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The effect of concurrent endometriosis on the prognosis of women with ovarian clear cell or endometrioid carcinoma

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Abstract

Objectives: To evaluate features of ovarian clear cell carcinoma (CCC) and endometrioid carcinoma (EC) by presence of endometriosis among women with endometriosis-associated ovarian cancer (EAOC).

Methods: A retrospective review of the medical records of 578 women diagnosed and treated for ovarian cancer at a university hospital in Korea between July 2004 and December 2016. Clinical and prognostic features of ovarian CCC and EC were compared between women with endometriosis and those without.

Results: Ovarian CCC and EC were diagnosed at an earlier FIGO stage for women with endometriosis than for those without (P=0.033). The 5-year disease-free survival (DFS) and overall survival (OS) were 77.6% vs 65.0% (P=0.038) and 80.3% vs 70.9% (P=0.048), respectively. In univariate analysis, advanced stage, higher grade, bilateral tumors, lymph node metastasis, residual tumor greater than 1 cm, and non-concurrent endometriosis were related to shorter DFS and OS; however, residual tumor greater than 1 cm was the only independent predictor in multivariate analysis (DFS: hazard ratio (HR), 9.83; 95% confidence interval (CI), 4.84–19.93; OS: HR, 5.07; 95% CI, 2.33–11.03). No factors affected survival after stratification by stage.

Conclusion: No association was found between the presence of endometriosis and the prognosis of ovarian CCC or EC.

KEYWORDS

Clear cell carcinoma; Endometrioid carcinoma; Endometriosis; Epithelial ovarian cancer; Prognostic factors; Survival

1 | INTRODUCTION

Endometriosis is a benign gynecologic disorder that is characterized by endometrial glands and stroma occurring outside the uterus. Since the first report of a malignant transformation in endometriosis in 1925,[1] an association between endometriosis and ovarian cancer has continued be documented.[2–4] The overall rate of malignant transformation in endometriosis has been estimated as 0.3%–0.8%, with relative risk ranging from 1.3 to 1.9.[2]

The relationship between endometriosis and ovarian cancer has been classified as either a transition from endometriotic lesions to invasive ovarian carcinoma, or the coexistence of ovarian cancer with

endometriosis without a transition.[5,6] Because the criteria for these types are poorly defined, they may be collectively called endometriosis-associated ovarian cancer (EAOC).

As compared with ovarian cancer without endometriosis, EAOC has been diagnosed in younger women and at an earlier stage.[7–9] Some studies have also reported a stronger association of endometriosis with ovarian clear cell carcinoma (CCC) and endometrioid carcinoma (EC) types of cancer.[2,5,8,10] However, whether endometriosis is a prognostic factor for women with ovarian CCC or EC remains unclear.[6,7,9–12] The aim of the present study was therefore to evaluate the clinical and prognostic features of ovarian CCC and EC, according to the presence of pathologically confirmed concurrent endometriosis, among women with EAOC.

2 | MATERIALS AND METHODS

In a retrospective study, medical records were reviewed for women diagnosed with ovarian cancer and treated at the Division of Gynecologic Oncology in the Department of Obstetrics and Gynecology, Chonnam National University Hospital, Gwangju, Korea, from July 1, 2004, to December 31, 2016. The study was approved by the Institutional Review Board of Chonnam National University Hospital. Due to the retrospective nature of the study, patient consent was not required.

All study women had their initial treatment at the study hospital or were referred for complementary treatment after their initial surgery. The women underwent surgery and most received postoperative therapy. Surgical staging included total abdominal hysterectomy with bilateral salpingo-oophorectomy or unilateral salpingo-oophorectomy without hysterectomy, lymph node (LN) dissection, omentectomy, and removal of all macroscopic lesions.[13] All pathologic analyses were confirmed by a single gynecologic pathologist at the study institution. Stages were adjusted in accordance with the revised 2014 FIGO classification.[14]

For the current study, EAOC was defined as any of the following: ovarian cancer with endometriosis identified histologically in the same ovary, endometriosis in one ovary and ovarian cancer in the contralateral ovary, or ovarian cancer with extra-ovarian pelvic endometriosis.

Data were collected on the clinical and pathologic characteristics of the study women, including age, menopausal status, parity, pre-operative serum cancer antigen 125 (CA-125), tumor size, distribution of histologic subtypes, stage, grade, laterality of tumor, LN metastasis, presence of residual tumor, synchronous endometrial pathology, primary treatments, and outcomes. The response to primary treatments and confirmation of disease recurrence were determined by computed tomography and/or positron emission tomography computed tomography. FIGO stage I was classified as early stage disease; higher stages were considered as advanced disease. Follow-up data were collected in August 2017, with a median follow-up of 35 months (range, 6–157 months).

Data were analyzed by using SPSS version 23.0 (IBM, Armonk, NY, USA). Clinical and prognostic features of ovarian CCC or EC, the most common histologic subtypes of the EAOC group, were compared between the presence and absence of endometriosis. Variables were compared between the two groups by using χ^2 or Fisher exact test.

Disease-free survival (DFS) was calculated as the number of months from the date of initial treatment to the date of disease progression and/or recurrence. Overall survival (OS) was defined in months from the date of initial treatment to the date of death or date at last contact. Survival comparisons were obtained by using the Kaplan–Meier log-rank test. To account for the potential confounding factors, the Cox proportional-hazards regression model was used to determine the hazard ratios (HR) and corresponding 95% confidence intervals (CIs). All reported *P* values were two-tailed, and a *P* value of 0.05 or less was considered to be statistically significant.

3 | RESULTS

During the study period, 578 women were diagnosed treated for ovarian cancer at the study institution. Of these, 40 (6.9%) women were found to have EAOC; the remaining 538 women had no pathologic evidence of endometriosis (non-EAOC group).

The clinical and pathologic characteristics of the 40 women with EAOC are summarized in Table 1. The mean age at diagnosis was 47.2 years (range, 28–77 years) and 26 (65%) women were premenopausal. Stage I disease was the most common stage at the time of diagnosis. The mean tumor size was 12.2 cm (range, 4–38 cm). Grade 3 tumors accounted for more than 50% of the cases. Most of the women had a unilateral tumor, no LN metastasis, and either no residual tumor or a tumor of 1 cm or smaller. One woman had synchronous endometrial cancer. All women underwent primary surgery. Of these, 35 (88%) received adjuvant chemotherapy (platinum-based regimens combined with taxanes). After their initial treatment, 36 (90%) women showed a complete or partial response, and 4 (10%) showed progressive disease. During the follow-up period, nine women had a recurrence, and eight of them died owing to disease progression.

The EAOC group comprised 15 (38%) cases of CCC, 15 (38%) cases of EC, 6 (15%) cases of mucinous carcinoma, 3 (8%) cases of serous carcinoma, and 1 (3%) case of non-epithelial tumor (low-grade endometrial stromal sarcoma). Among all women with CCC and EC, the frequency of endometriosis was 28% (15/53) and 23% (15/66), respectively.

The features of ovarian CCC and EC compared were compared between the presence and absence of endometriosis (Table 2). The mean age at diagnosis was approximately 4 years younger for women with endometriosis than for women without endometriosis; however, the difference was not significant. The proportion of premenopausal women was higher in the endometriosis group, although again the difference was not significant. Parity, pre-operative serum CA-125, prevalence of CA125 in normal range, tumor size, distribution of histologic subtypes and tumor grade, laterality of tumor, presence of LN metastasis, residual tumor greater than 1 cm, and presence of synchronous endometrial cancer did not differ between the two groups. In addition, no difference was observed in the initial treatment protocol or the response to treatment, or in the rate of relapse or death.

TABLE 1 Clinicopathologic characteristics of women with endometriosis-associated ovarian cancer.[a]

Characteristic	Value (n=40)
Age, y	47.2 ± 13.0 (28–77)
Menopausal status	
Pre	26 (65)
Post	14 (35)
Parity	2 (0–8)
CA-125, U/mL	90 (3–16 458)
≤35 U/mL	10 (25)
>35 U/mL	30 (75)
Tumor size, cm, median (range)	12 (4–38)
Histologic type	
Clear cell	15 (38)
Endometrioid	15 (38)
Mucinous	6 (15)
Serous	3 (8)
Non-epithelial (low-grade endometrial stromal sarcoma)	1 (3)
FIGO stage	
I	29 (73)
II	6 (15)
III	5 (13)
IV	0 (0)
Grade	
1	14 (35)
2	5 (13)
3	21 (53)
Laterality of tumor	
Unilateral	32 (80)
Bilateral	8 (20)
LN metastasis	
No	36 (90)
Yes	4 (10)
Residual disease	
None or ≤1 cm	31 (78)
>1 cm	9 (23)
Endometrial pathology	
Hyperplasia	2 (5)
Cancer	1 (3)
Primary treatments	
PS	4 (10)
PS + AC	35 (88)
PS + HT	1 (3)
Chemotherapy regimen[b]	
Paclitaxel + carboplatin	31 (89)
Docetaxel + carboplatin	4 (11)
Response to primary treatment	
CR	35 (88)
PR	1 (3)
SD	0 (0)
PD	4 (10)
Outcome	
Recurrence	9 (23)
Death	8 (20)

Abbreviations: AC, adjuvant chemotherapy; CA-125, cancer antigen 125; CR, complete response; HT, hormone therapy; LN, lymph node; PD, progressive disease; PR, partial response; PS, primary surgery; SD, stable disease.
[a]Values are given as mean ± SD (range), median (range), or number (percentage).
[b]Data for 35 women.

Endometriosis-associated tumors were diagnosed at stage I significantly more frequently (24/30 women, 80%) as compared with non-associated cases (52/89 women, 58%) (P=0.033).

After a median follow-up of 32 months (range, 6–156 months), the 5-year DFS and OS rates of women with endometriosis were 77.6% and 80.3%, respectively. The 5-year DFS and OS rates of women without endometriosis were, respectively, 65.0% and 70.9% after a median follow-up of 35 months (range, 8–157 months). During comparable follow-up periods in the two groups, concurrent endometriosis was associated with significantly higher 5-year survival rates (DFS, P=0.038; OS, P=0.048) (Table 2).

Univariate survival analysis showed that advanced stage, higher grade, bilateral tumor, LN metastasis, residual tumor greater than 1 cm, and non-concurrent endometriosis had a significant effect on shortening the 5-year DFS and OS. In multivariate analysis, however, residual tumor greater than 1 cm was the only independent predictor of survival (DFS: HR, 9.83; 95% CI, 4.84–19.93; P<0.001. OS: HR, 5.07; 95% CI, 2.33–11.03, P<0.001) (Table 3). After stratification by FIGO stage, which showed the only significant difference between the two groups (Table 2), no factor affected the 5-year survivals (Table 4).

4 | DISCUSSION

In the current study, approximately 7% of all ovarian cancers were associated with endometriosis, and three-quarters of EAOC cases were histologically CCC or EC. Previous studies have reported the presence of endometriosis in 10%–18% of ovarian cancers.[11,15] The mechanisms underlying the malignant transformation of endometriosis remain unclear. Among women of reproductive age, an immune imbalance and an hormonal environment marked by an excess of estrogen and a deficiency of progesterone might trigger a transition from benign endometriosis toward malignancy.[5,16] In particular, some

TABLE 2 Characteristics of women with ovarian CCC and EC by the presence of endometriosis.[a]

Characteristic	CCC and EC with endometriosis (n=30)	CCC and EC without endometriosis (n=89)	*P* value
Age, y	49.0 ± 12.7 (28–77)	53.4 ± 13.6 (33–78)	0.103
≤50	20 (67)	40 (45)	0.080
>50	10 (33)	49 (55)	
Menopausal status			0.125
Pre	18 (60)	39 (44)	
Post	12 (40)	50 (56)	
Parity	2 (0–7)	2 (0–8)	0.439
CA-125, U/mL	151 (7–16 458)	115 (10–9369)	0.953
≤35 U/mL	6 (20)	13 (15)	0.486
>35 U/mL	24 (80)	76 (85)	
Tumor size, cm, median (range)	12 (4–25)	11 (3–27)	0.922
Histologic type			0.486
Clear cell	15 (50)	38 (48)	
Endometrioid	15 (50)	51 (57)	
FIGO stage			0.033
I	24 (80)	52 (58)	
II & III	6 (20)	37 (42)	
Grade			0.283
1	10 (33)	18 (20)	
2	4 (13)	10 (11)	
3	16 (53)	61 (69)	
Laterality of tumor			0.157
Unilateral	26 (87)	66 (74)	
Bilateral	4 (13)	23 (26)	
LN metastasis			0.573
No	28 (93)	80 (90)	
Yes	2 (7)	9 (10)	
Residual disease			0.521
None or ≤1 cm	23 (77)	73 (82)	
>1 cm	7 (23)	16 (18)	
Endometrial cancer			0.156
No	29 (97)	78 (88)	
Yes	1 (3)	11 (12)	
Primary treatment			0.935
PS	3 (10)	7 (8)	
PS + AC	27 (90)	81 (91)	
NAC + IDS	0 (0)	1 (1)	
Chemotherapy regimen[b]			0.818
Paclitaxel + carboplatin	23 (85.2)	70 (85.4)	
Docetaxel + carboplatin	4 (14.8)	12 (14.6)	
Response to primary treatment			0.491
CR	26 (87)	81 (91)	
PR	1 (3)	4 (4)	
SD	0 (0)	1 (1)	
PD	3 (10)	3 (3)	

(*Continues*)

TABLE 2 (Continued)

Characteristic	CCC and EC with endometriosis (n=30)	CCC and EC without endometriosis (n=89)	*P* value
Recurrence			0.274
No	24 (80)	62 (70)	
Yes	6 (20)	27 (30)	
Death			0.362
No	25 (83)	67 (75)	
Yes	5 (17)	22 (25)	
Follow up, mo	32 (6–156)	35 (8–157)	
5-y DFS, %	77.6	65.0	0.038
5-y OS, %	80.3	70.9	0.048

Abbreviations: AC, adjuvant chemotherapy; CA-125, cancer antigen 125; CCC, clear cell carcinoma; CR, complete response; DFS, disease-free survival; EC, endometrioid carcinoma; IDS, interval debulking surgery; LN, lymph node; NAC, neo-adjuvant chemotherapy; OS, overall survival; PD, progressive disease; PR, partial response; PS, primary surgery; SD, stable disease.
[a]Values are given as mean ± SD (range), median (range), or number (percentage) unless stated otherwise.
[b]Data for 27 women (endometriosis group) and 82 women (non-endometriosis group).

studies have focused on a link between endometriosis and CCC or EC histology.[5,17] Recently, on the basis of 13 case–control studies including more than 23 000 women, endometriosis was found to be significantly associated with an increased risk of ovarian CCC or EC.[18] That finding, as well as those from other studies, suggests that endometriosis increases the risk of ovarian CCC and EC, despite the overall low incidence of ovarian cancer among women with endometriosis.

The role of concurrent endometriosis is controversial in the prognosis of ovarian cancer. In general, ovarian cancer is diagnosed at an advanced stage, whereas EAOC is diagnosed at an early stage; in addition, longer survival times have been reported for women with EAOC than for women with non-EAOC types of ovarian cancer.[7,8,11] However, other studies have found no clear association between the presence of endometriosis and ovarian cancer survival.[6,9,10,12] The current study showed

TABLE 3 Multivariate analysis of disease-free and overall survival among women with ovarian CCC and EC.

	Disease-free survival		Overall survival	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value
FIGO stage				
I	Ref.	0.829	Ref.	0.789
II & III	1.13 (0.37–3.49)		1.17 (0.37–3.68)	
Grade				
1	Ref.	0.402	Ref.	0.291
2	2.25 (0.63–8.08)		2.79 (0.73–10.66)	
3	2.00 (0.65–6.11)		2.17 (0.71–6.62)	
Laterality of tumor				
Unilateral	Ref.	0.454	Ref.	0.569
Bilateral	1.38 (0.59–3.22)		1.32 (0.51–3.42)	
LN metastasis				
No	Ref.	0.114	Ref.	0.270
Yes	2.04 (0.84–4.95)		1.88 (0.61–5.72)	
Residual disease				
None or ≤1 cm	Ref.	<0.001	Ref.	<0.001
>1 cm	9.83 (4.84–19.93)		5.07 (2.33–11.03)	
Endometriosis				
No	Ref.	0.155	Ref.	0.257
Yes	0.52 (0.22–1.28)		0.57 (0.21–1.52)	

Abbreviations: CCC, clear cell carcinoma; CI, confidence interval; EC, endometrioid carcinoma; HR, hazard ratio; LN, lymph node.

TABLE 4 Univariate analysis of disease-free and overall survival among women with ovarian CCC and EC stratified by FIGO stage.

	Stage I					Stage II & III				
Variable	No. (%) of women (n=76)	5-y DFS, %	*P* value	5-y OS, %	*P* value	No (%) of women (n=43)	5-y DFS, %	*P* value	5-y OS, %	*P* value
Age, y										
≤50	48 (63)	76.4	0.127	84.1	0.405	12 (28)	0	0.128	62.5	0.776
>50	28 (37)	92.3		68.4		31 (72)	54.5		56.6	
Menopausal status										
Pre	45 (59)	75.3	0.079	83.2	0.533	12 (28)	25.0	0.280	62.5	0.932
Post	31 (41)	93.1		69.3		31 (72)	52.9		53.8	
Histologic type										
CCC	36 (47)	88.4	0.325	83.7	0.363	17 (40)	37.6	0.583	48.4	0.747
EC	40 (53)	76.1		72.0		26 (60)	46.2		58.7	
Grade										
1	28 (37)	83.3	0.455	79.6	0.761	0 (0)		0.650		0.347
2	6 (8)	33.3		0		8 (19)	37.5		75.0	
3	42 (55)	90.1		85.5		35 (81)	46.7		50.9	
Laterality of tumor										
Unilateral	70 (92)	83.2	0.256	79.9	0.379	22 (51)	52.5	0.508	56.6	0.692
Bilateral	6 (8)	66.7		60.0		21 (49)	26.5		60.5	
Endometrial cancer										
No	70 (92)	84.1	0.240	74.9	0.249	37 (86)	32.9	0.122	50.2	0.066
Yes	6 (8)	50.0		100		6 (14)	100		100	
Endometriosis										
No	52 (68)	78.5	0.252	75.7	0.604	37 (86)	44.0	0.217	54.9	0.935
Yes	24 (32)	90.2		81.2		6 (14)	25.0		66.7	

Abbreviations: CCC, clear cell carcinoma; DFS, disease-free survival; EC, endometrioid carcinoma; OS, overall survival.

that ovarian CCC and EC cases with endometriosis were associated with better survival rates as compared with cases without endometriosis. The favorable prognostic role of endometriosis might be explained by the different distribution of stages between the two groups, because stage I disease was significantly more common in the EAOC group than in the non-EAOC group. No difference was found between the two groups in age at diagnosis, tumor features (size, grade, and laterality), LN metastasis status, residual tumor greater than 1 cm, or incidence of synchronous endometrial cancers. The only difference between the groups was disease detection at an earlier stage in the EAOC group.

It is known that CCC and EC with endometriosis are diagnosed earlier because endometriosis is frequently associated with specific symptoms, such as pelvic pain, dysmenorrhea, and dyspareunia.[16,19] In addition, women with endometriosis tend to have more continual medical care for their disorder, whereas ovarian cancers are frequently asymptomatic until an advanced stage.[2] Endometriosis often presents as a unilateral ovarian cyst. Tumors growing from the ovarian cyst are more likely to be confined within that ovary for a period of time before spreading, facilitating diagnosis at an early stage.[20,21] Orezzoli et al.[12] reported that some women with ovarian CCC associated with endometriosis presented with benign features. The women tended to be younger and to have a pelvic cystic mass at the time of diagnosis. They presented at a significantly earlier stage and their median OS was markedly longer than that of women without endometriosis, despite the limited number of study women. It seems, therefore, that ovarian cancers with endometriosis are often diagnosed at an early stage, which may lead to a better prognosis.

In general, age, menopausal status, histologic subtype, grade, stage, residual tumor status, LN metastasis, and type of treatment influence the survival of women with EAOC.[7,9,11] In the present univariate analysis, advanced stage, high grade, bilateral tumor, LN metastasis, residual tumor greater than 1 cm, and non-concurrent endometriosis were related to shorter DFS and OS among women with ovarian CCC and EC. However, only residual tumor status was an independent prognostic factor in the multivariate analysis. Thus, optimal cytoreductive surgery might significantly benefit women with ovarian CCC and EC. Furthermore, after stratification by FIGO stage, the presence of endometriosis did not improve the prognosis of ovarian CCC or EC. The higher survival rates of women with EAOC might be explained by the higher proportion of cases with early-stage ovarian cancer in that group.

The present study has some limitations. It was a retrospective analysis of data obtained from clinical records. During the long-term follow-up period, it is possible that the pathologic diagnoses and treatment protocols might have changed; however, a single pathologist and two gynecologic oncologists conducted all diagnoses and treatments. Furthermore, there was no significant difference in therapeutic regimens between the two groups. All study women underwent surgical procedures and more than 90% of them received platinum-based chemotherapies combined with taxanes. Another limitation relates to the inability to compare cases of ovarian cancer originating in endometriosis and cases in which endometriosis was not contiguous with the tumor but was detected incidentally in surgical specimens, owing to the small proportion of women with EAOC.

In conclusion, endometriosis was most frequently associated with CCC and EC histologic types among epithelial ovarian cancers. However, no clear association was observed between the presence of concurrent endometriosis and prognosis of ovarian CCC or EC. Ovarian CCC and EC with endometriosis are often diagnosed at an earlier stage relative to cases without endometriosis, and therefore have a more favorable prognosis.

AUTHOR CONTRIBUTIONS

JUC, KWD, and KSM all contributed to study conception and design; data acquisition, analysis, and interpretation; and writing and revising the manuscript.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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