

Clinicopathological risk factors and survival analysis of ovarian cancer with synchronous endometrial cancer diagnosed after surgery

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DOI: [10.31083/j.ejgo.2021.03.2336](https://doi.org/10.31083/j.ejgo.2021.03.2336)

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Submitted: 3 December 2020 Revised: 21 December 2020 Accepted: 11 January 2021 Published: 15 June 2021

Objective: In the present study, we tried to retrospectively evaluate the clinicopathological characteristics, prognosis and survival of patients with synchronous ovarian and endometrial cancer (SOEC). **Material and methods:** The data of patients with ovarian cancer who had been admitted to our hospital between February 2006 and March 2019 were retrospectively obtained from the hospital's electronic archive system collected after having obtained the ethics committee approval. Thirty-six patients with epithelial ovarian cancer and simultaneously diagnosed with primary endometrial cancer were included in the study. Patients with non-epithelial ovarian cancer, recurrent, metastatic and metachronous tumor, borderline ovarian tumor, uterine sarcoma and carcinosarcoma, and patients who had not attended regular controls were excluded from the study. Progression-free survival (PFS) and overall survival (OS) were compared using the Kaplan Meier survival analysis. The log rank test was used to test the effect of subgroups on survival. **Results:** The mean age of the SOEC patients included in the study was 52.05 ± 13.46 years. Of the patients, 8.3% had endometriosis and 16.7% had concurrent adenomyosis. Optimal surgery was seen to have been performed when evaluated with regard to post-operative residual tumor (R0, R1 and R2 61.1%, 33.3% and 5.6%, respectively). The histological grade was Grade 3 in most of the patients (44.4%). When the histology of SOEC patients was examined, endometrioid type was seen to be the most frequent in 18 patients (50%), followed by the serous type in 10 patients (27.8%). The least frequent was clear histology in 2 patients (5.6%). On the other hand, with regard to the endometrial cancer histology of SOEC patients, while the most common type was endometrioid type with 27 patients (75%), serous histological type was seen in 8 patients (22.2%). The five-year progression-free survival (PFS) was 43.6% for all patients, while the overall survival (OS) was 67.1%. The median PFS was 32 months, while the median OS was 89.6 months. In the subgroup analysis was performed as serous/serous histological type with SOEC patients with endometrioid/endometrioid, the median PFS was 53.8 months for the endometrioid/endometrioid type and 11.5 months for the serous/serous type, and it was statistically significant ($p: 0.001$). In terms of OS for both groups, it was 110.2 and 36.8 months, respectively, and it was statistically significant ($p: 0.001$). **Conclusion:** Endometrioid type endometrial cancer is more common than serous in synchronous ovarian and endometrial cancer patients and serous type has a worse prognosis than endometrioid.

Keywords

Synchronous epithelial ovarian cancer; Endometrial cancer; Endometriosis; Survival

1. Introduction

Simultaneous coexistence of primary ovarian and primary endometrial cancer is defined as synchronous ovarian and endometrial cancer (SOEC). Despite the absence of a clearly specified time interval in the literature, primary tumors detected within 4 months are also defined as synchronous tumors [1]. Primary synchronous tumors of the genital system are rare and occur in the range of 0.7% to 1.8% among all gynecological tumors [2, 3]. SOEC constitutes 50%–70% of synchronous tumors of the genital system [4]. While synchronous primary ovarian cancer is seen approximately at a rate 5% in endometrial cancer, synchronous primary endometrial cancer is seen at approximately 10% in ovarian cancer [5, 6]. However, when the literature was examined, it was noticed and discussed that these incidence rates were slightly higher due to the small number of patients. For this reason, population-based studies with large patient numbers have been conducted and while synchronous primary ovarian cancer was seen at a rate of 1.7%, synchronous primary endometrial cancer was seen at a rate of 3.6% [1]. Correct diagnosis of SOEC is very important, because in the light of current information, it is known that synchronous tumors have a better prognosis and survival than metastatic tumors [7–10]. In order to implement the following adjuvant treatment of the patients correctly, ovarian cancer stage 2A and endometrial cancer stage 3A should be clearly differentiated from primary synchronous tumor. Therefore, the histopathological criteria for SOEC or metastatic tumor differentiation were first defined by Ulbright and Roth, and later finalized by Scully *et al.* [11, 12]. Although these histopathological diagnosis-based criteria are widely used, they have been discussed in the literature. Because these tumors are very similar histologically, it is very difficult to distinguish them from metastatic tumors. Histopathological criteria may be inconclusive in the

diagnosis of SOEC, especially when the tumor has extensive involvement and the personal experience of the pathologist is important. Recently, synchronous ovarian and endometrial cancer can be diagnosed by performing mitochondrial DNA analysis, which is one of the molecular analysis methods, in cases where there is difficulty and uncertainty in diagnosis [13, 14]. Therefore, current diagnostic modalities such as new scoring systems, whole exome sequence analysis and clonality index were used for the differentiation of synchronous primary tumor from metastatic ovarian endometrial cancer [15, 16]. It is seen in aged (median age 40–50), obese, premenopausal and nulliparous women [17, 18]. At the same time, SOEC has been found to be associated with hyperestrogenic conditions (chronic anovulation, polycystic ovary syndrome (PCOS), unmet estrogen treatments) [19]. It should also be kept in mind that SOEC can be seen in individuals with a Lynch II history in their family [20]. Due to these factors (e.g., obesity, hyperestrogenism, etc.), the frequency of synchronous primary endometrial tumors in ovarian cancer has recently increased [21, 22]. In endometrial tumors, the frequency of synchronous primary ovarian tumors has decreased, especially due to the increase in the use of oral contraceptives [23, 24].

In this study, we tried to retrospectively evaluate the clinicopathological characteristics, prognosis and survival of patients with synchronous ovarian and endometrial cancer.

2. Materials and methods

The data of patients with ovarian cancer who had been admitted to our hospital between February 2006 and March 2019 were retrospectively obtained from the hospital's electronic archive system collected after having obtained the ethical approval. Thirty-six patients with epithelial ovarian cancer and simultaneously diagnosed with primary endometrial cancer were included in the study. Patients with non-epithelial ovarian cancer, recurrent, metastatic and metachronous tumor, borderline ovarian tumor, uterine sarcoma and carcinosarcoma, and patients who had not attended regular controls were excluded from the study. After the clinical evaluation, all patients had undergone radiological imaging, inferior, upper and thorax CT (computerized tomography) or MRI (magnetic resonance imaging). CA-125 and other tumor markers were examined in all patients. Patients with gastrointestinal complaints and a CA 125 and CEA rate of above 25 were subjected to upper and lower gastrointestinal evaluation. All patients with synchronous ovarian and endometrial cancer (SOEC) were diagnosed by our university's gynecopathologists using the Scully [12] criteria. The demographic and the clinical risk factors, the surgical procedure and the pathology reports of the patients were obtained from the hospital records. All patients in the study were staged according to the FIGO surgical staging (FIGO 2009 for endometrial cancer, FIGO 2014 staging for ovarian cancer). All patients were operated by experts in the field of gynecological oncology and during the operation, the abdomen was

entered through a sub-umbilical median incision, and total abdominal hysterectomy, bilateral salpingo-oophorectomy, sampling for abdominal cytology, total omentectomy, \pm systemic lymphadenectomy, small and/or large bowel resection due to tumoral involvement, splenectomy and necessary surgical procedures were performed. Maximum surgical effort was spent for complete (R0 = no residual tumor) or optimal (R1 = 1 cm residual tumor) cytoreduction for all patients. Adjuvant treatments (chemotherapy alone (3–6 cycles of carboplatin + paclitaxel), radiotherapy alone or chemoradiotherapy) were planned by the multidisciplinary gynecological oncology council (medical oncologist, gynecological oncologist, gynecopathologist, radiation oncologist, nuclear medicine specialist and radiologist). All patients were followed-up in the gynecological oncology clinic of our hospital after surgery. The patients were followed-up every 3 months during the first 2 years, every 6 months during the next 3 years, and then annual follow-up was carried out. At each follow-up visit, the CA (Cancer Antigen) 125 levels were measured by routine physical and gynecological examination, ultra-sonography (trans-vaginal and trans-abdominal) and vaginal cytology. Computed tomography or magnetic resonance imaging of the entire abdomen was requested from patients who were considered to have relapse according to clinical findings and the CA 125 levels. The progression-free survival (PFS) was defined as the time to recurrence after primary surgery. The overall survival (OS) was defined as the time the patient died or was last seen after primary surgery.

3. Statistical analysis

For the descriptive statistics, the mean, standard deviation, median, min-max values and frequencies were used, considering whether there was a normal distribution or not. The categorical data were expressed in numbers and percentages (%). Patients with ovarian cancer and synchronous primary endometrial cancer were compared in terms of stage and histology by cross-tabulation. Progression-free survival (PFS) and overall survival (OS) were compared using the Kaplan Meier survival analysis. The log rank test was used for the effect of subgroups on survival. The statistical Package for the Social Sciences (SPSS) 23 program (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) was used in the analysis of the data. The *p* values in all tests were two-sided, and when *p* values were lower than 0.05, it was considered to be statistically significant.

4. Results

The mean age of the SOEC patients included in the study was 52.05 ± 13.46 years. The median gravida and parities were 3 and 2, respectively. The median follow-up time was 52.2 (min; 2.7–max; 167.5) months. The clinical and pathological risk factors of the patients have been presented in Table 1. While the median BMI (Body Mass Index) of the patients was 25.9, the median CA 125 was found to be

Table 1. Clinical and Pathological risk factors of patients.

		Number/%	
Age (mean, sd)		52,05	±13, 46
Gravida (median, range)		3	0–10
Parity (median, range)		2	0–8
BMI (median, range)		25.9	18.9–38.2
CA 125 (median, range)		165.5	12.2–3512
Tumor diameter (mean, sd)		10, 18	±6, 49
Endometriosis	Yes	3	8.3
	No	33	91.7
Adenomyosis	Yes	6	16.7
	No	30	83.3
Stage (over)	I	11	30.6
	II	6	16.7
	III	14	38.9
	IV	5	13.9
CT status	Yes	32	88.9
	No	4	11.1
RT status	Yes	7	19.4
	No	29	80.5
Platin status	Sensitive	27	75
	Resistance	9	25
Surgical treatment	Nact + IDS	4	11.1
	PDS	32	88.9
	R0	22	61.1
Residual tumor	R1 (≤1 cm)	12	33.3
	R2 (>1 cm)	2	5.6
	Serous	10	27.8
	Endometrioid	18	50
Histology (over)	Mucinous	3	8.3
	Clear cell	2	5.6
	Mix	3	8.3
	1	7	19.4
Grade (over)	2	13	36.1
	3	16	44.4
Malignant cytology	Yes	17	47.2
	No	19	52.8
Omentum involvement	Yes	23	63.9
	No	13	36.1
Lymphadenectomy	Yes	27	75
	No	9	25
Lymph node involvement	Yes	8	29.6
	No	19	69.4
LVSI	Yes	6	16.7
	No	30	83.3
Recurrence	Yes	19	52.8
	No	17	47.2
Death	Yes	13	36.1
	No	23	63.9
Follow up (months)		52.2	2.7–167.5

SD, Standart deviation; BMI, Boddy Mass Index; CT, Chemotherapy; RT, Radiotherapy; LVSI, Lymphovascular space invation; PDS, Primary Debulking Surgery; Nact + IDS, Neo-adjuvant Chemotherapy + Interval Debulking Surgery.

Of the patients, 8.3% had endometriosis and 16.7% had adenomyosis. While NACT (neoadjuvant chemotherapy) was given to 4 patients, PDS (primary debulking surgery) was performed in the remaining patients. Thirty two patients (88.9%) were given adjuvant chemotherapy after surgery depending on histopathological risk factors. According to the platinum free interval, 25% of the patients were found to have platinum resistance. Considering postoperative residual tumor, it is seen that 94.4% of the patients undergo optimal surgery (R0, R1 and R2 61.1%, 33.3% and 5.6%, respectively). In terms of histological grade, the majority of the patients were seen to be Grade 3 (44.4%). Cytology positivity was detected in 47.2% of the patients, while 63.9% had omentum involvement. Lymphadenectomy was performed in 27 patients (75%). Lymph node involvement was detected in 8 (29.6%) of the patients who had undergone lymphadenectomy. Six patients (16.7%) had LVSI (lymphovascular space invasion). During the follow-up, 19 patients (52.8%) developed relapse and 13 patients (36.1%) died (Table 1). With regard to the histology of SOEC patients, endometrioid type was seen most frequently with 18 patients (50%), while the serous type was seen in 10 patients (27.8%). The least frequent was clear histology in 2 patients (5.6%). On the other hand, considering the endometrial cancer histology of SOEC patients, while the most common type was endometrioid type with 27 patients (75%), the serous histological type was observed in 8 patients (22.2%) and the least frequent was clear histological type with 1 patient (2.8%). The histopathological comparison of patients with synchronous ovarian and endometrial cancer has been presented in Table 2. The most common histological type was endometrioid/endometrioid seen in 18 patients (50%) followed by serous/serous histology in 7 patients (19.5%). When the ovarian cancer stages of SOEC patients were evaluated, the rates for stage I, II, III and IV were 30.6%, 16.7%, 38.9% and 13.9%, respectively. Stage IIIC (22.2%) was the most common, followed by stage IA (13.9%) and IC1 (13.9%). In terms of endometrial cancer, stage IA was seen most frequently with 27 patients (75%), and stage IB was the second most common with 6 patients (16.7%). One patient was stage II, one patient was stage IIIC1 and one patient had stage IIIC2 endometrial cancer. The FIGO staging of patients with ovarian and endometrial cancer had been displayed in Table 3. The five-year progression-free survival (PFS) for all patients was 43.6%, while the overall survival (OS) was 67.1%. The median PFS was 32 months, while the median OS was 89.6 months. When subgroup analysis was performed as serous/serous histological type with SOEC patients with endometrioid/endometrioid, the median PFS was 53.8 months for the endometrioid/endometrioid type and 11.5 months for the serous/serous type, and it was statistically significant ($p: 0.001$). In terms of OS for both groups, it was 110.2 and 36.8 months, respectively, and it was statistically significant ($p: 0.001$) Fig. 1.

165.5. The mean tumor diameter was 10.18 ± 6.49 cm.

Table 2. Histopathological comparison of patients with synchronous ovarian and endometrial cancer.

		Ovarian histology					
		Endometrioid	Serous	Mucinous	Clear cell	Mix (serous-endometrioid)	
Endometrial histology	Endometrioid	18	3	3	2	1	27 (75%)
	Serous	0	7	0	0	1	8 (22.2%)
	Clear cell	0	0	0	0	1	1 (2.8%)
		18 (50%)	10 (27.8%)	3 (8.3%)	2 (5.6%)	3 (8.3%)	36 (100%)

Table 3. FIGO staging of patients with ovarian and endometrial cancer.

		Ovarian stage										
		1A	1C1	1C3	2A	2B	3A1	3B	3C	4A	4B	
Endometrial stage	1A	4	4	0	2	1	1	2	8	2	3	27 (75%)
	1B	0	1	1	1	2	0	1	0	0	0	6 (16.7%)
	2	1	0	0	0	0	0	0	0	0	0	1 (2.8%)
	3C1	0	0	0	0	0	1	0	0	0	0	1 (2.8%)
	3C2	0	0	0	0	0	0	1	0	0	0	1 (2.8%)
		5 (13.9%)	5 (13.9%)	1 (2.8%)	3 (8.3%)	3 (8.3%)	2 (5.6%)	4 (11.1%)	8 (22.2%)	2 (5.6%)	3 (8.3%)	36 (100%)

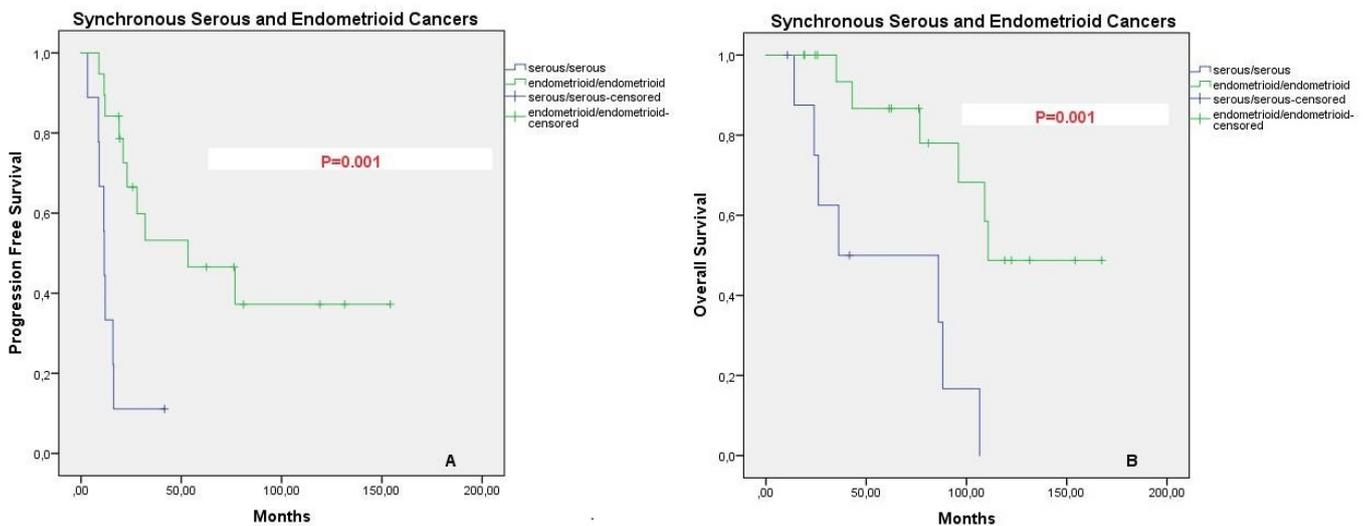


Fig. 1. Survival analysis of patients with synchronous serous/serous and endometrioid/endometrioid cancer. (A) Progression-free survival of patients with synchronous serous/serous and endometrioid/endometrioid cancer. (B) Overall survival of patients with synchronous serous/serous and endometrioid/endometrioid cancer.

5. Discussion

Ovarian cancer and synchronous primary endometrial cancer are rare conditions among gynecological malignancies [2, 3]. Although the frequency of SOEC is below 3% in population-based studies, it is around 10% in most studies in the literature [1, 25–27]. In our study, among the patients operated for epithelial ovarian cancer, 36 patients were diagnosed with synchronous primary endometrial cancer and our rate was found to be 8.8% (36/409). When the literature is reviewed, the number of patients in most studies on this subject does not exceed 100 [7, 28–30]. At the same time, the correct recognition of this clinical condition is extremely important as it affects the adjuvant treatment and survival, because some SOEC patients are mistakenly diagnosed with stage 2A ovarian cancer or stage 3A endometrial cancer. Previous stud-

ies have shown that SOEC patients have a better prognosis compared to ovarian cancer alone [7–10]. Since an accurate diagnosis is of vital importance, auxiliary diagnostic methods have also been used in addition to experienced gynecopathologists. Among these methods, immunohistochemical (IHC) methods such as P53, ER, PR, PTEN, k-ras and ki-67 have been used, as well as recent diagnostic modalities such as new scoring systems, whole exome sequence analysis and clonality index [15, 16, 31, 32]. However, it is not possible to use these widely all over the world. For this reason, it is still commonly diagnosed based on the Scully criteria [12].

Ovarian or endometrial cancer occurs in the sixth decade as an average age. However, the average age of our patients in our study seems to be 52. It has also been shown in other studies that SOEC occurs in the late 40–50 s [25, 26]. In the

studies of Bese *et al.* [7], it is seen that the average age is 52.6, and in the study of Sözen *et al.* [28], it is 53. Endometrial cancer is seen in approximately 10% under the age of 50. There are studies showing that in particular the endometrioid/endometrioid type SOEC patients are seen at a rate of up to 53% in the premenopausal period [5, 8, 33, 34]. The fact that women have postponed their request for children to late ages in recent years may explain this situation.

Maximal debulking should be the main goal in SOEC patients, since the amount of residual tumor is the most important prognostic factor in ovarian cancer [35, 36]. We see that residual tumor below 1 cm (including RO) is at a good level with 94.4% in our patients in the study. Although most of the patients in our study were at advanced stage, it is possible to notice that the surgical team made an effort and took good care for maximal debulking. Adjuvant chemotherapy and/or radiotherapy treatment was given to SOEC patients according to the postoperative risk factors. While 3–6 cycles of chemotherapy are given according to ovarian cancer risk factors (e.g., grade, stage, histological type), radiotherapy is added to those with uterine risk factors (e.g., more than 50% of myometrial invasion, high grade, cervical involvement, LVSI, non-endometrioid type).

It has been stated in previous studies that there may be a relationship between endometriosis and especially the endometrioid type ovarian cancer and clear cell cancer [37]. Ovarian cancer is seen at a rate of 0.7–1.0% in patients with endometriosis through unmet estrogen. The patients in our study had 8.3% endometriosis and 16.7% adenomyosis. It has been shown that patients with endometriosis have endometrioid and clear cell ovarian cancer 4-fold higher than patients without endometriosis [38]. For this reason, these clinical situations should be considered in patient evaluation as SOEC occurs mostly in young patients.

In ovarian cancer, 75–80% of patients are diagnosed at an advanced stage due to non-specific symptoms, whereas 80% of endometrial cancers are diagnosed at an early stage. The diagnosis of SOEC patients is early due to abnormal uterine bleeding associated with endometrial cancer. Soliman *et al.* [8] showed that there were 58% stage 1 and 7% stage 2 ovarian cancer, and 82% stage 1 and 10% stage 2 endometrial cancer in patients with synchronous EOC. In another study, these rates were given as 30%, 30%, 38.5% and 61.5%, respectively [39]. In another study, stage 1 and 2 ovarian cancer was observed at a rate of 52.1% [30]. In our study, stage 1 and 2 ovarian cancer was detected in 47.3%, while 75% stage 1 and 16.7% stage 2 endometrial cancer were found. The early onset of SOEC patients may explain the better prognosis than metastatic tumors. Stage 1/stage 1 synchronous ovarian endometrial cancer was found in 27.7% in the current study.

In patients with synchronous ovarian and endometrial cancer, endometrioid type tumors are seen most frequently (66–75%) and it is stated that they have a better prognosis [9, 34, 40, 41]. Especially in obese, infertile patients and patients with polycystic ovaries with excess unmet estrogen, such tu-

mors can be expected to be at a higher frequency. However, it is still not completely understood how synchronous endometrioid or serous tumors emerge [9]. To clarify this situation, looking at the theory of secondary müllerian system, it is said that the cervix, uterus, tuba uterina, ovary and peritoneal epithelium contain the same receptors and they act together in the oncological process and produce synchronous tumors. However, this theory cannot explain how endometrioid/serous histological types are formed. Further studies are needed for this situation. Sözen *et al.* [28] reported that patients with endometrioid/endometrioid type SOEC had a better progression-free survival than non-endometrioid type patients. However, Lim *et al.* [41] and Caldarella *et al.* [10] stated the opposite in their study. When we look at the histology of ovarian cancer in our study, we see that there is an endometrioid type tumor in 50% and in the histology of endometrial cancer 75%, and these rates are compatible with the literature. In addition, there was a statistically significant difference in both PFS and OS in the comparison of endometrioid/endometrioid and serous/serous histological type survey in the subgroup analysis of our patients. For this situation, the following can be considered; we notice that serous/serous type SOEC patients are at a more advanced stage and higher grade than endometrioid/endometrioid type SOEC patients. It is already known that patients with serous/serous histology are diagnosed late due to non-specific symptoms and come at an advanced stage. Another reason may be that endometrioid/endometrioid type tumors are seen in younger patients. We can say that these findings are similar to the literature [1, 9, 28, 34, 40, 41]. The 5-year PFS of SOEC patients is around 65% [28–30]. The 5-year overall survival is between 73–86% [30, 39]. However, Bese *et al.* [7] found the 5-year synchronous EOC surveillance as 67% and showed that metastatic EOC was better than the survival of patients. These rates appear to be better than stage 3A endometrial cancer alone and stage 2A ovarian cancer alone (56% and 70% in 5-year survey, respectively) [42, 43]. We found the 5-year PFS of the patients in our study to be 43%, while OS was 67.1%. It is seen that these rates are lower than the rates in the literature, but similar to the rates of Bese *et al.* [7]. When we look at the reasons for our low survival rates, it can be stated that the majority of patients have high grade, that the number of our advanced stage patients is high, that most of our patients receive adjuvant treatment and there are more patients with other than the endometrioid type.

Considering the limitations of our study, selective bias can naturally be seen in patient selection since it was retrospective. The other limitations of the study are the low number of patients, the absence of pathologically imminent histochemistry and gene analysis, and the lack of knowledge of familial comorbidities such as Lynch syndrome. It is very difficult to recruit patients for prospective studies, since the diagnosis of SOEC patients is made postoperatively and is a rare condition.

In conclusion, endometrioid type endometrial cancer is more common than serous in synchronous ovarian and endometrial cancer patients and serous type has a worse prognosis than endometrioid.

Author contributions

MSB and ÖB conceived and designed the study; MSB, ÖB, CK performed the study; MSB, TS, CK and SD analyzed the data; HAT, SD and TS contributed materials and evaluation; MSB wrote the paper. All authors have read and approved the manuscript.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Akdeniz University Hospital (approval number: KAEK-922).

Acknowledgment

Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

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