Significance of Ovarian Endometriosis on the Prognosis of Ovarian Clear Cell Carcinoma

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Introduction: The aim of this study was to evaluate the significance of ovarian endometriosis on the prognosis of ovarian clear cell carcinoma (OCCC).

Methods: Patients with OCCC were divided into 2 groups according to the presence of ovarian endometriosis: group 1, no coexisting ovarian endometriosis; group 2, clear cell carcinoma arising from ovarian endometriosis or the presence of ovarian endometriosis elsewhere in the ovary. Clinicopathologic characteristics, disease-free survival (DFS), and overall survival (OS) were compared between the 2 groups.

Results: Of 155 patients with OCCC, 77 were categorized into group 1 and 78 into group 2. Group 2 patients were younger than group 1 (median age, 48 vs 51 years; $P = 0.005$) and had higher incidence of early-stage disease (stage I, 77% vs 58%; $P = 0.001$) and lower incidence of lymph node metastasis (4% vs 17%; $P = 0.008$). Group 2 patients were observed to have a significantly higher 5-year DFS ($P < 0.001$) and OS ($P = 0.001$) compared with group 1. In stage I disease, group 2 had a significantly higher 5-year DFS ($P = 0.004$) and OS ($P = 0.016$) than did group 1. In the multivariate analysis, coexisting endometriosis and advanced International Federation of Obstetrics and Gynecology stage were significant factors for both DFS and OS rates.

Conclusions: Ovarian clear cell carcinoma with endometriosis was found more frequently in younger women and had a higher incidence of early-stage disease and a lower incidence of lymph node metastasis compared with OCCC without endometriosis. Ovarian endometriosis was associated with improved prognostic factors and a better DFS and OS even in stage I disease. Ovarian endometriosis was an independent prognostic factor for OCCC.

Key Words: Endometriosis, Ovarian cancer, Ovarian clear cell carcinoma, Ovary, Prognosis

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Epithelial ovarian cancer is the most lethal gynecologic cancer and the fourth leading cause of death due to cancer among women in developed countries.[1] In 2012, approximately 239,000 new cases of ovarian cancer and 152,000 deaths due to ovarian cancer worldwide were reported.[2] In Korea, ovarian cancer is estimated to be the third most common gynecologic cancer and the 10th most common cancer among women with 2374 new cases in 2015.[3]

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Furthermore, ovarian cancer is estimated to be the most lethal gynecologic malignancy and the eighth most common cause of death due to female cancer with 1075 cancer deaths in 2015.[3]

Clear cell carcinoma of the ovary is a rare histologic form of epithelial ovarian cancer. The incidence of ovarian clear cell carcinoma (OCCC) varies according to ethnicity and has been found to range between 1% and 25% of epithelial ovarian cancers.[4–6] Furthermore, OCCC is one of the most aggressive histologic types of epithelial ovarian cancer. Because OCCC has a distinct biology, they should be considered and have studies on their own. On the other hand, according to a recent dualistic model of ovarian carcinogenesis, clear cell carcinoma is regarded as type I ovarian cancer that has precursor lesions in the ovary.[7,8] Endometriosis is the most common precursor lesion for OCCC. Previous studies have evaluated the significance of the presence of endometriosis on the prognosis of OCCC.[9–14] However, many of these studies included only a small number of cases because of the rarity of OCCC and the previously reported controversial results. Further evaluation of the prognostic role of endometriosis in OCCC is required. The aim of this study was to evaluate the significance of ovarian endometriosis on the prognosis of OCCC.

MATERIALS AND METHODS

After obtaining the approval of the institutional review board of Asan Medical Center (AMC), Seoul, Korea, patients with OCCC who were treated at the AMC between 1991 and 2012 were recruited in the study following a database search. Demographic data were obtained from the patients' medical records and included age, parity, menopause, comorbid medical disease, and history of abdominal surgery. Clinical data were also obtained from the patients and included preoperative serum cancer antigen 125 (CA-125) levels, initial incomplete surgery, mode of surgery, surgical staging, fertility-sparing surgery, size of the largest residual tumor, the International Federation of Obstetrics and Gynecology (FIGO) staging system, tumor histology, presence of ovarian endometriosis, ovarian tumor size, bilateral ovarian involvement, tumor rupture, ascites, peritoneal cytology, lymphovascular space invasion, lymph node metastasis, adjuvant chemotherapy, recurrence, date of recurrence, date of the patient's last follow-up, patient's status at the last follow-up, and death.

Patients were divided into 2 groups according to the presence of ovarian endometriosis and the association between ovarian endometriosis and OCCC on pathology. The pathologic diagnosis was performed by a pathologist who was specialized in gynecology. All surgeries were performed by a gynecologic oncologist. The patients were classified as group 1 (without endometriosis) if they did not have coexisting ovarian endometriosis. The patients were classified as group 2 (with endometriosis) if clear cell carcinoma arose from ovarian endometriosis or if ovarian endometriosis was present and found elsewhere in the ovary. Clinicopathologic characteristics and survival outcomes were compared between the 2 groups.

The mean values between the 2 groups were compared using Student *t* test. Frequency distributions between the 2 groups were compared using the χ^2 test or Fisher exact test. Disease-free survival (DFS) time was calculated as the time interval between the date of initial surgery and the date of recurrence, censored, or the last follow-up and was presented in months. Overall survival (OS) time was calculated as the time interval between the date of initial surgery and the date of death, censored, or the last follow-up. Survival curves were plotted using the Kaplan-Meier method, and survival differences were compared using the log-rank test for categorical variables and Cox regression for continuous variables. Multivariate survival analysis was performed using Cox regression model including prognostic factors that were significant in univariate analysis.

TABLE 1. Patients' characteristics (n = 155)

Characteristics	Group 1 (Without Endometriosis, n = 77)	Group 2 (With Endometriosis, n = 78)	*P*
Age, median (range), y	51 (28–79)	48 (29–69)	0.005
≤49 y,* n (%)	35 (45.5)	49 (62.8)	0.030
>49 y,* n (%)	42 (54.5)	29 (37.2)	
Parity			
Nulliparous	22 (28.6)	28 (35.9)	0.329
Parous	55 (71.4)	50 (64.1)	
Menopause			
No	48 (62.3)	54 (69.2)	0.366
Yes	29 (37.7)	24 (30.8)	
Comorbid medical disease			
No	55 (71.4)	61 (78.2)	0.331
Yes	22 (28.6)	17 (21.8)	
Preoperative CA-125, mean ± SD, U/mL	406 ± 1461.3	139.4 ± 223.6	0.113
≤35 U/mL, n (%)	29 (37.7)	28 (35.9)	0.820
>35 U/mL, n (%)	48 (62.3)	50 (64.1)	

*Divided by median age.

TABLE 2. Surgical and pathologic characteristics (n = 155)

Characteristics	Group 1 (Without Endometriosis, n = 77)	Group 2 (With Endometriosis, n = 78)	*P*
Referred after incomplete surgery			
No	58 (75.3)	61 (78.2)	0.671
Yes	19 (24.7)	17 (21.8)	
Complete staging surgery			
No	6 (7.8)	15 (19.2)	0.037
Yes	71 (92.2)	63 (80.8)	
Surgery mode			
Laparotomy	70 (90.9)	61 (78.2)	0.029
Laparoscopy	7 (9.1)	17 (21.8)	
Fertility-sparing surgery			
No	71 (92.2)	62 (79.5)	0.023
Yes	6 (7.8)	16 (20.5)	
Largest residual tumor size			
0 cm	61 (79.2)	72 (92.3)	0.061
≤1 cm	9 (11.7)	4 (5.1)	
>1 cm	7 (9.1)	2 (2.6)	
FIGO stage			
I	45 (58.4)	60 (76.9)	0.001
II	4 (5.2)	10 (12.8)	
III	24 (31.2)	6 (7.7)	
IV	4 (5.2)	2 (2.6)	
Ovarian tumor size, mean ± SD, cm	11.2 ± 4.9	10.5 ± 4	0.334
≤10 cm,* n (%)	41 (53.2)	45 (57.7)	0.578
>10 cm,* n (%)	36 (46.8)	33 (42.3)	
Bilateral ovarian involvement			
Unilateral	62 (80.5)	70 (89.7)	0.106
Bilateral	15 (19.5)	8 (10.3)	
Ovarian surface involvement			
No	45 (58.4)	57 (73.1)	0.055
Yes	32 (41.6)	21 (26.9)	
Tumor rupture			
No	47 (61)	42 (53.8)	0.365
Yes	30 (39)	36 (46.2)	
Ascites			
Absent	38 (49.4)	48 (61.5)	0.127
Present	39 (50.6)	30 (38.5)	
Peritoneal cytology			
Negative	58 (75.3)	68 (87.2)	0.058
Positive	19 (24.7)	10 (12.8)	
Lymphovascular space invasion			
No	67 (87)	74 (94.9)	0.101
Yes	10 (13)	4 (5.1)	
Lymph node metastasis			
No	64 (83.1)	75 (96.2)	0.008
Yes	13 (16.9)	3 (3.8)	
Adjuvant chemotherapy			
No	3 (3.9)	5 (6.4)	0.719
Yes	74 (96.1)	73 (93.6)	

(Continued on next page)

TABLE 2. *(Continued)*

Characteristics	Group 1 (Without Endometriosis, n = 77)	Group 2 (With Endometriosis, n = 78)	*P*
Adjuvant chemotherapy regimen†			
Taxane + platinum	55 (74.3)	64 (87.7)	0.039
Other + platinum	19 (25.7)	9 (12.3)	
Adjuvant chemotherapy cycles,† mean ± SD, n	5.1 ± 2.3	5.1 ± 1.4	0.928
<6 Cycles, n (%)	28 (36.4)	27 (34.6)	0.820
≥6 Cycles, n (%)	49 (63.6)	51 (65.4)	

*Divided by mean values.
†One hundred forty-seven patients who received adjuvant chemotherapy were included.

$P < 0.05$ in a 2-sided test was regarded as statistically significant. For statistical analyses, SPSS software version 21.0 (IBM, Armonk, NY) was used.

RESULTS

During the study period, 155 patients with OCCC were treated and followed up at the AMC. Of these patients, 77 patients did not have coexisting ovarian endometriosis (group 1), and 78 patients had clear cell carcinoma arising from ovarian endometriosis or coexisting ovarian endometriosis elsewhere in the ovary. The patients' characteristics between the 2 groups are presented in Table 1. Group 1 patients were older than patients in groups 2 ($P = 0.02$). However, no differences were observed between the 2 groups in parity, menopause, comorbid medical disease, and preoperative serum CA-125 levels. A total of 134 patients (86.5%) had pure OCCC, but 21 patients (13.5%) had mixed OCCC. Even in patients with mixed OCCC, the OCCC component accounted for more than 50% of the tumor.

Surgical and pathological outcomes between the 2 groups are depicted in Table 2. No differences were found between the 2 groups in the number of patients referred after incomplete surgery. However, more patients in group 1 underwent complete staging operation, which was defined as peritoneal exploration, peritoneal washing cytology, omentectomy, and pelvic and para-aortic lymphadenectomy ($P = 0.037$). More patients in group 2 were observed to undergo laparoscopic surgery ($P = 0.029$) and fertility-sparing surgery ($P = 0.023$), which was defined as the preservation of the uterus and 1 adnexa. Optimal debulking surgery, which was defined as the size of the largest residual tumor less than or equal to 1 cm, was performed in 70 patients (90.9%) in group 1 and 76 patients (97.4%) in group 2 ($P = 0.061$). Advanced-stage disease ($P = 0.001$) and lymph node metastasis ($P = 0.008$) were more frequently found in group 1 than in group 2. When we compared FIGO stage and lymph node metastasis between groups 1 and 2 excluding incompletely staged patients, advanced-stage diseases were significantly more frequent in group 1 (42.3% vs 25.4%, $P = 0.040$), and lymph node metastasis was also significantly more frequent in group 1 (18.3% vs 4.8%, $P = 0.017$). However, there was no difference in ovarian tumor size, bilateral ovarian involvement, ovarian surface involvement, tumor rupture, ascites, positive peritoneal cytology, and lymphovascular space invasion between the 2 groups. After surgery, 74 patients (96.1%) in group 1 and 73 patients (93.6%) in group 2 received adjuvant chemotherapy ($P = 0.719$). More patients in group 2 patients received taxane/platinum chemotherapy regimen ($P = 0.039$). No difference in cycle numbers was observed between the 2 groups.

During the median follow-up time of 71 months (range, 4–275 months), 37 patients (48.1%) in group 1 and 14 patients (17.9%) in group 2 were found to have recurrence ($P < 0.001$). Of these, 32 patients (41.6%) in group 1 and 12 patients (15.4%) in group 2 died of disease progression ($P < 0.001$). Figure 1 depicts the DFS and OS of each group. The 5-year DFS of patients with endometriosis was observed to be significantly higher than that of patients without endometriosis (83% vs 51%; $P < 0.001$). The 5-year OS of patients with endometriosis was significantly higher than that of patients without endometriosis (84% vs 54%; $P = 0.001$). In patients with FIGO stage I ovarian cancer, the 5-year DFS and OS rates of patients with endometriosis (87% and 95%, respectively) were significantly higher than those of patients without endometriosis (70% and 76%, respectively; $P = 0.004$ and $P = 0.016$, respectively). When we included completely staged patients among those with stage I ovarian cancer, the 5-year DFS and OS rates of patients with endometriosis (70% and 96%, respectively) were significantly higher than those of patients without endometriosis (73% and 96%, respectively; $P = 0.002$ and $P = 0.010$, respectively). In patients with FIGO stages II–IV ovarian cancer, the 5-year DFS and OS rates of patients with endometriosis (44% and 49%, respectively) were higher than those of patients without endometriosis (24% and 19%, respectively), although this was not statistically significant ($P = 0.282$ and $P = 0.232$, respectively). When we included completely staged patients among stages II–IV ovarian cancer, the 5-year DFS and OS rates of patients with endometriosis (50% and 55%, respectively) were higher than those of patients without endometriosis (26% and 21%, respectively), although this was not statistically significant ($P = 0.203$ and $P = 0.164$, respectively). In the univariate survival analysis, significant prognostic factors for both DFS and OS were coexisting endometriosis, elevated preoperative serum CA-125 levels, advanced FIGO stage (stage I vs stages II–IV), ovarian surface involvement, positive peritoneal cytology, and suboptimal debulking. Coexisting endometriosis and advanced FIGO stage were

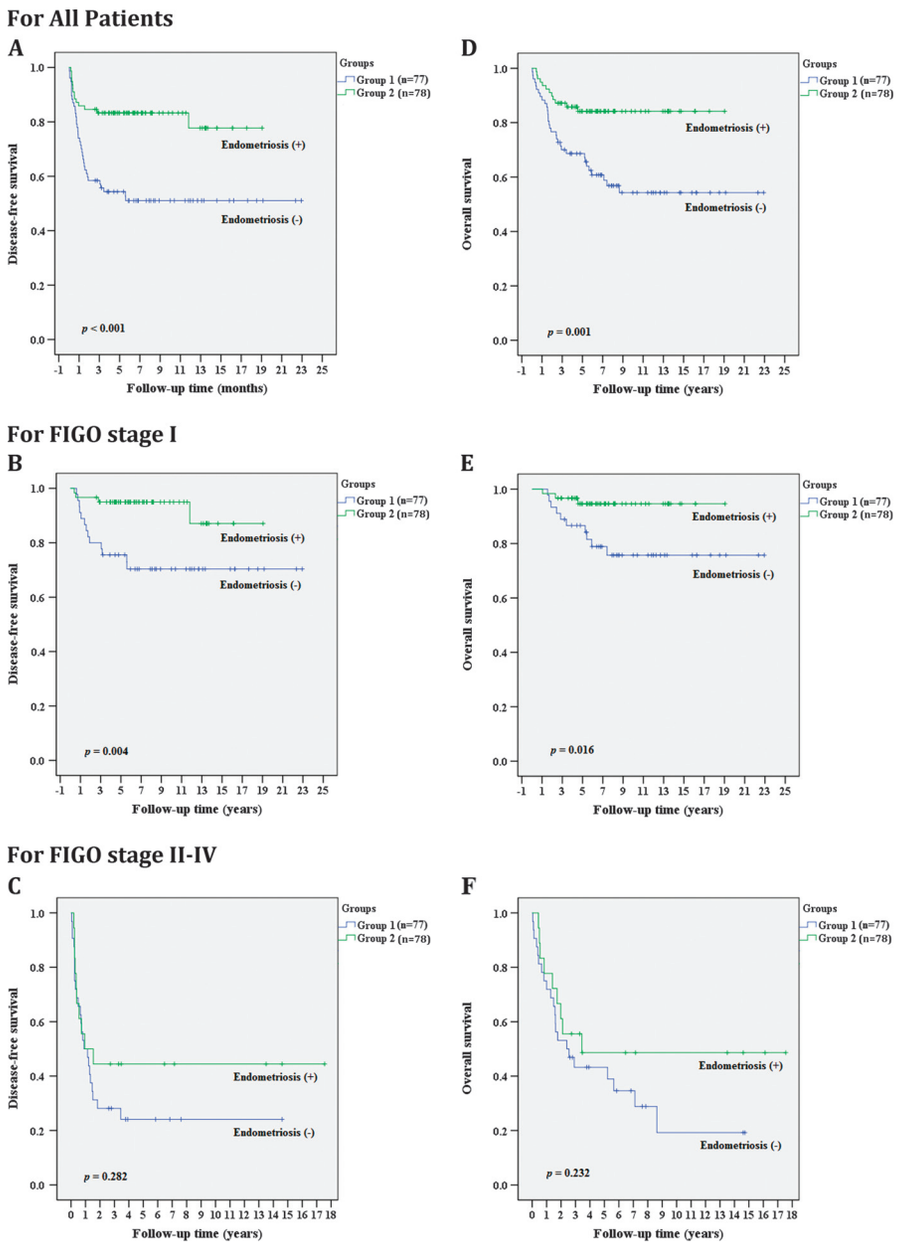

FIGURE 1. Left, Disease-free survival in patients with OCCC (A), in FIGO stage I OCCC (B), and in FIGO stages II–IV OCCC (C). Right, Overall survival in patients with OCCC (D), in FIGO stage I OCCC (E), and in FIGO stages II–IV OCCC (F).

significant factors for both DFS and OS in the multivariate analysis (Table 3).

DISCUSSION

In our study, OCCC with endometriosis was found more frequently in younger women and had a higher incidence of early-stage disease and a lower incidence of lymph node metastasis. The presence of endometriosis was associated with improved DFS and OS rates in clear cell carcinoma even in patients with stage I disease. The presence of endometriosis was an independent prognostic factor in multivariate analysis.

Several previous studies have evaluated the association between the presence of endometriosis and prognosis of epithelial ovarian cancer.[15,16] Clear cell carcinoma is the most frequent epithelial ovarian cancer that arises from or is associated with endometriosis.[7,17] A meta-analysis reported forest plots including published studies to evaluate the prognostic significance of the presence of endometriosis in OCCC.[14] To date, only 6 retrospective studies have specifically evaluated the prognostic role of endometriosis in OCCC (Table 4).[9–14] In the aforementioned studies, OCCC with endometriosis was found to be more common in younger women and was diagnosed at an earlier stage

compared with OCCC without endometriosis. Furthermore, the frequency of ascites, positive cytology results, and lymph node metastasis were lower in patients with OCCC with endometriosis. Only 1 previous study has compared the clinicopathologic characteristics between OCCC arising from endometriosis and OCCC with endometriosis elsewhere in the ovary.[10] In that study, OCCC arising from endometriosis was associated with younger age, early-stage disease, and a lower incidence of ascites compared with OCCC associated with endometriosis.[10]

As shown in Table 4, 3 studies have suggested an improvement in survival in OCCC with endometriosis,[9,10,12] although this was not observed in 3 other studies.[11,13,14] However, the latter 3 studies included only a small number of patients.[11,13,14] The improved survival in patients with OCCC with endometriosis may be due to better prognostic factors in these patients including young age, earlier stage of disease, and a lower frequency of lymph node metastasis. In both the study by Komiyama et al[9] and the present study, the prognosis of patients with endometriosis was improved even in patients with stage I disease. Furthermore, the presence of endometriosis was found to be an independent prognostic factor for DFS and OS in our study. Our study is the first to demonstrate the presence of endometriosis as an independent prognostic factor in OCCC.

In our study, OCCC with endometriosis occurred in young women and had favorable clinicopathologic characteristics including early FIGO stage and lower incidence of lymph node metastasis. It had better prognosis compared with OCCC without endometriosis in early-stage disease. This finding is important because often this disease will be diagnosed unexpectedly during surgery for young women with presumed endometrioma and need to be counseled about further staging surgery. In advanced-stage disease, OCCC with endometriosis showed a trend toward improved survival outcomes. This finding may suggest that there may be a difference in the way the tumors respond to chemotherapy, as well as in underlying biology. The pathogenesis of OCCC in patients with endometriosis may differ from other OCCC and therefore may have innate factors that improve prognosis. Further studies are required to focus on the molecular genetic and pathological characterization of different types of OCCC. In addition, large-scale population-based study or prospective observational study would helpful to confirm this finding.

Although this study is one of the largest conducted to evaluate the prognostic significance of endometriosis in OCCC, it has several limitations. These limitations include its retrospective nature and the relatively small number of study subjects. As previous studies have reported conflicting outcomes regarding the prognostic role of endometriosis in OCCC, larger studies are required to confirm the results of the present study and to define the exact carcinogenesis mechanism of OCCC with or without endometriosis.

In conclusion, OCCC with endometriosis was associated with younger age, a higher incidence of early-stage disease, and a lower incidence of lymph node metastasis. The presence of endometriosis was associated with improved DFS and OS rates in OCCC even in stage I disease and was found to be an independent prognostic factor.

TABLE 3. Multivariate survival analysis (n = 155)

		DFS			OS		
Variables	**n**	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Endometriosis							
Absent	77	1	1				
Present	78	0.5	0.3–0.9	0.022	0.5	0.2–0.9	0.03
Preoperative CA-125							
≤35 U/mL	86	1	1				
>35 U/mL	69	1.1	0.5–2.2	0.854	1.2	0.5–2.6	0.670
FIGO stage							
I	105	1	1				
II–IV	50	4.2	2.0–8.7	<0.001	4.8	2.1–10.7	<0.001
Ovarian surface involvement							
No	102	1	1				
Yes	53	1.8	0.8–3.9	0.134	1.6	0.7–3.7	0.301
Peritoneal cytology							
Negative	126	1	1				
Positive	39	1.9	0.9–3.8	0.052	1.9	0.9–3.9	0.07
Optimal debulking							
Optimal	146	1	1				
Suboptimal	9	1.4	0.6–3.1	0.454	1.6	0.7–3.7	0.267

OR, odds ratio; CI, confidence interval.

TABLE 4. Comparison of OCCC with and without endometriosis

Reference	Year	Groups	n	Mean Age, y	Early Stage, %	Mean Ovarian Tumor Size, cm	Bilateral Ovarian Involvement, %	Ascites, %	Cytology, %	Ovarian Surface Involvement, %	Lymph Node Metastasis, %	Optimal Debulking, %	5-y DFS	5-y OS
Komiyama et al[9]	1999	With EMS	20	49	65	17			14					100%,* 44%†
		Without EMS	33	54	58	14			64					60%,* 17%†
		P		NS		NS			0.03					<0.05,* < 0.05†
Orezzoli et al[10]	2008	Arising from EMS	15	49	79			7				85		75%
		Associated with EMS	26	56	36			24						
		Without EMS	43	59	33			55				79		34%
		P		0.03	0.04			0.002				NS		0.001
Noli et al[11]	2013	With EMS	19											57%‡
		Without EMS	28											46%‡
		P												0.934
Ye et al[12]	2014	With EMS	79	46	71	11		38			15	90	60%	70%
		Without EMS	131	54	32	11		65			34	57	40%	53%
		P		<0.001	<0.001	0.487		<0.001			0.003	<0.001	0.006	0.036
Scarfone et al[13]	2014	Arising from EMS	27	51	67		15	0						73 mo§
		Without EMS	46	58	50		37	20						60 mo§
		P		0.02	0.17		0.55							0.43
Present study	2015	Arising from EMS	21	46	81	11	9	32	5	18	4	98	83%	}84%
		Associated with EMS	57	47	67	10	14	57	33	52	5	95		
		Without EMS	77	51	58	11	20	51	25	42	17	91	51%	54%
		P		0.02	0.002	0.536	0.226	0.041	0.003	0.003	0.028	0.195	<0.001	0.001

*Stage 1.
†Stage 3.
‡Ten-year OS.
§Mean survival.
EMS, endometriosis; NS, not significant.

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