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RESEARCH

Prognostic value of the presence of serous endometrial intraepithelial carcinoma in uterine serous carcinoma

Uterin seröz karsinomda seröz endometrial intraepitelyal karsinom varlığının prognostik değeri

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Abstract

Purpose: To investigate the clinical-pathological findings, prognosis, and survival outcome of uterine serous carcinoma (USC) with or without serous endometrial intraepithelial carcinoma (SEIC) which is still a rare entity in literature.

Materials and Methods: A total of 98 patients with USC who underwent at least a hysterectomy were reviewed. After elimination for exclusion criteria, totally 76 patients with USC who had surgical staging were evaluated. SEIC was defined as the replacement of the surface and glands of the adjacent atrophic endometrium without invasion of the stroma by the highly atypical cells resembling invasive high-grade endometrial carcinoma. The period from surgery to death or last visit was defined as overall survival (OS).

Results: The presence of SEIC was observed in half (n:38). Patients who had USC with SEIC were older and had a higher polypoid pattern than those without SEIC. The 5-year overall survival (OS) was 44.8% and 62.4% in patients with and without SEIC, respectively. There was no statistical significance for other clinicopathological factors in patients who had USC with or without SEIC. The advanced stage was related to a statistically significant hazard ratio for death of 2.45. Furthermore, the stage was found as the only independent factor of OS for USC. And, lymphovascular space involvement was determined as the only independent prognostic factor for OS in patients that had USC with SEIC.

Conclusion: Although the presence of polypoid pattern was significantly higher in patients who had USC including SEIC, it was not associated with survival independently. The stage was the only prognostic factor related to OS for

Öz

Amaç: Literatürde halen nadir bir antite olan seröz endometrial intraepitelyal karsinom (SEIC) ile birlikte olan veya olmayan uterin seröz karsinomun (USC) klinik-patolojik bulgularını, prognozunu ve sağkalım sonuçlarını araştırmak.

Gereç ve Yöntem: En az histerektomi yapılmış toplam 98 USC hastası incelendi. Dışlama kriterlerinden sonra, cerrahi evreleme yapılan toplam 76 USC'li hasta değerlendirildi. SEIC, invaziv yüksek dereceli endometriyal karsinoma benzeyen oldukça atipik hücreler tarafından stromanın invazyonu olmaksızın komşu atrofik endometriyumun yüzeyinin ve glandlarının değiştirilmesi olarak tanımlandı. Ameliyattan ölüme veya son ziyarete kadar geçen süre genel sağkalım (OS) olarak tanımlanmıştır.

Bulgular: Hastaların yarısında (n:38) SEIC varlığı gözlendi. SEIC'li USC'li hastalar daha yaşlıydı ve SEIC olmayanlara göre daha yüksek polipoid paterni vardı. 5 yıllık genel sağkalım (OS), SEIC olan ve olmayan hastalarda sırasıyla %44,8 ve %62,4 idi. SEIC'li veya SEIC'siz USC'li hastalarda diğer klinikopatolojik faktörler için istatistiksel anlamlılık yoktu İleri evre istatistiksel olarak 2,45 kat fazla ölüm riski ile ilişkiliydi. Ayrıca, evre, USC için OS'nin tek bağımsız faktörü olarak bulundu. SEIC'li USC'li hastalarda ise OS için tek bağımsız prognostik faktör olarak lenfovasküler alan tutulumu saptandı.

Sonuç: Polipoid patern varlığı SEIC dahil USC hastalarında anlamlı olarak daha yüksek olmasına rağmen, bağımsız olarak sağkalım ile ilişkili değildi. Evre, USC için OS ile ilişkili tek prognostik faktördü. Bununla birlikte,

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USC. However, the presence of the SEIC had no prognostic effect on the survival of USC.
Keywords:. Serous adenocarcinoma, serous intraepithelial neoplasia, uterus, survival.

SEIC varlığının USC'nin sağkalımı üzerinde prognostik bir etkisi yoktu.
Anahtar kelimeler: Seröz adenokarsinom, seröz intraepitelyal neoplazi, uterus, sağkalım

INTRODUCTION

Endometrium cancer (EC) is the most common gynecologic malignancy in the World[1]. Although uterine serous carcinoma (USC) is rare accounting for less than 10% of endometrium cancers, mortality and recurrence rates are still high[2]. A study conducted on 4180 patients diagnosed with high-risk endometrial carcinoma subtypes and recorded in the Surveillance, Epidemiology, and End Results (SEER) United States National Cancer Database between 1988 and 2001 revealed that uterine serous carcinomas constituted 10 percent of all endometrial carcinomas. However, they were responsible for 39 percent of all deaths associated with endometrial carcinomas during that period[3]. The five-year survival rate for uterine serous carcinoma was 45 percent[4]. Due to the aggressiveness of USC, the underlying pathological factor and precursor are not clear as endometrioid type EC that has intraepithelial hyperplasia/neoplasia origin[5]. The diagnosis of intraepithelial neoplasia provides an early detection opportunity for endometrioid type endometrium cancer. However, the serous endometrial intraepithelial carcinoma (SEIC) has been asserted as the probable precursor for USC in recent years[5]. Although pure SEIC was a noninvasive pathological diagnosis, extrauterine spread was reported in 33%–60% of them, in contrast to the typical behavior of other intraepithelial pathologies[6,7]. Therefore, the ability of extrauterine metastasis of isolated SEIC which is a noninvasive pathological entity of the uterus thought some authors to consider SEIC as a subtype of noninvasive USC rather than a precursor lesion[8,9]. Although similarities in the immunohistochemical profile of SEIC were determined next to USC, divergence for immunohistochemical results of USC with SEIC from USC without SEIC was often determined[10,11]. Some authors pointed to the synchronized presentation of serous ovarian-peritoneal carcinoma and SEIC, although it was not clear whether extrauterine metastasis or two independent carcinomas[12-14]. Therefore, the clinicopathological findings, prognostic value, and management of SEIC with or without USC are still debated in the light of literature. In the World Health Organization (WHO) classification of tumors for female genital tracts[15]

, SEIC is considered as a separate entity in the carcinoma group, denoted to warrant special attention for metastasis in extrauterine sites. The hypothesis of this study was the presence of USC and SEIC simultaneously may cause to higher incidence for extrauterine metastasis and advanced stage. Therefore, the purpose of study is to investigate the clinical-pathological findings, prognosis, and survival outcome of USC with or without SEIC which is still a rare entity in literature.

MATERIALS AND METHODS

Sample and data collection

A total of 98 patients with serous endometrial adenocarcinoma who underwent at least a hysterectomy in the Ankara Bilkent City Hospital Gynecological Oncology Department between November 2008 and December 2021 were looked through. Ankara Bilkent City Hospital is the largest healthcare facility in Europe. The hospital has a specific allocation of 3810 beds for patients. As the Gynecological Oncology Department, 1000 operations are performed annually with a total bed capacity of 50. The procedures were carried out by specially trained gynecological-oncology surgeons. Data of patients were obtained from electronic database or patients' files retrospectively. The inclusion criteria of the study were as follows: undergoing at least a hysterectomy in our institution; and a pathological diagnosis of USC. The exclusion criteria of the study were receiving neoadjuvant chemotherapy, having a having a histological type other than USC, having a synchronized tumor, and having a having a follow-up time shorter than 1 month after surgery. Fourteen patients with serous adenocarcinoma whose pathological data was not reached in detail, 2 patients that were lost to follow-up after a bit of surgery, 3 patients who underwent neoadjuvant chemotherapy, and 3 patients with synchronized tumors were excluded from the study. Totally 76 patients with USC were analyzed.

Procedure

Institutional review board approval (October/ 2023/ E2-23-5415) was precured before the study from Ankara Bilkent City Hospital ethical committee. Informed consent that allows participating institution to use their clinical data was signed by all patients. Whole patients underwent surgery initially. According to having serious systemic medical history and obesity, the decision about the performing of lymphadenectomy was made at the discretion of the senior surgeon. Pelvic-paraaortic lymphadenectomy was performed in the area from the level of the left renal vein at the top to the deep circumflex iliac vein at the bottom. Specialized gynecologic-pathologists evaluated the obtained surgical specimens. The stage was recorded according to 2009 FIGO staging criteria [16]. Necessity of adjuvant therapy were decided by the senior surgeon or the gynecologic oncology counsel. Size of tumor was identified as the largest tumor diameter which was measured in 2 dimensions by gynecological pathologist. Depth of myometrial invasion was categorized as a tumor invading inner half (< 50% of full-thickness) or outer half (≥50%) of the myometrium. In the presence of the tumoral cells or cell clusters holding on vessels' walls stained via hematoxylin and eosin in the pathologic sections containing both surrounding healthy tissue and tumor was described as lymphovascular space invasion. SEIC was defined as the replacement of the surface and glands of the adjacent atrophic endometrium without invasion of the stroma by the highly atypical cells resembling invasive high-grade endometrial carcinoma.

All patients examined every three months for the first two years, every six months until five years and then annually in the follow-up period. In case of doubt of recurrent disease, further radiological evaluation was performed according to symptoms. The period from surgery to last visit or death was described as overall survival (OS). The exitus status was obtained from the national survival database.

Statistical analysis

Statistical Package for Social Sciences (IBM SPSS Inc, Chicago, IL, USA) version 20.0 was used for statistical analysis. Normality of continuous variable distributions was analyzed by Kolmogorov-Smirnov test. Pearson X^2 test were used for analysis of categorical variables that were expressed as numbers and percentage. Additionally, Fisher's exact test was employed if any expected values were below 5 for analysis of categorical variables. Survival analysis was made using Kaplan-Meier method. The log-rank test was used for comparation of survival curves. Multivariate analysis was applied using Cox proportional hazards models. In univariate analysis, variables with a p-value <0.25 identified as potential risk factors for evaluation of the correlation among variables. In multivariate analysis, model was set up for death. Statistically significance was considered in the presence of less than 0.05 p value. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated.

RESULTS

The median age of entire cohort was 67 years (range: 40-88). The median tumor size was 35 mm (range: 1-140). Seventy-four patients underwent lymphadenectomy. Two patients did not undergo lymphadenectomy due to medical co-morbidities. The median removed lymph node count was 49 (14-107). The median paraaortic and pelvic lymph node numbers removed were 15 (range:1-48) and 31 (range:2-68). Twenty-seven patients (35.5%) had early stage (stage 1&2) disease. There was polypoid tumoral pattern in 43 (56.6%) patients. The clinic-pathological findings of cohort were demonstrated in Table 1 in detail.

SEIC was present in 38 patients (50%). Patients who had USC with SEIC were older than those without SEIC (p=0.030). Polypoid tumoral pattern was present in 72.1% of USC with SEIC, whereas this was 27.9% of those without SEIC (p<0.001). There was no statistical significance for stage, the diameter of the tumor, myometrial invasion, serosal involvement, lymphovascular space involvement, cervical involvement, adnexal involvement, omentum involvement, lymph node involvement in patients who had USC with or without SEIC. Two patients (patient≠1 and patient≠2), who had serous adenocarcinoma according to preoperative endometrial curettage biopsy, had vanishing tumor of serous adenocarcinoma in hysterectomy specimen. However, SEIC was reported in their hysterectomy specimen. Furthermore, in one of these patients (patient≠1), there was extrauterine metastasis (cytology, adnexal and omental) at first diagnosis (Table 3).

The 5-year OS of cohort was 53.3%. The median follow-up time was 27 months ranged from 2 to 157 months. In patients with and without SEIC, 5-year

OS was 44.8% and 62.4%, respectively (p=0.09). In entire cohort, the 5-year OS was significantly poor in the presence of advanced stage (3&4) (p=0.037), adnexal involvement (p=0.014), serosal involvement (p=0.043), lymphovascular space involvement (p=0.033), polypoid pattern (p=0.012) and omental involvement (p=0.018). After the correlation among the factors which had p<0.25 was determined in table 4, model included stage (1&2 *vs.* 3&4) and SEIC (absent *vs.* present). Advanced stage was associated with statistically significant hazard ratio for death of 2.45 (95% CI=1.083-5.580, p=0.031) in patients with USC. Stage was found as the only independent factor of OS (Table 5, Figure) for the entire cohort.

Table 1. Clinico-pathological findings of the entire cohort

Variable		**n**	**%**
SEIC	Absent	38	50
	Present	38	50
Polypoid pattern	Absent	33	43.4
	Present	43	56.6
Stage	1A	14	18.4
	1B	10	13.2
	2	3	3.9
	3A	2	2.6
	3B	1	1.3
	3C1	4	5.3
	3C2	13	17.1
	4A	1	1.3
	4B	28	36.8
Tumor diameter	≤3.5cm	41	53.9
	3.5cm<	33	43.4
	UK	2	2.6
Myometrial invasion	<1/2	28	36.8
	1/2≤	48	63.2
Serosal involvement	Absent	57	75
	Present	19	25
Lymphovascular space involvement	Absent	26	34.2
	Present	49	64.5
	UK	1	1.3
Cervical involvement	Absent or glandular	59	77.6
	Stromal	17	22.4
Cytology	Absent	56	73.7
	Present	10	13.2
	UK	10	13.2
Adnexal involvement	Absent	48	63.2
	Present	28	36.8
Omental involvement	Absent	53	69.7
	Present	22	28.9
	UK	1	1.3
Presence of metastatic lymph node	Absent	37	48.7
	Present	35	46.1
	UK	4	5.3
Recurrence	Absent	46	60.5
	Present	19	25.0
	UK	11	14.5
Exitus	Absent	43	56.6
	Present	33	43.4

SEIC: serous endometrial intraepithelial carcinoma, UK: unknown

Table 2. Clinico-pathological characteristics of patients who had USC with and without SEIC

Variable		n	SEIC Absent	SEIC Present	P
Age (years)	<67	37	23 (62.2%)	14 (37.8%)	**0.030***
	67≤	33	12 (36.4%)	21 (63.6%)	
Polypoid pattern	Absent	33	26 (78.8%)	7 (21.2%)	**<0.001***
	Present	43	12 (27.9%)	31 (72.1%)	
Stage	1&2	27	14 (51.9%)	13 (48.1%)	0.811
	3&4	49	24 (49%)	25 (51%)	
Diameter of tumor	≤3.5cm	41	19 (46.3%)	22 (53.7%)	0.336
	3.5cm<	33	19 (57.6%)	14 (42.4%)	
Myometrial involvement	<1/2	28	11 (39.3%)	17 (60.7%)	0.152
	1/2≤	48	27 (56.3%)	21 (43.8%)	
Serosal involvement	Absent	57	29 (50.9%)	28 (49.1%)	0.791
	Present	19	9 (47.4%)	10 (52.6%)	
Lymphovascular space involvement	Absent	26	15 (57.7%)	11 (42.3%)	0.291
	Present	49	23 (44.9%)	27 (55.1%)	
Cervical involvement	Absent or glandular	61	29 (49.2%)	30 (50.8%)	0.550
	Stromal	18	9(52.9%)	8 (47.1%)	
Adnexal involvement	Absent	48	26 (54.2%)	22 (45.8%)	0.341
	Present	28	12 (42.9%)	16 (57.1%)	
Omentum involvement	Absent	53	29 (54.7%)	24 (45.3%)	0.146
	Present	22	8 (36.4%)	14 (63.6%)	
Presence of metastatic lymph node	No	37	17 (45.9%)	20 (54.1%)	0.642
	Yes	35	18 (51.4%)	17 (48.6%)	
Presence of Metastatic Paraaortic lymph node	No	44	22 (50%)	22 (50%)	0.767
	Yes	28	13 (46.4%)	15 (53.6%)	
Presence of Metastatic Pelvic lymph node	No	40	17 (42.5%)	23 (57.5%)	0.245
	Yes	32	18 (56.3%)	14 (43.8%)	
Recurrence	No	46	23 (50%)	23 (50%)	0.846
	Yes	19	10 (52.6%)	9 (47.4%)	
Exitus	No	43	24 (55.8%)	19 (44.2%)	0.246
	Yes	33	14 (42.4%)	19 (57.6%)	

USC: uterine serous carcinoma, SEIC: serous endometrial intraepithelial carcinoma

Table 3. Characteristics of patients who had vanishing tumor in hysterectomy specimen

	Age	Preop. end. bx	Hysterectomy specimen	S	LN met.	Cytology	Adnexal inv.	Omental inv.	recurrence	exitus	FUT (months)
patient≠1	62	USC	SEIC	4B	Yes (Pelvic and Paraaortic)	Malign	Yes (both ovary and fallopian tube)	Yes	Yes (10 month later) (liver, abdominal, pelvic)	yes	11
patient≠2	72	USC	SEIC	1A	No	No	No	No	No	Alive without disease	21

USC: uterine serous carcinoma, SEIC: serous endometrial intraepithelial carcinoma, S: stage, inv.: involvement; LN met.: lymph node metastasis, Preop. end. Bx: Preoperative endometrial biopsy, FUT: Follow-up time

Subgroup analysis was performed for patients who had USC with SEIC. The 5-year OS was significantly shorter in the presence of lymphovascular space (p=0.018), omental (p=0.001) and adnexal (p=0.006) involvement in the subgroup. Age, polypoid pattern, stage, tumor size, myometrial invasion, serosal involvement, presence of metastatic lymph node and status of receiving adjuvant therapy were not related to OS. Presence of the cervical stromal involvement tended to be significantly shorter in subgroup

(p=0.062). After the correlation among the factors which had p<0.25 was determined in table 4, lymphovascular involvement (absent *vs.* present) and cervical involvement (absent *vs.* present) were included in the model. The independent prognostic factor for OS in patients that had USC with SEIC was determined as lymphovascular space involvement (p=0.041).

Table 4. Factors related to overall survival for entire cohort and subgroup

Clinicopathological factors		**Univariate analysis**			
		entire cohort		Subgroup[€]	
		5 year OS	P	5 year OS	P
Age	<67	44.6	0.430	32.5	0.424
	67≤	68.9		66.3	
Polypoid pattern	Absent	70.9	**0.012***	42.9	0.669
	Present	39.6		43.8	
SEIC	Absent	62.4	0.09	-	-
	Present	44.8		-	
Stage	1&2	81.3	**0.037***	72.5	0.093
	3&4	35.1		25.6	
Tumor diameter	≤3.5cm	54.7	0.548	47.9	0.374
	3.5cm<	54.3		42.4	
Myometrial invasion	<1/2	71.6	0.465	63.1	0.205
	1/2≤	44		33	
Serosal involvement	Absent	62.0	**0.043***	54.1	0.098
	Present	30.6		22	
Lymphovascular space involvement	Absent	79.5	**0.033***	85.7	**0.018***
	Present	35		25	
Cervical involvement	Absent or glandular	55.1	0.520	51	0.062
	stromal	51.1		29.2	
Adnexal involvement	Absent	65.6	**0.014***	65	**0.006***
	Present	31.7		16	
Omentum involvement	Absent	62.8	**0.015***	63.7	**0.001***
	Present	31.5		17	
Presence of metastatic lymph node	Absent	68.9	0.204	59.3	0.251
	Present	31.9		22	
Receiving adjuvant therapy	No	66	0.546	66.7	0.858
	Receive	52.8		42.4	

USC: uterine serous carcinoma, SEIC: serous endometrial intraepithelial carcinoma, OS: overall survival
[€] Patients who had USC with SEIC, *P<0.05 is statistically significance

Table 5. Multivariate analysis

Entire cohort		
	Hazard Ratio (95% CI)	**p value**
Stage (1&2 vs. 3&4)	2.45 (1.083-5.580)	0.031*
SEIC (absent vs. present)	1.99 (0.954-4.163)	0.067
USC with SEIC (subgroup)		
LVSI (absent vs. present)	3.82 (1.056-13.8	0.041*
Cervical involvement (absent vs. present)	2.30 (0.742-7.1)	0.149

USC: uterine serous carcinoma, SEIC: serous endometrial intraepithelial carcinoma, LVSI: lymphovascular space involvement
*P<0.05 is statistically significance

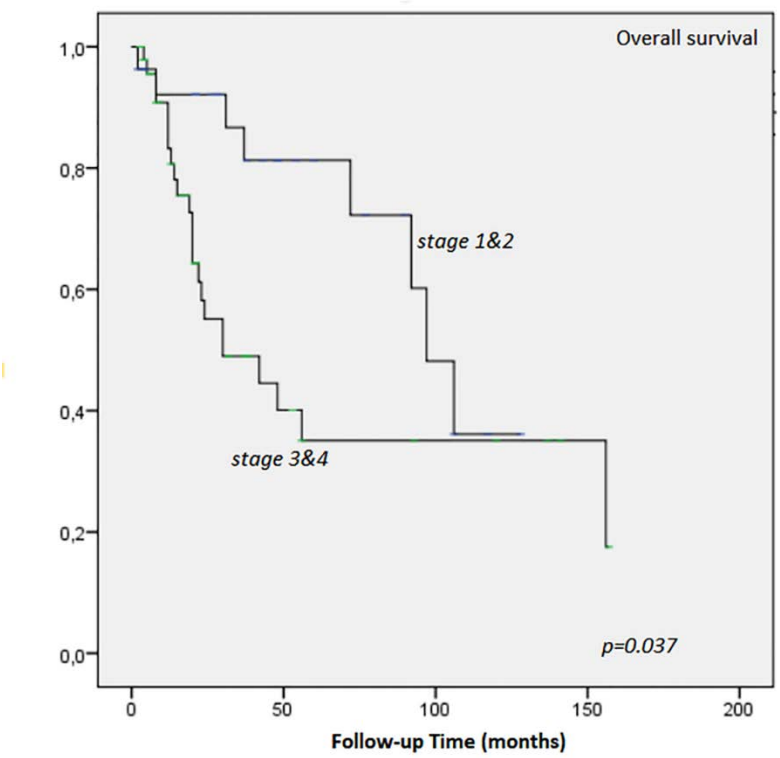

Figure 1. Association between stage and overall survival: Advanced stage (stage 3&4) was significantly related to lower overall survival than early stage in patients with USC.

DISCUSSION

This study illustrated that patients who had USC with SEIC were significantly older and had a higher rate of polypoid tumor pattern. There was no significant difference among other pathological factors and for overall survival between USC with and without SEIC. Only stage was an independent prognostic factor among patients with USC. However, presence of the lymphovascular involvement was only independent prognostic factor related to lower OS in patients who had USC with SEIC.

SEIC is a rare entity that is defined as a non-invasive lesion of endometrial epithelium[5]. Due to the strong similarity with pathological appearance and behavior of USC, it is thought to be a precursor of USC[17]. However, because of the ability of extrauterine spread despite non-invasive uterine involvement of pure SEIC, that is considered as another subtype of noninvsive USC rather than a precursor by some authors[8,18]. Surgically identifiable extrauterine metastasis was 33-60%[6, 8]. Furthermore, pathological inspection for micro-metastasis in extrauterine tissues, such as omentum and peritoneum, is recommended in the presence of the pure SEIC to identify the correct stage and prognosis [19]. There is still no consensus or guideline about the management of pure SEIC. The preferred primary treatment is surgery, according to case series or reviews in the literature[14,20]. There is no consensus for optimal surgical treatment. Slaager et al. found that the surgical approach varied among the gynecologists, from hysteroscopy to complete surgical staging[20].The major preferred approach reported was complete surgical staging to exclude extrauterine disease in their study[20].

Although there is a coexistence of atrophic endometrium with USC, over 50% of SEIC or minimal invasive serous carcinoma was determined in the background of endometrial polyp[21-23]. Yadav et al. reported that OS was not different between SEIC with or without polyp[23]. Similar to previous studies,

the presence of polypoid pattern was significantly higher in patients who had USC including SEIC in our study. Polypoid pattern was not associated with survival in patients that had USC or in subgroup including USC patients with SEIC independently.

Similar immunohistochemical results such as high p53, high p16, low or no estrogen receptor, low or no progesterone receptor expressions, and similar molecular signatures with USC were shown in most studies[18, 24-26]. However, the presence of extrauterine metastasis in defiance of intraepithelial localization; the similar strong estrogen receptor expression with concomitant serous ovarian carcinoma; similar molecular and immunohistochemical results with neoplasm of the fallopian tube; differences in immunohistochemical signatures of polypoid SEIC that had lower rates of p53 and p16 expressions, higher rates of estrogen and progesterone receptors, high rates of WT-1 contrast to USC without SEIC, pointed to the thought of different subtype of tumor for SEIC[6,8,11,27,28]. Ronsini et al. determined that the presence of extrauterine disease in SEIC was associated with poor outcomes regardless of adjuvant treatment[14]. In light of these knowledges, whether this divergence reflects clinical behavior and survival outcomes or not becomes more of an issue. Those brought to mind the question that the presence of USC and SEIC simultaneously may cause a higher incidence of extrauterine metastasis, advanced stage, or poor prognosis in contrast to pure USC. Wheeler et al. evaluated patients with SEIC or minimal invasive serous carcinoma measuring of invasion 1 cm or less[29]. They reported that SEIC or minimal invasive serous carcinoma without extrauterine disease had similar survival outcome. The only prognostic factor related to survival was the stage at presentation according to their study group[29]. Hou et al., in their study which evaluated the survival of patients with pure SEIC and USC, determined that stage 1 pure SEIC had poorer survival outcomes than stage 1 USC[8]. Nonetheless, they found that advanced stage pure SEIC and USC had similar survival outcomes[8]. In our study, OS was not significantly different for patients that had USC with and without SEIC. Therefore, Simultaneously SEIC and USC has no impact on survival contrast to pure USC according to our study's results. Similar to previous reports[30,31], only stage was an independent prognostic factor for USC. The presence of lymphovascular space invasion was determined as an independent prognostic factor in subgroup including cases who had USC with SEIC.

The present study's primary limitations were its small sample size and retrospective design. One of the advantages of the study was being first study that compared the patients who had USC with or without SEIC according to our knowledge. The other strengths of the study were as follows; all except two patients underwent comprehensive surgical staging by experienced gynecological oncologists and the pathologic results were evaluated by experienced gynecological pathologists.

In conclusion, the presence or absence of the SEIC had no prognostic effect on the survival of USC. The advanced stage was the only prognostic factor related to poor OS for USC. There is a need for larger prospective studies to draw distinct conclusions for survival outcomes and also to optimize the treatment.

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