UTERİN SERÖZ KARSİNOM VE UTERİN BERRAK HÜCRELİ KARSİNOM TANISI ALAN HASTALARDA KLİNİKOPATOLOJİK ÖZELLİKLERİN VE SAĞ KALIM SONUÇLARININ KARŞILAŞTIRILMASI

Comparison Of Clinicopathologic Characteristics And Survivals In Patients With Uterine Serous And Clear Cell Carcinoma

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ÖZET

Amaç: Uterin seröz karsinom (USK) ve uterin berrak hücreli karsinomların (UBHK) klinikopatolojik özelliklerinin ve hastaların sağ kalım sonuçlarının karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Final patoloji raporlarına göre, USK ve UBHK tanısı alan hastalar çalışma grubunu oluşturmaktadır. Demografik, kilnikopatolojik ve sağkalım verileri analiz edildi.

Bulgular: USK grubunda 69 ve UBHK grubunda 36 hasta analiz edildi. USK grubunda hastaların UBHK grubundaki hastalarla karşılaştırıldığında, istatistiksel olarak anlamlı derecede daha ileri evre hastalığı sahip olduğu saptandı (sırasıyla %61,1 ve %36,2, p=0.015). USK grubundaki hastaların UBHK grubundaki hastalar ile karşılaştırıldığında daha fazla omental metastaza (17/69 ve 2/36, p=0,016) ve peritoneal sitoloji pozitifliğine (25/69 ve 5/36, p=0,016) sahip olduğu bulundu. Tüm kohort için multivaryan analizde sadece peritoneal sitoloji pozitifliğinin azalmış hastalıksız sağkalım (DFS) için bağımsız risk faktörü olduğu bulundu (HR 5,07 95% CI 2,07-12,42; p<0,001). Tüm kohort için, multivaryan analizde sadece peritoneal sitolojinin pozitif olması azalmış kaba sağkalım (OS) için bağımsız risk faktörü olarak bulundu (HR 3,50 95% CI 1,31-9,33; p=0,012).

Sonuç: Sonuç olarak çalışmamızda USK ve UBHK tanısı alan hastalarda sitoloji pozitifliğini hem DFS hem de OS için bağımsız prognostik faktör olarak saptadık. Ayrıca USK grubundaki hastalarda omental metastaz oranlarının yüksek olması nedeniyle omentektominin cerrahi evrelemenin bir komponenti olması gerektiğini düşünmekteyiz.

Anahtar kelimeler: *Endometriyal karsinom; Uterin berrak hücreli karsinom; Uterin seröz karsinom.*

ABSTRACT

Aim: We aimed to compare the clinicopathological characteristics and survivals between uterine serous carcinoma (USC) and uterine clear cell carcinoma (UCCC).

Materials and Methods: The study population consists of women who were diagnosed with USC and UCCC according to the final pathology reports. Demographic, clinicopathological and survival data were collected and analyzed.

Results: A total of 69 patients with USC and 36 patients with UCCC were included in the final analysis. Patients in the USC group tend to have more advanced stage disease compared to the patients in the UCCC group and this was statistically significant between the groups (61.1% vs 36.2%, respectively; p=0.015). Patients with USC were more likely to have omental metastasis (17/69 vs 2/36, p=0.016) and positive peritoneal cytology (25/69 vs 5/36, p=0.016). In the multivariate analysis, only positive peritoneal cytology remained as an independent prognostic factor for decreased disease free survival (DFS) for the entire cohort (HR 5.07, 95% CI 2.07-12.42; p<0.001). Only positive peritoneal cytology was an independent prognostic factor for decreased overall survival (OS) for the entire cohort (HR 3.50, 95% CI 1.31-9.33; p=0.012) in the multivariate analysis.

Conclusion: We concluded that positive peritoneal cytology was an independent prognostic factor for both DFS and OS in patients with USC and UCCC in the current study. Because of the high rate of omental metastasis in the USC group, we also suggest performing an omentectomy as a part of the comprehensive surgical staging surgery.

Key words: Endometrial carcinoma; Uterine clear cell carcinoma; Uterine serous carcinoma

INTRODUCTION

Uterine clear cell carcinoma (UCCC) and uterine serous carcinoma (USC) are rare histologic subtypes of endometrial carcinoma (EC) and according to Gynecologic Oncology Group 210 protocol, rates of USC and UCCC are 11.4% and 3.5%, respectively (1). However, these histological types account for up to 50% of deaths and recurrences due to endometrial cancer (2-4).

The standard surgical treatment for both histologic subtypes are similar, including total hysterectomy with bilateral salpingo-oophorectomy and retroperitoneal lymphadenectomy, omentectomy or omental biopsy as well as debulking of intraperitoneal disease in advanced stages (5). The adjuvant treatment strategies are similar as well, most patients receive chemotherapy, radiation therapy or both (6). However, there is a lack of prospective data for prognostic factors and treatment and existing data is based on retrospective studies, case series or expert opinion. In fact, these two histologic subtypes are obviously distinct entities with different precursor lesions and different genetic alterations (4, 7). Additionally, they have different clinical behaviors such as USC tends to spread via intraperitoneal route similar to serous ovarian carcinoma, however UCCC presents with hematogenous or lymphatic dissemination (3, 4). In our study, we aimed to compare the clinicopathological characteristics between USC and UCCC.

MATERIALS AND METHODS

The patients with EC who underwent surgical treatment between June 2007 and December 2018 were reviewed retrospectively. The clinical and pathological information of the patients were acquired retrospectively from prospectively maintained database of our institution after receiving Institutional Review Board approval. Informed consent forms were obtained from all patients at the time of admission to the hospital.

The study population consists of women who were diagnosed with USC and UCCC according to the final pathology reports. Women who had secondary primary tumors, tumors with histologic subtype other than USC and UCCC, and incomplete medical records were excluded from study. We also excluded women who received neoadjuvant chemotherapy.

All surgical staging procedures which include peritoneal washing, hysterectomy, bilateral salpingo-oophorectomy, omentectomy, systematic pelvic and paraaortic lymphadenectomy were performed by gynecologic oncologists. All pathological specimens were evaluated by gynecopathologists. The histologic classification was reported in accordance with the guidelines of World Health Organization (8). Tumor stage was defined by using the FIGO 2009 staging system (9). The stage of disease for the patients who were diagnosed before 2009 was adopted to the International Federation of Gynecology and Obstetrics (FIGO) classification system which was revised in 2009 (9).

Adjuvant therapy indications were determined by the multidisciplinary tumor board. After initial treatment, patients were followed-up quarterly during the first 2 years, biannually over 5 years, and annually thereafter. The survival status of the patients was determined as alive or dead at the time of the last follow-up. Disease-free survival (DFS) was defined as the interval from the time of initial surgery until the first event (recurrence or death, whichever occurs first) or the last contact. Overall survival (OS) was defined as the interval from the time of initial surgery until the date of death or the last contact. Surviving patients were censored at their last known follow-up.

Statistical analysis:

SPSS version 24.0 (IBM Corp., Armonk, NY, USA) was used to perform the statistical analyses. Continiuos variables were expressed as medians and ranges, and binary variables were reported as counts and percentages. Student-t test was used to compare the means of the continuous variables with normal distribution and Mann Whitney-U test was used to compare medians of the continuous variables without normal distribution. Chi-square test was used to compare nominal and binary variables. Kaplan-Meier plots were used to generate survival curves of the patients. A long rank test was performed to compare the survival curves. Logistic regression analysis was performed to determine the possible correlations

between clinicopathological factors and survival of the patients. We included the factors with a p value less than 0.05 in to the multiple regression analysis. A p value <0.05 was considered as statically significant.

RESULTS

A total of 69 patients with USC and 36 patients with UCCC, who were diagnosed according to final pathology reports, were included in the final analysis. Table 1 demonstrates the demographic and clinicopathologic characteristics of the study population. The median age of the patients in the USC group was 65, (range, 46-80), and 66.5 (range, 45-84) in the UCCC group. Primary tumor diameter, lymphovascular space invasion, myometrial invasion (MMI), cervical involvement, isthmus involvement, adnexal metastasis and adjuvant

Table 1. Comparison of clinicopathologic characteristics of USC and UCCC

Characteristics	USC (n=69)	UCCC (n=36)	*p*
Age, y (median, range)	65 (46-80)	66.5 (45-84)	0.48
Menopausal status (n, %)			
Premenopausal	2 (2.9%)	5 (13.9%)	0.032
Postmenopausal	67 (97.1%)	31 (86.1%)	
Tumor diameter, cm (median, range)	3.5 (0.1-14)	3.25 (1-13)	0.54
FIGO Stage (n, %)			
I,II	25 (36.2%)	22 (61.1%)	0.015
III,IV	44 (63.8%)	14 (38.9%)	
LVSI (n, %)			
Negative	26 (37.7%)	13 (36.1%)	0.87
Positive	43 (62.3%)	23 (63.9%)	
MMI (n, %)			
< 50%	31 (44.9%)	18 (50.0%)	0.62
≥ 50%	38 (55.1%)	18 (50.0%)	
Cervical involvement (n, %)			
Absent	47 (68.1%)	24 (66.7%)	0.88
Present	22 (31.9%)	12 (33.3%)	
Isthmus involvement (n, %)			
Absent	42 (60.9%)	20 (55.6%)	0.68
Present	27 (39.1%)	16 (44.4%)	
Adnexal metastasis (n, %)			
Absent	45 (63.4%)	26 (72.2%)	0.59
Present	26 (36.6%)	10 (27.8%)	
Omental metastasis (n, %)			
Absent	52 (75.4%)	34 (94.4%)	0.016
Present	17 (24.6%)	2 (5.6%)	
Peritoneal cytology (n, %)			
Negative	44 (63.8%)	31 (86.1%)	0.016
Positive	25 (36.2%)	5 (13.9%)	
Adjuvant treatment (n, %)			
Absent	4 (5.8%)	6 (16.7%)	
Chemotherapy	29 (42.0%)	15 (41.7%)	0.13
Radiotherapy	9 (13.0%)	1 (2.8%)	
Chemoradiotherapy	27 (39.1%)	14 (38.9%)	
Follow-up time, m (median, range)	47 (2-131)	83 (5-142)	0.006

Abbreviations: USC Uterine serous carcinoma, UCCC Uterine clear cell carcinoma, LVSI Lymphovascular space invasion, MMI Myometrial invasion, n Number, y Year, m Months

treatments were similar between the groups.

The number of postmenopausal patients in the USC group were higher compared to the UCCC group (97.1% vs 86.1%, respectively; p= 0.032). At the time of diagnosis, patients in the USC group tend to have more advanced stage disease compared to the patients in the UCCC group and this was statistically significant between the groups (61.1% vs 36.2%, respectively; p=0.015). Patients with USC were more likely to have omental metastasis (17/69 vs 2/36, p=0.016) and positive peritoneal cytology (25/69 vs 5/36, p=0.016). Systematic pelvic and para-aortic LND were performed in all patients. The median number of total LN and

Table 2. Comparison of LN characteristics of USC and UCCC

Characteristics	USC (n=69)	UCCC (n=36)	*p*
Number of LN removed (median, range)			
Total LN	55 (13-161)	63.5 (18-108)	0.16
Pelvic LN	36 (11-88)	40 (16-82)	0.053
Para-aortic LN	18 (3-74)	20 (2-40)	0.71
LN metastasis (n, %)			
Absence	41 (57.7%)	23 (36.1%)	0.65
Presence	28 (39.4%)	13 (63.9%)	
Pelvic LN metastasis (n, %)			
Absence	45 (65.2%)	25 (69.4%)	0.66
Presence	24 (34.8%)	11 (30.6%)	
PA LN metastasis (n, %)			
Absence	48 (67.9%)	24 (66.7%)	0.76
Presence	21 (29.6%)	12 (33.3%)	
Isolated pelvic LN metastasis (n, %)	7 (10.1%)	1 (2.8%)	0.17
Isolated PA LN metastasis (n, %)	4 (5.8%)	2 (5.6%)	0.96

Abbreviations: USC Uterine serous carcinoma, UCCC Uterine clear cell carcinoma, n Number, LN Lymph node, PA Paraaortic

rates of LNs metastasis were similar between the groups (Table 2).

The median follow-up time was 47 (range; 2-131) and 83 months (range; 5-142) in the USC and UCCC groups, respectively, and this was statistically significantly different between the groups (p=0.006). The five-year DFS rate was lower in the USC group than in the UCCC group (62.8% vs 81.1%, p=0.016) (Figure 1). The five-year OS rate was 70.7% in the USC group and 84.2% in the UCCC (p=0.085) (Figure 2).

The recurrence rate of the patients with USC was 13% and the corresponding value was 2.8% in patients with UCCC group. There were 4 loco-regional and 5 distant recurrences among the USC group. However only one patient had loco-regional recurrence in the UCCC group. At the end of the follow-up time, there were 21 deaths in the USC group and 7 deaths in the UCCC group.

The five-year DFS and OS rates were 69.3% and 75.6% respectively for the entire cohort. The univariate analyses revealed that USC histologic type (0.017), advanced-stage disease (p=0.02), omental metastasis (p=0.003), adnexal metastasis (0.01) and positive peritoneal cytology (p<0.001) were significant prognostic factors for decreased DFS (Table 3).

Figure 1. Kaplan-meier plots for DFS of USC and UCCC

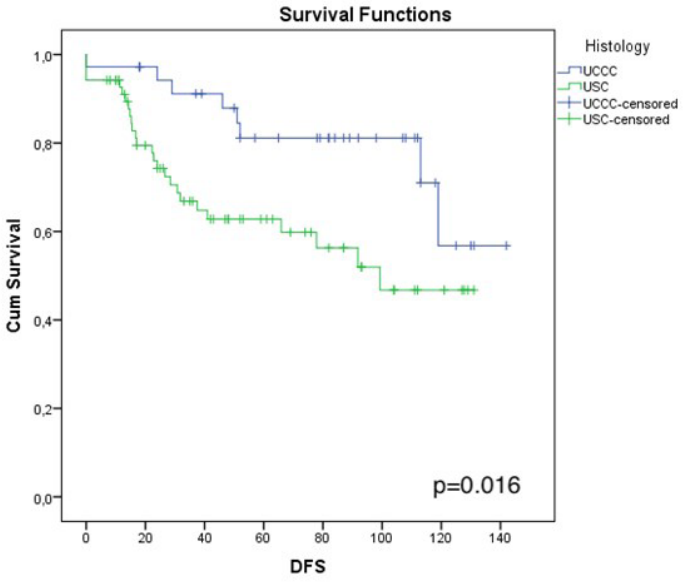
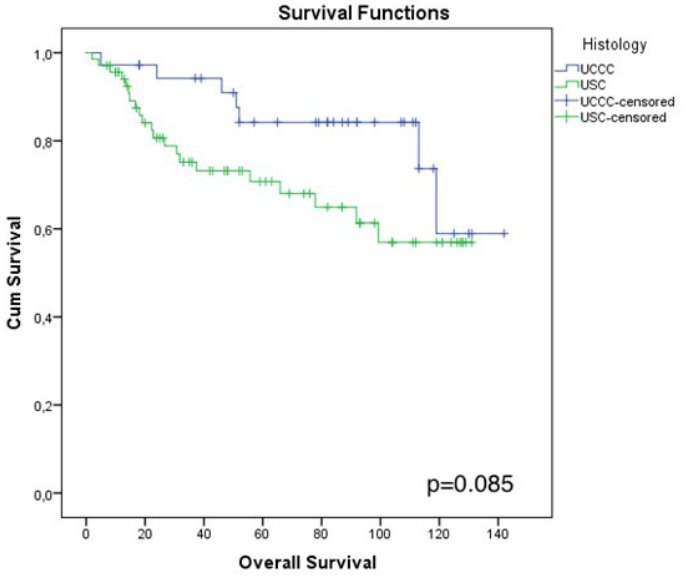


Figure 2. Kaplan-meier plots for OS of USC and UCCC



In the multivariate analysis, only positive peritoneal cytology remained as an independent prognostic factor for decreased DFS for the entire cohort (HR 5.07, 95% CI 2.07-12.42; p<0.001) (Table 3). For entire cohort, in the univariate analyses, advanced-stage disease (p=0.016), omental metastasis (p=0.003), adnexal metastasis (p=0.003) and positive peritoneal cytology (p<0.001) were associated with decreased OS in the current study (Table 4). In the multivariate analysis, only positive peritoneal cytology was an independent

Table 3. Univariate and multivariate analyses for disease free survival for the entire cohort

	Univariate analyses of DFS[a] n of events (%)		Multivariate Analysis of DFS[a]		
		p	HR	CI 95%	*p*
Age, y					
< 65	14/47 (63.7%)				
≥ 65	14/58 (73.0%)	0.63			
Menopause status					
Premenopausal	1/7 (80.0%)				
Postmenopausal	27/98 (68.5%)	0.39			
PTD, cm					
≤ 3.5	13/60 (74.9%)				
> 3.5	15/45 (61.8%)	0.06			
LVSI					
Negative	6/39 (82.7%)				
Positive	22/66 (60.7%)	0.12			
LN metastasis					
Absent	13/64(76.3%)				
Present	15/41 (58.4%)	0.10			
Cervical involvement					
Absent	15/71 (74.8%)				
Present	13/34 (58.1%)	0.26			
MMI					
< 50%	9/49 (79.3%)				
≥ 50%	19/56 (59.7%)	0.11			
Histologic Subtype					
UCCC	6/36 (81.1%)				
USC	22/69 (%62.8)	0.017			
Stage					
I-II	7/47 (82.4%)				
III-IV	21/58 (58.1%)	0.02			
Adnexal metastasis					
Absent	14/71 (75.6%)				
Present	14/34 (55.2%)	0.01			
Omental metastasis					
Absent	19/86 (74.3%)				
Present	9/19(43.7%)	0.003			
Peritoneal cytology					
Negative	10/75 (83.9%)				
Positive	18/30 (33.5%)	<0.001	5.07	2.07-12.42	<0.001

[a]: 5- year disease free survival

Abbreviations: CI Confidence interval, HR Hazard ratio, LVSI Lymphovascular space invasion, MMI Myometrial invasion, n Number, LN Lymph node, DFS Disease free survival, y Year, USC Uterine serous carcinoma, UCCC uterine clear cell carcinoma, PTD Primer tumor diameter

Table 4. Univariate and multivariate analyses for overall survival for the entire cohort

	Univariate analyses of OS[a] n of events (%)		Multivariate Analysis of OS[a]		
		p	HR	CI 95%	*p*
Age, y					
< 65	10/47 (75.4%)				
≥ 65	12/58 (76.3%)	0.78			
Menopause status					
Premenopausal	0/7 (100.0%)				
Postmenopausal	22/98 (74.0%)	0.15			
PTD, cm					
≤ 3.5	10/60 (80.6%)				
> 3.5	12/45 (69.0%)	0.08			
LVSI					
Negative	5/39 (85.6%)				
Positive	17/66 (69.3%)	0.36			
LN metastasis					
Absent	11/64(79.6%)				
Present	11/41 (69.4%)	0.48			
Cervical involvement					
Absent	13/71 (77.5%)				
Present	9/34 (71.5%)	0.98			
MMI					
< 50%	7/49 (79.3%)				
≥ 50%	15/56 (67.6%)	0.25			
Histologic Subtype					
UCCC	5/36 (84.2%)				
USC	17/69 (70.6%)	0.08			
Stage					
I-II	4/47 (85.6%)				
III-IV	18/58 (63.8%)	0.016			
Adnexal metastasis					
Absent	9/71 (83.4%)				
Present	13/34 (58%)	0.003			
Omental metastasis					
Absent	14/86 (80.7%)				
Present	8/19(49.0%)	0.003			
Peritoneal cytology					
Negative	7/75 (88.4%)				
Positive	15/30 (44.6%)	<0.001	3.50	1.31-9.33	<0.012

[a]: 5- year overall survival
Abbreviations: CI Confidence interval, HR Hazard ratio, LVSI Lymphovascular space invasion, MMI Myometrial invasion, n Number, LN Lymph node, OS Overall survival, y Year, USC Uterine serous carcinoma, UCCC uterine clear cell carcinoma, PTD Primer tumor diameter

prognostic factor for decreased OS for the entire cohort (HR 3.50, 95% CI 1.31-9.33; p=0.012) (Table 4).

DISCUSSION

In the present study, we concluded that patients with USC had worse 5 -year DFS rates compared to patients with UCCC (62.8% vs 81.1%, p=0.016) even though the patients in the UCCC group had shorter follow-up time. The 5-year OS rates were similar between the groups (70.7% vs 84.2%, p=0.085). The difference for omental metastasis (24.6% vs 5.6%, p=0.016), positive peritoneal cytology (36.2% vs 13.9%, p=0.016) and advanced-stage disease rates (61.1% vs 36.2%, p=0.015) were statistically significant between the groups, respectively.

There is no consensus about performing an omentectomy during staging procedure for EC with non-endometrioid histologic type. Even though, without MMI or minimal MMI, extrauterine spread of disease is common in USC (10, 11). Chan et al. found that omental metastasis rate was 25% in the noninvasive USC in their study (10). In a multicenter retrospective study, 7 out of 33 patients (21.2 %) had omental metastasis in the women with noninvasive USC and omentum was the most common metastatic site of disease in this study (11). The corresponding value for the rate of omental metastasis was 24.6% in our study. According to European Society of Gynecological Oncology guidelines for endometrial carcinoma, they recommend to perform staging omentectomy for USC but not for UCCC (level of evidence IV) (12). However, according to the National Comprehensive Cancer Network version 4.2019 performing an omental biopsy is advised in staging surgery for both USC and UCCC (13).

Gehrig et al. (14) stated that 52 patients with USC who underwent omentectomy in the staging surgery, eighteen of these patients had omental metastases. Sixten of the 18 patients had macroscopic metastasis and the remaining two patients had microscopic omental disease. Luz et al. (15) designed a study including 106 patients with USC in 2016. In this study, 66 out of 106 patients were undergone omentum biopsy (54; 82%) or omentectomy (12; 18%) and they found that only eight women (12%) had omental metastasis. Additionally, only two of 8 patients had micrometastasis in this study (15). Therefore, the authors concluded that omentectomy as a part of comprehensive surgical staging for UPSC may not be necessary according to these two studies (14, 15). However, this study represents that the rate of omental metastasis is consistent with the previous studies, as high as 21-25%, which suggests omentectomy or omental biopsy should be a part of the staging procedure for USC (10, 11).

Fifty-three patients with noninvasive UCCC were evaluated in a multicenter retrospective study and omental metastasis rate was found 17% (9/53) in this study (16). Five out of 9 patients had omental metastasis as the only metastatic site, and they reported that the most common metastatic site was omentum (16). They concluded that omentectomy should be a part of surgical staging in UCCC even for patients with noninvasive disease (16). On the other hand, Thomas et al. stated that 39 patients with UCCC were undergone omental biopsy, and none of them were upstaged due to this procedure (17). In our study, the omental metastasis was found in 2 out of 36 patients in the UCCC cohort and if there is no macroscopic disease in the omentum, omentectomy/ omental biopsy may be omitted for surgical staging in UCCC.

Although positive peritoneal cytology does no longer alter the disease stage according to the FIGO 2009 staging system, it is recommended to obtain peritoneal washings and get noted in the pathology report (9). Hanley et al. (18) evaluated the prognostic significance of positive peritoneal cytology in 33 patients with polyp-confined USC in their study. They found that positive peritoneal cytology rate was 24% (8/24) and it was significantly associated with disease recurrence (p=0.0013) (18). In a multi-institutional study, 414 patients with FIGO stage IA USC and UCCC were evaluated, and positive peritoneal cytology was found to increase the risk of distant and regional recurrence in these patients (19). In our study, patients with USC had a higher rate of positive peritoneal cytology compared to the patients with UCC (36.2% vs 13.9%, p=0.016, respectively). The positive peritoneal cytology was

found as an independent risk factor for both decreased DFS (HR 5.07 ,95% CI 2.07-12.42; p<0.001) and OS (HR 3.5,95% CI 1.31-9.33; p=0.012) for the entire cohort in our study.

Scarfone et al. (20) evaluated one hundred twenty-eight patients with USC or UCCC for survival outcomes. The 5-year OS rate were found 72.7% for the entire cohort; it was 70.5% and 76.7% for USC and UCCC, respectively in the current study (20). We found similar results with Scarfone et al. (20) in regards of OS and the corresponding values were 75.6%, 70.7% and 84.2% in our study, respectively. Mattes et al. (5) assessed the prognostic factors for patients with USC (685/972) or UCCC (287/972) and they demonstrated that advanced-stage disease (p<0.001), older age (p<0.001) and lymph node metastasis (p<0.001) were associated with decreased OS significantly. In the multivariate analysis, they were all independent prognostic factors for decreased OS (5). In this study, patients with USC had a lower 5-year OS rate compared to patients with UCCC (60% vs 67%, p=0.09; respectively) (5). In current study, we showed that patients with USC had worse 5-year DFS rates compared to patients with UCCC (62.8% vs 81.1%, respectively; p=0.016) even though patients with USC had shorter follow-up time. Additionally, there was a trend towards statistical significance in terms of 5-year OS rates between the USC and UCCC groups (70.7% vs 84.2%, p=0.085).

The rate of patients with FIGO stage III or IV USC was approximately 38% and the corresponding value is 16% for endometrioid type EC in the literature (21). Compared to the literature, there were more women with FIGO stage III or IV disease in USC cohort (38% vs 61.1%, respectively) in our study (21). In a retrospective cohort study by Nguyen et al., 146 patients with UCCC were evaluated and, they reported a similar rate of patients with FIGO stage III or IV disease compared to our study (36.2% vs 35%, respectively) (22). In the present study, all patients were undergone comprehensive surgical staging with adequate number of dissected lymph nodes, therefore we may have identified more patients with the advanced-stage disease. And also, FIGO stage III or IV disease rate was significantly lower among patients with UCCC compared to patients with USC (61.1% vs 36.2%, respectively; p=0.015) in our study.

Retrospective design is the major limitation of the current study. Additionally, low patient number may be another limitation. However, USC and UCCC are uncommon histological subtypes of EC, and compared with the previous studies, it can be said that the number of patients is sufficient (20, 23, 24). The major strengths of our study are that all patients were undergone comprehensive surgical staging by the gynecological oncologists and that pathology specimens were evaluated by the gynecopathologists. We concluded that positive peritoneal cytology was an independent prognostic factor for both DFS and OS in patients with USC and UCCC in the current study. Therefore, after the surgical staging, the decision for adjuvant treatment is made, positive peritoneal cytology should be considered to worsen the survival of this group of patients. Because of the high rate of omental metastasis in the USC group, we suggest performing an omentectomy as a part of the comprehensive surgical staging surgery.

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