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ORIGINAL RESEARCH ARTICLE

Synchronous primary endometrial and ovarian cancers: a multicenter review of 63 cases

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ABSTRACT

Aims: To investigate clinicopathologic characteristics, therapeutic methods, and prognostic factors in women with synchronous primary endometrial and ovarian cancers (SEOCs).

Methods: A retrospective review of 2 cancer registry databases in Turkey was conducted to identify patients diagnosed with SEOCs between January 1995 and December 2012. Patients with recurrent, metastatic, and metachronously occurring tumors were excluded. Multivariate logistic regression models were used to identify prognostic predictors for progression-free survival (PFS) and overall survival (OS).

Results: The analysis included 63 women with SEOCs. Seventy-six percent of the patients had stage I endometrial cancer, and 60% of the patients had stage I ovarian cancer. Thirty-seven patients (58.7%) had endometrioid/endometrioid histology. Optimal cytoreduction was obtained in 47 (74.6%) patients. Recurrence developed in 17 patients (27%). Multivariate analysis confirmed lymphovascular space invasion (LVSI) as an independent poor prognostic factor for OS (odds ratio [OR] 3.1, p = 0.045), whereas early-stage disease and optimal cytoreduction were found to be independent good prognostic factors for both PFS (OR 12.85, p<0.001 and OR 4.58, p = 0.004, respectively) and OS (OR 7.31, p = 0.002 and OR 2.95, p = 0.028, respectively). The 3- and 5-year OS rates were 74% and 69%, respectively.

Conclusions: Our study demonstrated that optimal cytoreduction, early-stage disease, and LVSI are the most significant factors affecting survival in women with SEOC.

Keywords: Early-stage disease, Lymphovascular space invasion, Optimal cytoreduction, Survival, Synchronous endometrial and ovarian cancer

Introduction

Synchronous primary tumors of the genital tract are rare and occur in 0.7%-1.8% of women with gynecologic tumors (1-4). Synchronous primary endometrial and ovarian cancers (SEOCs) are the most common subtype. The definition of such tumors is controversial; however, 2 or more primary tumors that develop close in time are generally termed synchronous tumors (5). The etiology is unknown, but SEOCs are typically diagnosed in obese, nulliparous, and premenopausal women. The most common presenting symptoms are abnormal vaginal bleeding and pelvic pain (6-8). Synchronous primary endometrial and ovarian cancers are generally diagnosed at an early stage and have a good overall prognosis (8, 9).

In this study, we assessed the clinicopathologic characteristics, treatment, and prognosis of SEOCs.

Methods

Patients

All patients who had undergone surgery for SEOCs at the Tepecik Education and Research Hospital, Izmir, and Medical School of Celal Bayar University, Manisa, Turkey, between January 1995 and December 2012 were retrospectively reviewed. This study was performed in accordance with the ethical standards of the Declaration of Helsinki and approved by the local ethics committee of our institution. Patients with recurrent, metastatic, and metachronously occurring tumors were excluded from the study. In addition, 4 patients were excluded because of missing data.

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Data collection

Demographic data, such as age, presenting symptoms, parity, menopausal status, and laboratory findings (e.g., preoperative CA125 levels and platelet counts), were obtained from medical records. Pathologic findings, such as histology, stage, grade, lymphovascular space invasion (LVSI), and nodal involvement, were obtained from surgical pathology reports. All the pathology slides were reviewed by experienced gynecologic pathologists according to the criteria described by Young and Scully (10). The pathologic criteria for SEOCs were as follows: (1) histologic dissimilarity of the tumors; (2) no or only superficial myometrial invasion of endometrial tumor; (3) no vascular space invasion of endometrial tumor; (4) atypical endometrial hyperplasia additionally present; (5) absence of other evidence of spread of endometrial tumor; (6) ovarian unilateral tumor (80%-90% of cases); (7) ovarian tumor located in parenchyma; (8) no vascular space invasion, surface implants, or predominant hilar location in ovary; (9) absence of other evidence of spread of ovarian tumor; (10) ovarian endometriosis present; (11) different ploidy of DNA indices, if aneuploid, of the tumors; and (12) dissimilar molecular genetic or karyotypic abnormalities in the tumors.

Surgical technique

During the study period, the surgical management of cases varied among the practitioners, particularly with respect to the role of lymphadenectomy. As a routine surgical procedure, peritoneal washing cytology, total abdominal hysterectomy plus bilateral salpingo-oophorectomy (BSO), and frozen section analysis were performed in all cases. No lymph nodes were sampled in some patients, bilateral pelvic (P) lymph node dissection (LND) was performed in some patients, and some patients underwent complete staging with bilateral P and para-aortic (PA) LND. The decision to perform a systematic P, PA LND, and appendectomy was made at the surgeon's discretion. Staging criteria were determined postoperatively based on the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system. According to the definition in a previous study (11), optimal cytoreduction was defined as the largest residual tumor nodule measuring 1 cm or less. In general, maximal effort was made to remove all gross disease and to achieve optimal cytoreduction.

Adjuvant treatment

Adjuvant therapy, including chemotherapy alone, radiotherapy (RT, including internal RT and external RT [ERT]) alone, or a combination of both, was administered to patients based on stage, age, nodal status, performance status, and the presence/absence of medical comorbidities. The chemotherapy and RT regimens were as follows: paclitaxel (175 mg/m^2) or docetaxel (75 mg/m^2) was administered in combination with carboplatin at an area under the curve (AUC) of 5 or 6. Cisplatin was administered at a dose of 60 mg/m^2 in combination with paclitaxel (175 mg/m^2) or doxorubicin (50-60 mg/m^2). The courses were repeated every 3 weeks for a total of 6 courses. External RT was administered at a median dose of 50.4 Gy (range 45-54) in 1.8- to 2.0-Gy fractions 5 days a week. Internal RT (2 × 6.5 Gy and 3 × 6 Gy when combined with ERT; 3 × 7 Gy when applied as the sole RT modality) was delivered via a vaginal applicator fitted with a source of high-dose-rate iridium-192.

Clinical follow-up

The patients returned for follow-up evaluations every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Follow-up evaluations consisted of physical and vaginal examinations, vaginal cytology, ultrasonography, and the assessment of serum CA125 values. Computed tomography or magnetic resonance imaging was performed annually.

Progression-free survival (PFS) was defined as the time from the date of primary surgery to the detection of recurrence or the latest observation. Overall survival (OS) was defined as the time from the date of primary surgery to death or the latest observation.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 15.0 (SPSS Inc., Chicago, IL, USA). Visual and analytical methods were used to assess the variables to determine whether they were normally distributed. Continuous data were analyzed using the Mann-Whitney *U* test for non-normally distributed data. The chi-square test was used to compare the proportions between groups. Univariate and multiple logistic regression models were used to identify risk factors. The Kaplan-Meier method was used to generate the survival curve, and comparisons were made using the log-rank test. A p value <0.05 was defined as statistically significant.

Results

A total of 63 patients who had undergone surgery for SEOCs and fulfilled our inclusion criteria were included in this study. The median age was 50 years (range 43-56 years). Abnormal vaginal bleeding (44.5%) was the most common presenting complaint. Patient characteristics are presented in Table I.

Among the patients, 51% had FIGO grade 1 endometrial cancer (EC) and 49.5% had grade 2 ovarian cancer (OC). Only 14.3% of the patients exhibited LVSI. Forty-five patients (71.4%) had myometrial invasion of ≤50%. Seventy-six percent of the patients had FIGO stage I EC, and 60% of the patients had FIGO stage I OC. Forty-one patients (65.1%) presented with early disease (FIGO stages I and II), and 22 (34.9%) were diagnosed with advanced disease (FIGO stages III and IV). Thirty-seven patients (58.7%) had concordant endometrioid histology of both sites, whereas 26 patients (41.3%) had different histologies.

Total abdominal hysterectomy plus BSO and omentectomy were performed in 10 patients (15.9%). In addition to this procedure, bilateral P lymphadenectomy was performed in 13 (20.6%) patients, and 40 (63.5%) patients underwent bilateral P and PA lymphadenectomy. Appendectomy was performed in 33 (52.4%) patients, and 3 (4.8%) of them

TABLE I - Clinical, surgical, and pathologic characteristics of the study population (n = 63)

Characteristics	No. (%) or median (Q1-Q3)
Age, y	50 (43-56)
≤50	32 (50.8)
>50	31 (49.2)
Menopause	34 (54)
Nulliparity	18 (28.6)
Symptom	
Vaginal bleeding	28 (44.5)
Abdominal/pelvic pain	25 (39.7)
Pelvic mass	9 (14.3)
Weight loss	1 (1.6)
Platelet count, cells/mm^3	282,000 (230,000-364,000)
Presence of ascites	19 (30.2)
LVSI	
No	54 (85.7)
Yes	9 (14.3)
CA125, U/mL	49 (10-190)
Number of removed LNs	
Pelvic	15 (5-22)
Para-aortic	2 (0-9)
Residual tumor at initial surgery, cm	
≤1	47 (74.6)
>1	16 (25.4)
Histologic type	
Endometrioid/endometrioid	37 (58.7)
Others	26 (41.3)
Adjuvant therapy	
None	9 (14.3)
Only chemotherapy	26 (41.3)
Only RT	3 (4.8)
Combination	25 (39.7)
PFS, mo	47 (13-114)
OS, mo	62 (19-118)

LN = lymph node; LVSI = lymphovascular space invasion; OS = overall survival; PFS = progression-free survival; RT = radiotherapy.
Values for the continuous variables are presented as median (Q1-Q3). Values for the categorical variables are presented as number (%) of cases.

had metastasis to the appendix. Optimal cytoreduction was obtained in 47 (74.6%) patients.

During the postoperative period, 9 (14.3%) patients did not receive adjuvant treatment. The remaining 54 patients received at least one of the adjuvant treatment modalities, including RT only, chemotherapy only, or combined chemotherapy and RT. The distribution of the adjuvant therapies administered was as follows: 26 (41.3%) patients received only chemotherapy, 3 (4.8%) patients received only RT, and 25 (39.7%) received chemotherapy and RT.

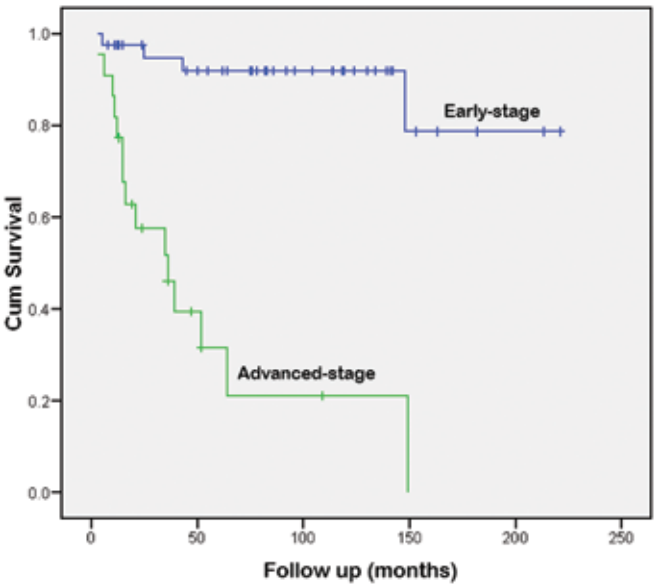

Fig. 1 - Overall survival of all patients (n = 63) when grouped according to stage (early stage vs advanced stage; p<0.001).

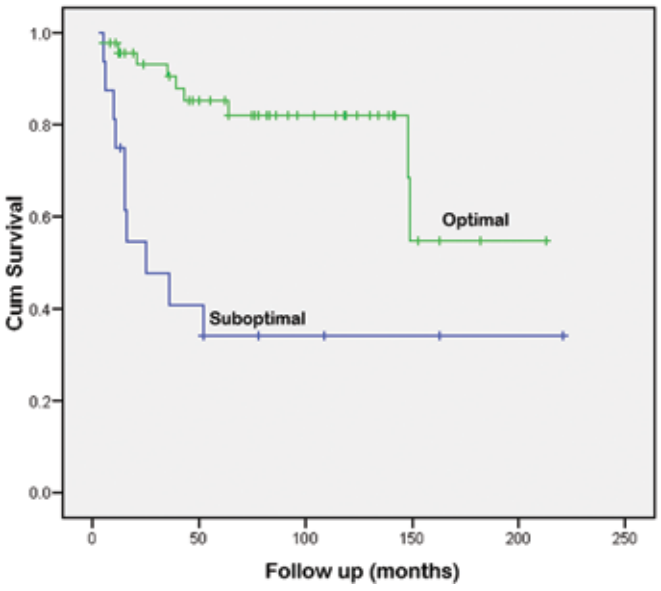

Fig. 2 - Overall survival of all patients (n = 63) when grouped according to cytoreduction (optimal vs suboptimal; p<0.001).

The survival rates were analyzed in relation to the above mentioned clinicopathologic features. The mean PFS and OS rates for patients with early-stage disease were significantly better than those of patients with advanced disease (187.7 ± 12 vs 41.6 ± 14 months, p<0.001, and 195.4 ± 12 vs 54 ± 13 months, p<0.001, respectively) (Fig. 1). The mean PFS and OS rates of patients who had optimal cytoreduction were significantly better than those of patients with suboptimal cytoreduction (162.7 ± 14 vs 57.9 ± 19 months, p<0.001, and 163.2 ± 14 vs. 88.1 ± 24 months, p<0.001, respectively) (Fig. 2). Patients with LVSI had significantly lower mean PFS and OS rates than the patients who did not have LVSI (20.6 ± 5 vs 158 ± 13 months,

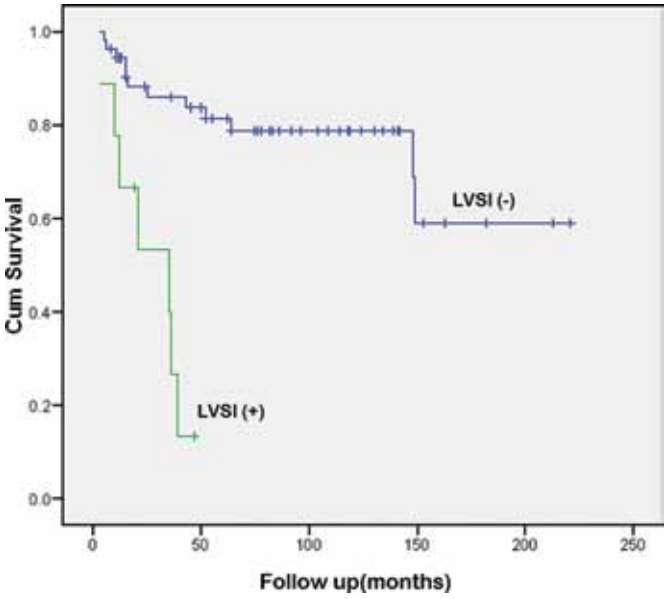

Fig. 3 - Overall survival of all patients (n = 63) when grouped according to lymphovascular space invasion (LVSI; p<0.001).

p<0.001, and 26.5 ± 5 vs 165.5 ± 13 months, p<0.001, respectively) (Fig. 3). Patients with histologic grade 1 OC or EC had a more favorable prognosis and better survival than patients with high-grade lesions (p<0.001 and p = 0.001, respectively). In contrast, age, parity, menopausal status, presence of ascites, coexistence of endometrioid histology at both sites versus coexistence of other types, and >50% myometrial invasion were not significantly associated with survival.

Multivariate analysis confirmed LVSI as an independent poor prognostic factor for OS (odds ratio [OR] 3.18, 95% confidence interval [CI] 1.02-9.89; p = 0.045). However, early-stage disease and optimal cytoreduction were found to be independent good prognostic factors for both PFS (OR 12.85, 95% CI 3.81-43.28; p<0.001, and OR 4.58, 95% CI 1.60-12.98; p = 0.004, respectively) and OS (OR 7.31, 95% CI 2.01-26.5; p = 0.002, and OR 2.95, 95% CI 1.12-7.81; p = 0.028, respectively) (Tab. II). The overall 3- and 5-year survival rates were 74% and 69%, respectively, and the progression-free 3- and 5-year survival rates were 72% and 69%, respectively.

The median follow-up period was 62 months (range 3-221 months). Recurrence developed in 17 patients (27%). Among them, 4 patients had vaginal recurrence, and the remaining 13 patients had distant recurrences (lymph node recurrence in 8 patients, lung recurrence in 4 patients, and liver recurrence in 1 patient).

Discussion

We conducted a retrospective multicenter study of 63 cases with SEOCs who were treated over an 18-year period. To our knowledge, this is one of the largest series of such patients to be reported in the literature. Synchronous primary endometrial and ovarian cancers account for approximately 10% of all OC cases and 5% of all EC cases (2, 7, 12-14). Such tumors are rarely seen and are often misdiagnosed as FIGO stage III EC or stage II OC (14). In our study, the incidence was 8.9% of patients with OC and 4.1% of patients with EC.

In our study population, most of these synchronous cancers were diagnosed at early stages and low grades. Soliman et al (7) detected stage I and II OC in 58% and 7% of women with SEOCs, respectively, and detected stage I and II EC in 82% and 10% of women with SEOCs, respectively. In a study by Gungor et al (4), the percentages were 30.8%, 30.7%, 38.5%, and 61.5%, respectively. In line with the previous findings, 68% of women in the present study had stage I EC, 9.5% had stage II EC, 60% had stage I OC, and 8% had stage II OC. In contrast to patients with SEOCs, the majority of patients with OC are diagnosed at an advanced stage because of its nonspecific symptoms, such as abdominal distension, discomfort, and pelvic pain (15). In contrast, approximately 75% of EC cases are detected at early stages due to irregular bleeding (12). These early symptoms of EC occur in 46% of women with SEOCs and lead to an earlier diagnosis (7, 16). Similarly, abnormal vaginal bleeding was the most frequent complaint in the present study. Because the majority of women with SEOCs are diagnosed at an early disease

TABLE II - Multivariate analysis of the factors that affect progression-free survival and overall survival using logistic regression models

Characteristic	PFS		OS	
	OR (95% CI)	*p*	OR (95% CI)	*p*
FIGO stage				
Early	Reference category		Reference category	
Advanced	12.85 (3.81-43.28)	<0.001	7.31 (2.01-26.50)	0.002
LVSI				
No			Reference category	0.045
Yes			3.18 (1.02-9.89)	
Cytoreductive surgery				
Suboptimal	Reference category		Reference category	
Optimal	4.58 (1.60-12.98)	0.004	2.95 (1.12-7.81)	0.028

CI = confidence interval; FIGO = International Federation of Gynecology and Obstetrics; LVSI = lymphovascular space invasion; OR = odds ratio; OS = overall survival; PFS = progression-free survival.
A *p* value of <0.05 was considered statistically significant.

stage and a younger age, they tend to have better survival compared with patients with OC and EC with metastases to the ovaries (17).

It has been shown that women with such tumors have better prognoses, particularly in cases of endometrioid histology (18-20). Moreover, Chiang et al (21) and Liu et al (22) indicated that the stage had a greater influence on survival than histology. In contrast, Lim et al (20) and Caldarella et al (13) reported no statistically significant differences in survival between endometrioid/endometrioid and nonendometrioid groups. Similarly, we did not find a significant difference in survival between different histologic categories, but the influence of early stage on prognosis demonstrated statistical significance in the multivariate analysis. It has been reported that women with SEOCs have a 5-year survival of 73%-86% (3, 4, 6, 12). In the present study, women with SEOCs had a 5-year survival rate of 69%.

Synchronous primary endometrial and ovarian cancers occur in women approximately 10 years younger than those with either EC or OC. The reported median ages were 49-50 years (6-8). Similarly, we observed a median age of 50 years in the present study. Chiang et al (21) and Tong et al (23) reported younger median ages of 47.2 and 45.2, respectively. Yamanoi et al (24) and Eser et al (25) reported that patients with SEOCs were significantly younger than those with EC and OC. Lim et al (20) emphasized the impact of age on survival and reported that patients under 50 years of age had a better overall prognosis. Caldarella et al (13) emphasized the relationship between age and OS and reported 5-year survival rates of 94.1% and 53.7% in patients ≤50 and >50 years of age, respectively ($p = 0.004$). In our study, age did not have a significant effect on overall prognosis.

Nulliparity is one of the most common risk factors for EC and OC. However, this issue is controversial for SEOCs. Soliman et al (7) verified the potential role of nulliparity and Ree et al (26) found that 50% of women with SEOCs in their study were nulliparous. However, no significant difference has been reported in the prevalence of nulliparity between women of different histologic types (7, 8). Similarly, in the present study, no significant difference was noted in nulliparity and menopausal status between the endometrioid/endometrioid group and groups with other histologic types.

In addition to pathologic features, such as stage, grade, and histologic type, which have been thoroughly discussed and are considered well-known prognostic factors in EC, some studies have investigated the prognostic role of >50% myometrial invasion, optimal cytoreduction, and LVSI in patients with SEOCs. Soliman et al (7) reported that patients in the endometrioid/endometrioid group had better median OS rates than patients in other groups (119 and 48 months, respectively; $p = 0.002$), whereas EC stage, grade, depth of myometrial invasion, presence of LVSI, and lymph node metastasis had no effect on survival. Zaino et al (6) found that >50% myometrial invasion was associated with recurrence or disease-related death in 77% of patients. Although there have been few studies investigating the prognostic role of LVSI in patients with SEOCs, many studies have investigated this role in patients with EC. For example, Guntupalli et al (27) and Solmaz et al (28) revealed that LVSI is highly associated with nodal metastasis. In the present study, we found LVSI to be one of the independent prognostic predictors associated with a significantly lower OS in patients with SEOCs. In contrast, >50% myometrial invasion and a primary tumor diameter >2 cm were not associated with survival.

Surgical intervention is the preferred treatment for EC and OC. The treatment of OC is generally based on adjuvant chemotherapy comprising a paclitaxel plus cisplatin regimen. Eifel et al (12) recommended adjuvant RT for patients with EC possessing the following risk factors: papillary serous adenocarcinoma or adenosquamous carcinoma histology, grade 2 or 3 tumor, and deep myometrial invasion. However, adjuvant RT and/or chemotherapy for SEOCs is controversial. We have found optimal cytoreduction to be an independent prognostic predictor of survival in women with SEOCs. Therefore, it is essential to achieve optimal cytoreduction, particularly when LVSI is present.

The main limitation of this study is its retrospective nature. Additionally, some patients were treated by nongynecologic oncologic surgeons; therefore, patients were treated with different types of surgical approaches over the 18-year time period. Retrospective cohort studies are subjected to selection bias, recall bias, and unknown confounding variables, which may negatively impact the accuracy of the results. Moreover, during the 18-year study period, significant improvements in surgical techniques and adjuvant treatment may have also affected the results. The postoperative management was not consistent; the preferred choice of treatment method differed due to the long study period and the different radiation and medical oncologists involved. Finally, the data did not allow definitive and comparative analyses assessing the heterogeneity of the different adjuvant therapy regimens. Despite these limitations, a large number of patients with similar demographic characteristics were included in this study, and good follow-up data were available. Additionally, the pathologic slides were reviewed by an experienced gynecologic pathologist. All of these factors most likely increased the validity of the results and mitigated the limitations.

In conclusion, SEOCs differ from primary OC, can usually be detected in the early stage, and have a good prognosis. Although rare, their identification and optimal management play a major role in the reduction of OC mortality. Therefore, optimal cytoreductive surgery should be the standard approach for the initial treatment of SEOCs. Lymphovascular space invasion can be used as a marker to predict the need for comprehensive staging surgery in cases of SEOC diagnosed postoperatively, particularly in unstaged patients. Further prospective randomized studies are required to confirm our findings and fully describe the effect of different adjuvant treatment modalities.

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Disclosures

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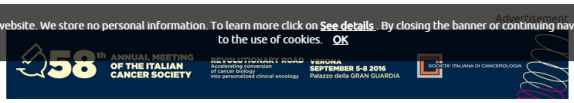

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Medical conditions, family history of cancer, and the risk of biliary tract cancers

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