. The presacral lymphatic tissue was harvested separately. The upper limit of paraaortic lymphadenectomy was renal veins.

Factors identifying the lymph node metastasis were compared by applying chi-square test for categorical parameters and by using Anova Table Test for continuous parameters in univariate analysis. Factors that were statistically significant in the univariate analysis were analyzed with Logistic Regression Analysis in multi-variant analysis. The statistical analysis was performed by using SPSS 17.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago IL, USA) and p-value <0.05 was accepted as a statistically significance.

RESULTS

The mean age of the entire cohort was 61.4 years ranged between 32 and 77. The mean tumor size was 38 mm (range; 1-155). The tumor type was serous in 65 patients, clear cell in 55, undifferentiated in 23 and mucinous in 8. According to FIGO 2009, 61 patients had stage I, 6 patients had stage II, 47 patients had stage III and 36 of them had stage IV disease. Whereas 26 (17.3%) patients did not have myometrial invasion, myometrial invasion was equal or above the half ($\geq 1/2$) in 68 (45.4%) patients. Uterine serosal involvement was determined in 19 (12.7%) of these patients. Cervical involvement was identified in 48 (32%) patients and among them, cervical spread was observed as a stromal invasion in 35 cases. There were LVSI in 65 (42.7%) patients and malignity positive peritoneal cytology in 30 (20%) patients. The tumor spread to adnexa in 39 (26%) patients. Thirty-three (23.9%) of the 138 patients who underwent omentectomy had omental metastasis. Non-nodal extra-uterine disease was detected in 54 (36%) patients. The distribution of surgical and pathological factors detailed in Table 1.

Table 1. Clinical, pathological and surgical characteristics of all cohort

Characteristics	Mean / n	Median (range) / %
Age at initial diagnosis (year)	61.4	62 (32-77)
Tumor size (mm)	38	35 (1-150)
	IA	49
	IB	12
	II	6
FIGO 2009 stage	IIIA	7
	IIIC1	17
	IIIC2	23
	IVB	36
	Serous	65
	Clear cell	55
Tumor type	Mucinous	8
	Undifferentiated	23
	No invasion	26
Depth of myometrial invasion	< ½	56
	≥ ½ ¹	49
	Serosal invasion	19
	Negative	102
Cervical invasion	Glandular	13
	Stromal	35
	Negative	55
Lymphovascular space invasion	Positive	64
	Not reported	31
	Negative	107
Peritoneal cytology	Positive	30
	Not reported	13
	Negative	110
Adnexal metastasis	Positive	39
	Not reported	1
	Negative	105
Omental metastasis	Positive	33
	Omentectomy not performed	12
	Negative	96
Non-nodal extrauterine disease	Positive	54
Number of harvested lymph node	50.5	52 (2-118)
Number of metastatic lymph node	10.5	5 (1-55)
	Negative	80
	Isolated pelvic	29
Lymph node metastasis	Isolated paraaortic	9
	Pelvic & paraaortic	31
	Metastatic region unknown	1

¹: Except for uterine serosal invasion

Median removed lymph node number was 52 (range; 2-118). This number was 15 (range; 2-55) for the paraaortic region and 37 (range; 1-69) for the pelvic region. The removed lymph node number was 25 or more in 84% of the patients. The lymph node metastasis was identified in 80 (46.7%) patients. Lymphatic spread was observed at only paraaortic region in 9 (6%) patients, at only pelvic area in 29 (19.3%) patients and at both paraaortic and pelvic areas in 31 (20.7%) patients. Data about the metastatic lymph node count was not available for 1 patient. Median metastatic lymph node number was 5 ranging from 1 to 55. The number of removed lymph nodes did not change with the type of tumor. Median of the total number of removed lymph nodes was 53 (range; 13-80) for undifferentiated type, 54 (range; 14-118) for serous type, 47 (range; 2-102) for clear cell type and 34 (range; 10-69) for mucinous type ($p=0.082$). The number of removed lymph nodes did not differ according to the stage ($p=0.871$). The median removed lymph node number were 52 (range; 2-99) in 36 patients with stage IV and lymph node metastasis was identified in 30 (83.3%) of these patients.

The association between surgical-pathologic factors and lymphatic spread was evident. As an outcome of univariate analysis; tumor type, depth of myometrial invasion, cervical spread, LVSI, tumor positivity in peritoneal cytology, adnexal metastasis, omental involvement and presence of non-nodal extra-uterine disease were significant for tumor spread to lymph nodes (Table 2). Age and tumor size did not determine the lymphatic spread. In the case of undifferentiated tumor type, lymphatic metastasis was detected in 65.2% of patients (paraaortic lymph node metastasis in 43.5% and pelvic lymph node metastasis in 60.9%), whereas this rate was 51.6% (paraaortic lymph node metastasis in 32.8%, pelvic lymph node metastasis in 43.8%) in serous tumor type and 38.2% for clear cell type (paraaortic lymph node metastasis in 18.5%, pelvic lymph node metastasis in 30.9%). Lymph node metastasis was detected in 12.5% of cases with mucinous tumor type, and none of them had paraaortic spread.

Table 2. Factors predicting lymph node metastasis

Factors	Positive lymph node (%)		Paraaortic	P value	Total	P value
	Pelvic	P value				
Age						
≤65 years	39.4	0.833	23	0.107	44.4	0.447
>65 years	41.2		365		51	
Tumor type						
Serous	43.8	0.030	32.8	0.034	51.6	0.027
Clear Cell	30.9		18.5		38.2	
Mucinous	12.5		0		12.5	
Undifferentiated	60.9		43.5		65.2	
Depth of myometrial invasion						
No invasion	15.4	0.001	24	0.394	23.1	0.002
Invasion < ½	30.4		17.9		35.7	
Invasion ≥ ½ ¹	55.1		29.2		61.2	
Serosal invasion						
Negative	36.6	0.027	23.3	0.002	42.7	0.012
Positive	63.2		57.9		73.7	
Lymphovascular space invasion						
Negative	25.5	0.004	9.3	<0.0001	29.1	0.001
Positive	51.6		42.2		59.4	
Cervical invasion						
Negative	39.4	<0.0001	15	<0.0001	35.7	<0.0001
Glandular	46.2		30.8		53.8	
Stromal	68.6		62.9		77.1	
Peritoneal cytology						
Negative	29.9	<0.0001	19	<0.0001	34.6	<0.0001
Positive	73.3		60		86.7	
Adnexal involvement						
Negative	60	<0.0001	17.6	<0.0001	34.5	<0.0001
Positive	71.5		56		82	
Omental metastasis						
Negative	31.4	<0.0001	21.2	0.001	36.2	<0.0001
Positive	66.7		51.5		81.8	
Non-nodal extrauterine disease						
Negative	24	<0.0001	12.8	<0.0001	28.1	<0.0001
Positive	68.5		53.7		79.6	
Tumor size (mm)						
≤35 mm	33.3	0.100	25.5	0.169	43.1	0.184
>35 mm	50		38.6		56.8	

There were a significant correlation between tumor type and clinical or surgical-pathologic factors. Whereas patients with serous tumor type were older, tumor size was significantly larger in undifferentiated type (p=0.011 and p=0.001, respectively) (Table 3). Surgical-pathologic factors were worse in the undifferentiated type than the others.

Deep myometrial invasion and LVSI were more in this tumor type; besides, the possibility of the disease spread out of the uterine corpus (cervical invasion and non-nodal extra-uterine spread) was evident (Table 3). Non-nodal extra-uterine disease was present in 60.9% of patients with undifferentiated type. This rate was 43.8% for serous tumor type and 21.8% for clear cell tumor type (p=0.001). Non-nodal extra-uterine spread was not present in the mucinous tumor type.

Table 3. The relationship with tumor type and other factors

Factors	Tumor type			
	Serous Mean (median; range)	Clear Cell	Mucinous	Undifferentiated
Age (year)	63.5 (64; 46-76)	61.4 (62; 32-77)	56.8 (56; 50-71)	57.4 (59; 35-75)
P value	0.011			
Tumor size (mm)	29 (26; 1-60)	42 (33; 15-150)	39 (28; 10-90)	58 (50; 25-100)
P value	0.001			
Patient number (%)				
Depth of myometrial invasion				
No invasion	14 (25.5)	12 (23.1)	0	0
Invasion < ½	18 (32.7)	27 (51.9)	4 (50)	7 (43.8)
Invasion ≥ ½ ¹	23 (41.8)	13 (25)	4 (50)	9 (56.2)
P value	0.050			
Serosal invasion				
Negative	55 (85.9)	52 (94.5)	8 (100)	16 (69.6)
Positive	9 (14.1)	3 (5.5)	0	7 (30.4)
P value	0.015			
Lymphovascular space invasion				
Negative	23 (42.6)	26 (63.4)	5 (100)	1 (5.3)
Positive	31 (57.4)	15 (36.6)	0	18 (94.7)
P value	<0.0001			
Cervical invasion				
Negative	40 (62.5)	41 (74.5)	8 (100)	13 (56.5)
Glandular	4 (6.3)	8 (14.5)	0	1 (4.3)
Stromal	20 (31.2)	6 (10.9)	0	9 (39.1)
P value	0.015			
Peritoneal cytology				
Negative	44 (74.6)	42 (84)	8 (100)	13 (65)
Positive	15 (25.4)	8 (16)	0	7 (35)
P value	0.127			
Adnexal involvement				
Negative	43 (67.2)	46 (85.2)	8 (100)	13 (56.5)
Positive	21 (32.8)	8 (14.8)	0	10 (43.5)
P value	0.009			
Omental metastasis				
Negative	42 (68.9)	40 (81.6)	7 (100)	16 (76.2)
Positive	19 (31.1)	9 (18.4)	0	5 (23.8)
P value	0.188			
Non-nodal extrauterine disease				
Negative	26 (56.2)	43 (78.2)	8 (100)	9 (39.1)
Positive	28 (43.8)	12 (21.8)	0	14 (60.9)
P value	0.001			

Logistic regression analysis was performed to determine the correlation among predicative factors that were found to be significant for lymph node metastasis in univariate analysis.

Based on this, multi-variant analysis was performed by modeling including tumor type (undifferentiated vs. others), cervical invasion (positive vs. negative), and omental metastasis (positive vs. negative). Three parameters used in the model were independent prognostic factors in terms of lymph node metastasis (Table 4).

Table 4. Factors predicting lymph node metastasis, multivariate analysis

Factors	OR	%95 Confidence Interval	p value
Tumor type (undifferentiated vs. other)	3.489	1.413-10.650	0.028
Cervical invasion (positive vs. negative)	3.606	1.551-8.386	0.003
Omental metastasis (positive vs. negative)	8.074	2.917-22.346	<0.001

DISCUSSION

The relationship between surgical-pathologic factors; especially lymph node metastasis, and tumor type is evident in EC (3, 4, 9). Compared to endometrioid type, local and systemic spread of tumor is significantly higher in non-endometrioid type. Age, tumor type, grade, depth of myometrial invasion, LVSI, cervical spread, pelvic and/or paraaortic lymph node metastasis and extra-uterine non-nodal spread determine the survival of the disease (7, 13-20).

There is a close association between lymph node metastasis and surgical-pathologic risk factors that predict poor prognosis in EC. Lymphatic spread is an important predictor of survival in EC. Tumor type is associated with lymphatic spread, other surgical-pathological factors such as cervical spread, LVSI, myometrial invasion depth, tumor positivity in peritoneal cytology,

adnexal involvement, omental spread and presence of non-nodal extra-uterine disease, and mortality. Boruta et al. reported that the presence of extra-uterine disease was more likely in patient with serous EC than those with endometrioid EC even with grade 3 tumor (21). Hamilton et al. defined that the rate of extra-uterine spread at the initial diagnosis was 64%, 50% and 40% for uterine serous carcinomas, clear cell carcinomas and endometrioid carcinoma, respectively (7). Additionally, non-endometrioid types were found to be more risky in terms of nodal/non-nodal extra-uterine disease at the time of diagnosis (stage III-IV; 52% in serous type, 36% in clear cell type and 29% in endometrioid type grade 3) (7). In spite of that, Ureyen et al. reported that there were no significant difference between clear cell EC and serous EC with respect to lymphatic spread, myometrial invasion, cervical involvement, tumor positivity in peritoneal cytology, tumor size, adnexal involvement, omental metastasis and LVSI (15).

In this study which the association between non-endometrioid tumor type and disease spread was investigated, lymphatic spread and non-nodal extra-uterine disease were detected in 47% and 36% of patients, respectively. The type of tumor predicted the lymphatic spread, deep myometrial invasion, serosal involvement, adnexal spread, cervical invasion and omental metastasis. Tumor type (undifferentiated vs. others), cervical invasion and omental metastasis were independent prognostic factors for lymphatic spread. Pelvic and/or para-aortic lymphatic spread was 12.5% in mucinous type, 38.2% in clear cell type, 51.6% in serous type and 65.2% in undifferentiated type. The likelihood of lymphatic spread in the undifferentiated type was increased about 3.5-fold (OR: 3.489, CI: 1.413-10.650; p=0.028). Whereas the surgical-pathologic factors were significantly worse in the undifferentiated type than other tumor types, the opposite was true in the mucinous type.

In a multicenter study involving 112 cases with mucinous adenocarcinoma of the endometrium, mucinous histological type alone was found to be an independent risk factor for lymph node involvement (OR: 2.2, CI: 1.1-4.5; p=0.02) (19). Additionally, it was shown that the presence of more than half ($\geq 1/2$) myometrial invasion, positivity of LVSI and tumor grade were associated with lymph node involvement (19).

Nomura et al. reported that paraaortic lymph node metastasis in EC was related with tumor grade, myometrial invasion, pelvic lymph node metastasis, vascular space invasion, parametrial invasion, cervical involvement and adnexal metastasis (22). Kumar et al. found that tumor histology, myometrial invasion, grade and extra-uterine metastatic disease were related with lymph node metastasis in EC (23). Pelvic and paraaortic lymph node metastases were highly associated with deep myometrial invasion, high grade and presence of the macroscopic extra-uterine disease (23). These findings of Kumar et al. are consistent with our study.

The main limitation of this study is its retrospective nature. In addition, tumor types other than serous and clear cell type are limited. On the other hand, the strengths of this study are originating from a single medical center, complete lymphadenectomy performed in most of the patients, high number of removed lymph nodes and evaluated of the specimens by experienced gynecopathologists.

In conclusion, mucinous type differs from other non-endometrioid types in terms of nodal/non-nodal spread of the disease in EC. In general, there were lymph node metastasis in 47% of patients with non-endometrioid type EC and paraaortic lymph nodes in 40% of them. However, the lymphatic spread rate was 65% for undifferentiated tumor type and 12.5% for mucinous tumor type. Whereas non-nodal extra-uterine disease was detected in more than half of the patients with serous type and undifferentiated type and in one third of clear cell type, none of the the patients with mucinous type had it. Although the number of patients with mucinous type EC is not sufficient to produce a clear conclusion in the present study, the mucinous type appears to behave differently among the non-endometrioid types. Multicenter studies are needed to clarify the pathological spread and clinical behavior of the mucinous type.

Conflict of interest

No conflict of interest was declared by the authors.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011; 61:69-90.
2. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer* 1987; 60(8 Suppl):2035-41

3. Lewin SN, Herzog TJ, Barrena Medel NI, et al. Comparative performance of the 2009 international Federation of gynecology and obstetrics' staging system for uterine corpus cancer. *Obstet Gynecol* 2010; 116:1141-9
4. Announcements: FIGO (the International Federation of Obstetricians and Gynecologists) stages: 1988 revision. *Gynecol Oncol* 1989; 35:125-6
5. Meeting Report. The new FIGO staging system for cancers of the vulva, cervix, endometrium and sarcomas. *Gynecol Oncol* 2009; 115:325-8
6. Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol* 1983; 15:10-7
7. Hamilton CA, Cheung MK, Osann K, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. *Br J Cancer* 2006; 94:642-6
8. Nonnett BM, Zaino JR, Hendric K. Endometrial carcinoma. In: Kurman RJ, editor. *Blaustein's pathology of the female genital tract.* 5th ed. New York: Springer-Verlag. 2002; 551–9
9. Silva EG, Deavers MT, Malpica A. Undifferentiated carcinoma of the endometrium: A review. *Pathology* 2007; 39: 134-8
10. Altrabulsi B, Malpica A, Deavers MT, Bodurka DC, Broaddus R, Silva EG. Undifferentiated carcinoma of the endometrium. *Am J Surg Pathol* 2005; 29: 1316-21
11. Ureyen I, Ilgin H, Turan T, et al. Undifferentiated uterine carcinoma: analysis of eighteen cases. *J Obstet Gynaecol* 2015; 35: 372-6
12. Ross JC, Eifel PJ, Cox RS, Kempson RL, Hendrickson MR. Primary mucinous adenocarcinoma of the endometrium. A clinicopathologic and histochemical study. *Am J Surg Pathol* 1983; 7:715-29
13. Felix AS, Weissfeld JL, Stone RA, et al. Factors associated with Type I and Type II endometrial cancer. *Cancer Causes Control* 2010; 21: 1851-6
14. Scarfone G, Secomandi R, Parazzini F, et al. Clear cell and papillary serous endometrial carcinomas: survival in a series of 128 cases. *Arch Gynecol Obstet* 2013; 287:351-6
15. Ureyen I, Karalok A, Cirik DA et al. A comparison of clinico-pathological characteristics of patients with serous and clear cell carcinoma of the uterus. *Turk J Obstet Gynecol* 2016; 13: 137-43
16. Lax SF, Kurman RJ, Pizer ES, Wu L, Ronnett BM. A binary architectural grading system for uterine endometrial endometrioid carcinoma has superior reproducibility compared with FIGO grading and identifies subsets of advance-stage tumors with favorable and unfavorable prognosis. *Am J Surg Pathol.* 2000; 24:1201-8
17. Scholten AN, Smit VT, Beerman H, van Putten WL, Creutzberg CL. Prognostic significance and interobserver variability of histologic grading systems for endometrial carcinoma. *Cancer* 2004; 100:764-72
18. Zaino R. Pathologic indicators of prognosis in endometrial adenocarcinoma: selected aspects emphasizing the GOG experience. *Pathol Ann* 1995; 30(pt1):1-28
19. Gungorduk K, Ozdemir A, Ertas IE, et al. Is mucinous adenocarcinoma of the endometrium a risk factor for lymph node involvement? A multicenter case-control study. *Int J Clin Oncol.* 2015; 20:782-9
20. Sakuragi N, Hareyama H, Todo Y. Prognostic significance of serous and clear cell adenocarcinoma in surgically staged endometrial carcinoma. *Acta Obstet Gynecol Scand* 2000; 79: 311-6.
21. Boruta DM 2nd, Gehrig PA, Groben PA, et al. Uterine serous and grade 3 endometrioid carcinomas: is there a survival difference. *Cancer.* 2004; 101:2214–21.
22. Nomura H, Aoki D, Suzuki N. Analysis of clinicopathologic factors predicting para-aortic lymph node metastasis in endometrial cancer. *Int J Gynecol Cancer* 2006; 16: 799-804.
23. Kumar S, Podratz KC, Bakkum-Gamez JN. Prospective assessment of the prevalence of pelvic, paraaortic and high paraaortic lymph node metastasis in endometrial cancer. *Gynecol Oncol* 2014; 132: 38-43.