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GYNECOLOGIC ONCOLOGY

Is the presence of endometriosis associated with a survival benefit in pure ovarian clear cell carcinoma?

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Abstract

Background The purpose of this study was to compare the prognoses of women with pure ovarian clear cell carcinoma (OCCC) arising from endometriosis to those of women with pure OCCC not arising from endometriosis treated in the same manner.

Methods A dual-institutional, retrospective database review was performed to identify patients with pure OCCC who were treated with maximal or optimal cytoreductive surgery (CRS) followed by paclitaxel/carboplatin chemotherapy between January 2006 and December 2016. Patients were divided into two groups according to the detection of cancer arising in endometriosis or not, on the basis of pathological findings. Demographic, clinicopathological, and survival data were collected, and prognosis was compared between the two groups.

Results Ninety-three women who met the inclusion criteria were included. Of these patients, 48 (51.6%) were diagnosed with OCCC arising in endometriosis, while 45 (48.4%) had no concomitant endometriosis. OCCC arising in endometriosis was found more frequently in younger women and had a higher incidence of early stage disease when compared to OCCC patients without endometriosis. The 5-year overall survival (OS) rate of the patients with OCCC arising in endometriosis was found to be significantly longer than that of women who had OCCC without endometriosis (74.1 vs. 46.4%; $p = 0.003$). Although univariate analysis revealed the absence of endometriosis ($p = 0.003$) as a prognostic factor for decreased OS, the extent of CRS was identified as an independent prognostic factor for both recurrence-free survival (hazard ratio (HR) 8.7, 95% confidence interval (CI) 3.15–24.38; $p < 0.001$) and OS (HR 11.7, 95% CI 3.68–33.71; $p < 0.001$) on multivariate analysis.

Conclusion Our results suggest that endometriosis per se does not seem to affect the prognosis of pure OCCC.

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Introduction

Ovarian clear cell carcinoma (OCCC), accounting for 10% of epithelial ovarian cancers (EOCs) [1], has been known to be associated with endometriosis for a long time [2–4]. The clinical features and oncologic outcomes of patients with endometriosis-associated OCCC are topics of active investigation [5]. However, the previous studies have reached discrepant conclusions regarding the impact of endometriosis on the prognoses of women with OCCC [6–13]. These conflicting results might have arisen due to the number of patients included, study design, and adjustment for potential confounding factors [14]. The differences in the study design of the previous studies leave the possibility open that endometriosis may be a prognostic modifier in OCCC [10].

The probable limitations associated with the previous studies investigating the prognostic impact of endometriosis on OCCC can be summarized as follows: First, most of the previous studies reporting on endometriosis-associated ovarian cancer included patients with both OCCC, and ovarian endometrioid carcinoma, and analyzed these two different histotypes simultaneously [12, 15–18]. However, it has been recently reported that endometrioid and clear cell cancers associated with endometriosis should be no more considered as a single entity with similar prognostic factors [13].

Second, it has been reported that OCCC arising in endometriosis should be differentiated from endometriosis-associated OCCC from a histologic point of view [13]. However, some of the prior studies included patients both with OCCC arising from endometriosis and endometriosis-associated OCCC and analyzed them all together [6, 8]. Third, some of the previous studies [10, 18] were hampered by the inclusion of patients with mixed histology. It has been suggested that ovarian cancers of mixed histology arising in endometriosis not only presented a morphologically heterogeneous group but also tended to be of lower stage and had an improved prognosis [10]. Finally, other potential confounding factors such as the variations in the optimality of cytoreductive surgery (CRS) and variations in adjuvant chemotherapy regimens [8, 19] might have biased previous conclusions to some extent. Kim et al. [14] have already reported that optimality of CRS and adjuvant chemotherapy should be adjusted for the evaluation of the effect that endometriosis has on the prognosis of OCCC.

In the light of aforementioned considerations, we designed this retrospective, dual-institutional study to shed some more light on this issue with the aid of a well-defined, homogenous study population. In the current study, we aimed to compare the clinical features and prognoses of women with "pure" OCCC arising from endometriosis that underwent maximal or optimal CRS followed by paclitaxel plus carboplatin chemotherapy to those of women with "pure" OCCC not arising from endometriosis who were treated in the same manner.

Materials and methods

Study design and eligibility

This retrospective study was approved by the Institutional Review Board of Zekai Tahir Burak Women's Health Training and Research Hospital (approval date: August 1, 2017; approval number: 06). A written informed consent was obtained for the surgical procedure to be performed and for research use of their medical information from all patients at admission. The study was conducted in accordance with the principles of Helsinki Declaration.

The study was conducted in two tertiary gynecologic oncology centers in Ankara, Turkey between January 2006 and December 2016. The EOC databases were retrospectively reviewed and women with OCCC who were treated with upfront surgery were identified. The study population included women who had histopathologically proven pure OCCC arising in endometriosis. Women were included, if they previously underwent primary surgical treatment including total hysterectomy plus bilateral salpingo-oophorectomy with bilateral pelvic and para-aortic lymphadenectomy and other surgical procedures resulting in maximal or optimal CRS and subsequently received paclitaxel plus carboplatin as the primary chemotherapy regimen. All patients had to have residual disease (RD) of 1 cm or less to be eligible. Patients who were cytoreduced to greater than 1 cm of RD were excluded. Exclusion criteria also consisted of women with incomplete staging, those with mixed histologies, and women who had OCCC associated with but not arising in endometriosis. We also excluded patients who received neoadjuvant chemotherapy, women with synchronous malignancies, women who were lost to follow up within 1 month after surgery, and those with incomplete medical records.

Clinical information

With the eligible cases, the following information was abstracted from the medical records: demographic characteristics, preoperative serum CA 125 level, date and type of surgical procedure, presence or absence of ascites, the status of peritoneal cytology examination (negative or positive), size of the primary tumor, lymphovascular

space invasion (LVSI) (negative or positive), size of residual tumor after surgery, number of lymph nodes (LNs) removed, presence of retroperitoneal LN metastasis, presence of omental involvement, stage of disease, the date of diagnosis, length of follow-up, and survival. Tumor characteristics were obtained using the original pathology reports.

All operations were performed by gynecologic oncologists with the intent of achieving maximal or optimal cytoreduction. Lymphadenectomy was performed after completion of other cytoreductive procedures. All tumors were staged according to the 2014 International Federation of Gynecology and Obstetrics (FIGO) staging system [20]. In patients treated before 2014, the stage of disease was classified retrospectively on the basis of surgical and pathological assessment.

All pathological slides were reviewed by two independent gynecologic pathologists. Both pathologists were blinded to the patient outcomes. The histological cell types were determined according to the criteria of World Health Organization (WHO) classification [21]. Pure OCCC was defined as the presence of typical clear or hobnail cells in a papillary, solid or tubulocystic pattern, with each individual component comprising no < 90% of the tumor. Lymphovascular space invasion was defined as the presence of a cluster of tumor cells within a lymphatic or vascular lumen. For the pathological examination, one section at least per cm was obtained from the patients in whom the tumor diameter was ≤ 10 cm, whereas two sections per cm were obtained from those in whom the tumor diameter was > 10 cm. If the tumor was localized within the cyst, additional tissue samples showing continuity of the cyst wall were collected.

The treatment policies were decided by the attending physician or by the multidisciplinary tumor board at each participating institution. Adjuvant chemotherapy was administered to all patients. The standard primary chemotherapy regimen included paclitaxel 175 mg/m^2 plus carboplatin dosed at an area under curve of five or six every 21 days for six cycles. Targeted agents were not used to treat any of the patients during primary treatment.

Patients were scheduled for follow-up every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Clinical examinations performed at each visit included pelvic examination, ultrasonographic scan, and CA-125 determination, in addition to computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography–CT (PET–CT) scans when indicated. Survival data were last calculated on 31 December 2016. The survival status of the patients was determined as alive or dead at the time of the last follow-up. For all non-survivors, the status was confirmed using the Social Security Death Index.

Definitions

The patients were divided into two groups according to the detection of cancer arising in endometriosis or not, on the basis of pathological findings. The definition of ovarian cancer arising in endometriosis was given according to the Sampson's [22] and Scott's [23] criteria which included: (1) the coexistence of carcinoma and endometriosis in the same ovary; (2) the presence of tissue similar to endometrial stroma surrounding characteristic epithelial glands; (3) the exclusion of a metastatic tumor of the ovary; and (4) the presence of benign endometriosis histologically contiguous to the malignant tissue.

Optimal cytoreduction was defined as less than or equal to 1 cm maximal diameter of the largest residual tumor nodule at the completion of the primary operation, whereas suboptimal debulking was defined as > 1 cm of residual disease after primary CRS. Maximal cytoreduction was defined as no gross RD after primary CRS.

Recurrence was documented by the histologic evidence of disease in tumor biopsy or fine-needle biopsy and/or the appearance of new lesions on imaging examination. Recurrence-free survival (RFS) was defined as the time, in months, from surgery to the first detection of recurrence by radiologic imaging and serum CA 125 measurement or all-cause mortality, whichever occurred first, or the date of the last contact for survivors without recurrent disease. Overall survival (OS) was defined as the time period between primary CRS to the date of death or the last follow-up. Survivors at the time of their last visit were censored. The primary outcome of the current study was 5-year OS.

Statistical analysis

Statistical analyses were performed using the SPSS version 23.0 statistical software (IBM Corp., Armonk, NY, USA). The data were expressed in median and range for continuous variables. The continuous variables such as age, baseline serum CA 125 level, and tumor size were divided into categories according to the median values. Binary variables were expressed in numbers and percentages. Categorical variables were evaluated using the Chi-square test or Fisher's exact test as appropriate for the group size.

The survival curves were generated using the Kaplan–Meier method, and the differences between the survival curves were calculated using the log-rank test. To evaluate the prognostic factors for RFS and OS, a univariate Cox-regression model was used. A p value of less than 0.05 in the univariate analysis was included into multivariable analysis. A p value < 0.05 was considered statistically significant.

Results

A total of 93 women met the inclusion criteria. Of these patients, 48 (51.6%) were diagnosed with OCCC arising in endometriosis, while 45 (48.4%) had no concomitant endometriosis.

The women with OCCC arising in endometriosis tended to be significantly younger (median age 48 vs. 57; $p = 0.007$) and premenopausal (27/48 vs. 8/45; $p < 0.001$), and were more likely to present with early stage disease (38/48 vs. 17/45; $p < 0.001$) compared to those who had OCCC without endometriosis. However, the median preoperative serum CA 125 level was significantly higher in women who had OCCC without endometriosis compared to the women with OCCC arising in endometriosis (133 vs. 38.5 IU/ml; $p = 0.014$). The women who had OCCC without endometriosis were more likely to have ascites (19/45 vs. 9/48; $p = 0.014$), positive peritoneal cytology (21/45 vs. 8/48; $p = 0.002$), and positive LVSI (23/45 vs. 11/48; $p = 0.005$). Retroperitoneal LN metastases and omental involvement were significantly more common in the women who had OCCC without endometriosis compared to the women with OCCC arising in endometriosis (18/45 vs. 7/48; $p = 0.006$, and 21/45 vs. 4/48; $p < 0.001$, respectively). The women with OCCC arising in endometriosis were more likely to undergo maximal CRS compared to the women who had OCCC without endometriosis (43/48 vs. 28/45; $p = 0.002$). The clinicopathological characteristics of patients with regard to endometriosis are presented in Table 1. None of the patients had a synchronous endometrial carcinoma.

The median follow-up was 43 months (range 6–122 months). The 5-year RFS rate of the patients with OCCC arising in endometriosis was significantly longer than that of women who had OCCC without endometriosis (71.9 vs. 44.6%; $p = 0.002$) (Fig. 1). Similarly, the 5-year OS rate of the women with OCCC arising in endometriosis was 74.1%, whereas this figure was found to be 46.4% for the women who had OCCC without endometriosis ($p = 0.003$) (Fig. 2).

Univariate analysis revealed that age > 53 years ($p = 0.009$), postmenopausal status ($p = 0.049$), absence of endometriosis ($p = 0.002$), presence of ascites ($p < 0.001$), positive peritoneal cytology ($p < 0.001$), positive LVSI ($p < 0.001$), stage III/IV disease ($p < 0.001$), retroperitoneal LN metastasis ($p = 0.001$), omental involvement ($p < 0.001$), and the extent of CRS ($p > 0.001$) were significant factors for decreased RFS (Table 2). At the end of multivariate analysis, presence of ascites (hazard ratio (HR) 2.2, 95% confidence interval (CI) 1.03–5.06; $p = 0.04$) and the extent of CRS (HR 8.7, 95% CI 3.15–24.38; $p < 0.001$) remained as independent risk factors for decreased RFS (Table 2).

Univariate analysis revealed age > 53 years ($p = 0.006$), absence of endometriosis ($p = 0.003$), presence of ascites ($p < 0.001$), positive peritoneal cytology ($p < 0.001$), positive LVSI ($p < 0.001$), retroperitoneal LN metastasis ($p < 0.001$), omental involvement ($p < 0.001$), stage III/IV disease ($p < 0.001$), and the extent of CRS ($p < 0.001$) as significant factors for decreased OS (Table 3). However, the presence of ascites (HR 2.6, 95% CI 1.13–6.20; $p = 0.024$), retroperitoneal LN involvement (HR 2.5, 95% CI 1.04–6.42; $p = 0.039$), omental involvement (HR 3.5, 95% CI 1.06–11.77; $p = 0.04$), and the extent of CRS (HR 11.7, 95% CI 3.68–33.71; $p < 0.001$) was found to be independent risk factors for decreased OS at the end of multivariate analysis (Table 3). At the time of reporting, of the 93 patients with OCCC, 60 (64.5%) were still alive, whereas 33 patients (35.5%) died.

Discussion

The key findings of the current study indicated that OCCC arising in endometriosis occurred more frequently in younger women and had favorable clinicopathologic characteristics including earlier FIGO stage, lower incidence of LN involvement, and higher rate of undergoing maximal CRS when compared to women with OCCC without endometriosis. Although we have shown an improved RFS and OS in the women with OCCC arising in endometriosis, we were unable to define the presence of endometriosis as an independent prognostic factor for prolonged survival in women with OCCC.

Nonetheless, limitations of the current study include the relatively small number of patients with OCCC arising in endometriosis, the relatively short median follow-up, its retrospective study design, and the lack of central pathology review. Although two experienced gynecologic pathologists reviewed all the tumor pathology, there is likely to be some variation in not having a single pathology review. Despite these limitations, our study provides additional information to the body of knowledge on this topic.

In consistence with the results of our study, OCCC arising in endometriosis have been reported to occur more frequently in premenopausal women and present with early stage disease [10, 13, 19, 24–26]. These favorable characteristics were suggested to increase the probability of optimal CRS [14], which is known as one of the most important prognostic factors in EOC. Our patients with OCCC arising in endometriosis were younger, had earlier FIGO stage, and had a higher rate of maximal CRS when compared with those who had no endometriosis. Patients who have OCCC not arising from endometriosis are likely to have advanced-stage disease due to a lack of specific symptoms, whereas OCCC patients with endometriosis may experience specific

Table 1 Clinicopathological characteristics of patients with regard to the presence or absence of endometriosis in a cohort of 93 women with pure ovarian clear cell carcinoma

Characteristics	Endometriosis (−) ($n = 45$)	Endometriosis (+) ($n = 48$)	p
Age, years (median)	57 (31–72)	48 (30–70)	**0.007**
Menopausal status, *n*			**< 0.001**
Postmenopausal	37 (82.2%)	21 (43.7%)	
Premenopausal	8 (17.8%)	27 (56.3%)	
LVSI, *n*			**0.005**
Positive	23 (51.1%)	11 (22.9%)	
Negative	22 (49.9%)	37 (77.1%)	
Tumor size, cm (median)	10 (2–26)	10 (2.5–21)	0.566
Serum CA 125 (median, IU/ml)	133 (5–2335)	38.5 (6–1429)	**0.014**
Ascites, *n*			**0.014**
Yes	19 (42.2%)	9 (18.7%)	
No	26 (57.8%)	39 (81.3%)	
Peritoneal cytology, *n*			**0.002**
Positive	21 (46.6%)	8 (16.6%)	
Negative	24 (53.4%)	40 (83.4%)	
Number of LNs removed (median)	50 (27–102)	49 (25–106)	0.773
Number of pelvic LNs removed	33 (19–71)	34 (18–93)	0.770
Number of para-aortic LNs removed	11 (5–70)	14 (5–45)	0.425
Retroperitoneal LN involvement, *n*			**0.006**
Yes	18 (40%)	7 (14.5%)	
No	27 (60%)	41 (85.5%)	
Recurrence, *n*			**0.044**
Yes	18 (40%)	10 (20.8%)	
No	27 (60%)	38 (79.2%)	
Stage, *n*			**< 0.001**
I–II	17 (37.8%)	38 (79.1%)	
III	28 (62.2%)	10 (20.9%)	
Omental involvement, *n*			**< 0.001**
Yes	21 (46.6%)	4 (8.3%)	
No	24 (53.4%)	44 (91.7%)	
CRS			
Optimal	17/45 (37.7%)	5/48 (10.4%)	**0.002**
Maximal	28/45 (62.2%)	43/48 (89.5%)	
Status			**0.002**
Alive	22 (48.9%)	38 (79.1%)	
Dead	23 (51.1%)	10 (20.9%)	

Characters in bold indicate statistical significance

n number, *LVSI* lymphovascular space invasion, *LN* lymph node, *CRS* cytoreductive surgery

symptoms such as dysmenorrhea and chronic pelvic pain and may tend to be followed up more closely [13], which contributes to the early detection of OCCC and increased possibility of receiving maximal debulking surgery [13, 26].

In addition, ascites was reported to be a less common finding in women with OCCC arising in endometriosis [27]. The patients with OCCC arising in endometriosis were less likely to have ascites in our study, consistent with the previous studies. Endometriosis presents more commonly as a unilateral ovarian cyst. More favorable outcomes have been reported for cystic clear cell carcinomas [13]. Tumors growing intracystically are more likely to be confined to the ovary for longer periods of time before spreading, thereby allowing them to be diagnosed at lower stage [13]. This might also explain the increased frequency of ascites in tumors not arising in endometriosis. Thus, unilaterality and reduced presence of ascites seem to be the consequence of an endometriotic and ,therefore, cystic origin.

Endometriosis has been reported to be associated with improved RFS and OS in some of the previous studies [6,

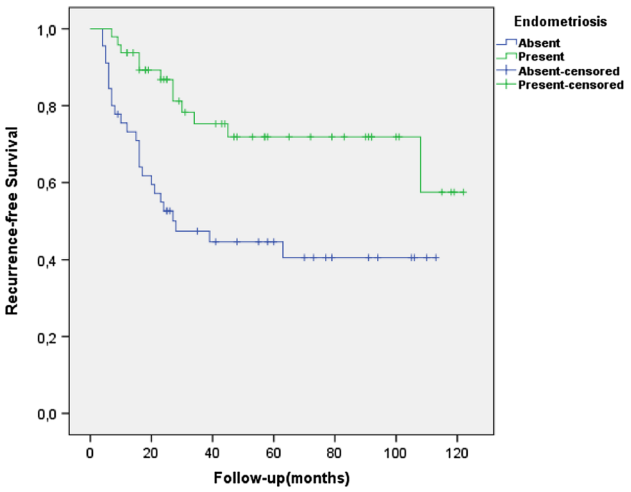

Fig. 1 Five-year recurrence-free survival curves of women with pure ovarian clear cell carcinoma according to the presence or absence of endometriosis

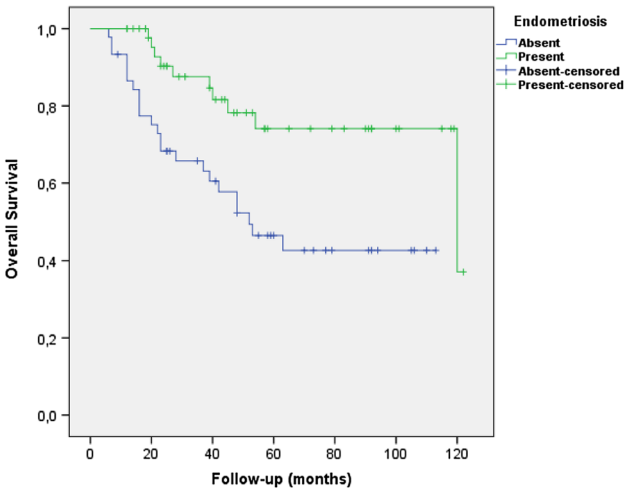

Fig. 2 Five-year overall survival curves of women with pure ovarian clear cell carcinoma according to the presence or absence of endometriosis

8, 28]. In a meta-analysis of 444,255 patients [14], in crude analysis, endometriosis-associated ovarian cancer was found to be associated with an improved OS (HR 0.778, 95% CI 0.655–0.925) but not progression-free survival (PFS) (HR 1.023, 95% CI 0.712–1.470), compared to non-endometriosis-associated ovarian cancer. However, in the subgroup analyses, RFS and OS were not found to be different between the groups [14].

Among 144 ovarian cancer patients, Cuff and Longacre [10] showed no difference in PFS, consistent with the findings of Scarfone et al. [13] who reported no significant difference in the OS between these groups in a cohort of 73 patients. In another study of 109 women with OCCC, Kim et al. [26] reported that endometriosis, per se, may not affect the prognosis of OCCC arising in endometriosis after the initiation of carcinogenesis despite favorable factors such as young age, early stage disease, and higher optimal cytoreduction rates. The aforementioned authors reported no significant differences in the PFS and OS between the patients with OCCC who had endometriosis and those without endometriosis in a meta-analysis of 11 cohort studies including 743 patients [26].

Noli et al. [12] and Garrett et al. [29] both demonstrated improved survival in women with endometriosis-associated ovarian cancer in the univariate analysis which was not statistically significant in the multivariate analysis. These findings seem to be consistent with our findings. In a study of 201 patients, Davis et al. [30] demonstrated an improved 5-year PFS of 75% in ovarian cancer patients with endometriosis compared to a 55% of 5-year PFS in women with ovarian cancer without endometriosis ($p = 0.03$). Although our study included women only with OCCC, the corresponding figures were found to be 71.9 and 44.6%, respectively.

Cytoreductive surgery is recommended for patients with Stage II–IV ovarian clear cell carcinoma. Takano et al. [31] reported no significant prognostic difference between the patients who underwent optimal cytoreduction and those who had residual disease of greater than 1 cm. Complete surgery without residual macroscopic disease was found to be the only independent prognostic factor in that study. In a study by the Gynecologic Oncology Group, the markedly poor prognosis of OCCC was observed, even when the patients had small-volume disease [32]. Consistent with these findings, we found that maximal CRS was an independent prognostic factor for RFS and OS in a cohort of 93 women with OCCC. The impact of endometriosis on the probability of maximal CRS, the most important prognostic factor in EOC, was determined in the current study, suggesting a survival benefit for patients receiving maximal CRS.

There may be a difference in underlying molecular biology between OCCC arising in endometriosis and OCCC without endometriosis [33]. The pathogenesis of OCCC in patients with endometriosis may differ from other OCCC and, therefore, may have innate factors that might improve prognosis [33]. However, the intrinsic relationship between endometriosis and OCCC warrants further investigation [19].

Heterogeneity in adjuvant chemotherapy regimens can also be a limitation for the comparison of the prognoses of women with OCCC arising from endometriosis with those with OCCC not arising from endometriosis. The previous studies by Orezzoli et al. [8] and Bai et al. [19] identified long periods of time during which adjuvant treatment modalities changed and paclitaxel was introduced into the first-line chemotherapy regimen for EOC. As previously mentioned, thus, the optimality of CRS and adjuvant chemotherapy

Table 2 Univariate and multivariate analyses for recurrence-free survival in women with pure ovarian clear cell carcinoma

	RFS[a] (%)	Events[b]	Univariate *p*	Multivariate		
				HR	95% CI	*p*
Age (years)						
≤ 53	71.5	12/44 (27.2%)	**0.009**			
> 53	46.6	25/49 (51%)				
Menopausal status						
Premenopausal	69.6	10/35 (28.5%)	**0.049**			
Postmenopausal	51.9	27/58 (46.5%)				
Stage						
I–II	84.9	8/55 (14.5%)	**< 0.001**			
III–IV	20.9	29/38 (76.3%)				
Endometriosis						
Yes	71.9	12/48 (25%)	**0.002**			
No	44.6	25/45 (55.5%)				
Peritoneal cytology						
Positive	33.5	19/29 (65.5%)	**< 0.001**			
Negative	69.1	18/64 (28.1%)				
Tm size (cm)						
< 10	53.4	21/45 (46.6%)	0.321			
≥ 10	63.3	16/48 (33.3%)				
CA-125 (IU/ml)						
< 35	65.9	11/35 (31.4%)	0.174			
≥ 35	54.1	26/58 (44.8%)				
LVSI						
Yes	36.4	21/34 (61.8%)	**< 0.001**			
No	71.4	16/59 (27.1%)				
Ascites						
Yes	23.2	20/28 (71.4%)	**< 0.001**	**2.2**	**1.037–5.064**	**0.040**
No	72.3	17/65 (26.1%)				
LN involvement						
Yes	16.3	19/25 (76%)	**0.001**			
No	73.8	18/68 (26.4%)				
Omental involvement						
Yes	18.6	20/25 (80%)	**< 0.001**			
No	73.1	17/68 (25%)				
CRS						
Maximal	76.6	16/71 (22.5%)	**< 0.001**	**8.9**	**3.209–25.105**	**< 0.001**
Optimal	–	21/22 (95.4%)				

Characters in bold indicate statistical significance

RFS recurrence-free survival, *LN* lymph node, *LVSI* lymphovascular space invasion, *HR* hazard ratio, *CI* confidence interval, *CRS* cytoreductive surgery

[a]5-year recurrence-free survival rate

[b]The number of cases with recurrence or death whichever occurred first

should be adjusted for the evaluation of the effect of endometriosis on the prognosis of OCCC [14].

The discrepancies in the literature may be explained by the rarity of the disease as well as the heterogeneity of previously published studies. Compared to the previous studies, our cohort seems to be more homogenous with all patients having a diagnosis of pure clear cell histology; all patients have undergone maximal or optimal CRS despite of having different FIGO stages. In addition, all patients were treated with the standard paclitaxel plus carboplatin regimen postoperatively. These factors seem to minimize bias and seem to make our results more persuasive.

In conclusion, although patients with OCCC arising in endometriosis had a significantly better RFS and OS,

Table 3 Univariate and multivariate analyses for overall survival in women with pure ovarian clear cell carcinoma

	OS[a] (%)	Events[b]	Univariate			Multivariate	
			p	HR	CI 95%		*p*
Age (years)							
≤ 53	74.4	10/44 (22.7%)	**0.006**				
> 53	47	23/49 (46.9%)					
Menopausal status							
Premenopausal	70.5	9/35 (25.7%)	0.067				
Postmenopausal	53.3	24/58 (41.3%)					
Stage							
I–II	85	7/55 (12.7%)	**0.001**				
III–IV	26.5	26/38 (68.4%)					
Endometriosis							
Yes	74.1	10/48 (20.8%)	**0.003**				
No	46.4	23/45 (51.1%)					
Peritoneal cytology							
Positive	35.8	18/29 (62%)	**< 0.001**				
Negative	71.1	15/64 (23.4%)					
Tm size (cm)							
< 10	57	18/45 (40%)	0.574				
≥ 10	62.8	15/48 (31.2%)					
CA-125 (IU/ml)							
< 35	72.4	8/35 (22.8%)	0.054				
≥ 35	52.3	25/58 (43.1%)					
LVSI							
Positive	33.5	20/34 (58.8%)	**< 0.001**				
Negative	74.8	13/59 (22%)					
LN involvement							
Yes	27.3	16/25 (64%)	**< 0.001**	**2.5**	**1.049–6.425**		**0.039**
No	72.1	17/68 (25%)					
Ascites							
Yes	17.2	20/28 (71.4%)	**< 0.001**	**2.6**	**1.139–6.199**		**0.024**
No	77.4	13/65 (20%)					
Omental involvement							
Yes	20	19/25 (76%)	**< 0.001**	**3.5**	**1.059–11.770**		**0.040**
No	75.2	14/68 (20.5%)					
CRS							
Maximal	79	13/71 (18.3%)	**< 0.001**	**11.7**	**3.684–37.715**		**< 0.001**
Optimal	–	20/22 (90.9%)					

Characters in bold indicate statistical significance

OS overall survival, *LN* lymph node, *LVSI* lymphovascular space invasion, *HR* hazard ratio, *CI* confidence interval, *CRS* cytoreductive surgery

[a]5-year overall survival

[b]The number of cases with death

compared to the patients who had OCCC without endometriosis, we were unable to identify "endometriosis" as an independent prognostic factor in OCCC. Based on our findings, we conclude that endometriosis per se does not seem to affect the prognosis of OCCC, although it is associated with favorable factors such as young age, early stage disease, and lower rates of LVSI, ascites, positive peritoneal cytology, retroperitoneal LN metastasis, and omental involvement. The reason for not translating endometriosis as an independent prognostic factor should be studied in further large-scale, long-term studies.

Author contributions HS: project development, data collection, data analysis, and manuscript writing. MES: project development, data

collection, and data analysis. ZFC: data collection. ANH: data collection, and manuscript editing. LS: data collection and manuscript editing. GC: data collection. IY: data collection. TG: manuscript editing. HC: manuscript editing. MMM: project development, data collection and manuscript writing/editing. AA: manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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