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RESEARCH PAPER

Endometriosis-associated ovarian cancer is a single entity with distinct clinicopathological characteristics

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ABSTRACT

Objective: To compare the clinicopathological features and chemotherapy response of ovarian clear cell carcinoma (CCC) and endometrioid carcinoma (EC) associated with endometriosis or not.

Methods: This was a retrospective study of 128 patients diagnosed with CCC and EC from 2002 to 2017. Clinicopathological features and chemotherapy response were analyzed.

Results:There were 34 women with endometriosis-associated ovarian cancer (EAOC) and 94 with non-endometriosis associated ovarian cancer (non-EAOC) according to Sampson's and Scott's criteria. The mean diagnosis age in the EAOC group was 48.65 vs. 54.39 years in non-EAOC ($p = 0.002$). Compared with non-EAOC, the EAOC patients were more likely to have an earlier menarche age (13 vs. 14 years, $p = 0.001$), a higher incidence of infertility (26.47% vs. 10.64%, $p = 0.026$), and an earlier stage tumor (91.18% vs. 73.40% in stages I–II, $p = 0.032$). At a median follow-up time of 32.9 months, overall survival among patients with EAOC was significantly longer (109.8 vs. 47.4 months, $p = 0.007$). Association with endometriosis ($p = 0.033$) was the significant favorable prognostic factors associated with survival. However, stratifying by stage, the overall survival advantage of EAOC was not significant. Although EAOC had a better prognosis, no difference was observed in chemotherapy response between the two groups ($p = 0.535$).

Conclusions: The EAOC patients were often diagnosed at a younger age, an earlier stage, and related to nulliparity and infertility. Patients with EAOC had a better prognosis than non-EAOC, early stage rather than association with endometriosis may be the driver of survival.

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Ovarian cancer; endometriosis; clinicopathological features; prognosis; chemotherapy response

Introduction

Ovarian cancer, the gynecological malignancies with the highest mortality rate, is a serious threat to women's health and life.[1] The case numbers are increasing and overall five-year relative survival is below 45%.[2] There are around 22,240 new cases of ovarian cancer and 14,070 ovarian cancer deaths expected in the United States in 2018.[3] The causes of ovarian cancer remain unclear and many researches have shown that endometriosis is closely associated with the occurrence of ovarian cancer.

Endometriosis is a common gynecologic disorder, with a prevalence of about 5–15% in women of reproductive age. Endometriosis is considered a benign disease, while it has similar characteristics to invasive neoplasms such as uncontrolled growth, neo-angiogenesis, local invasion and distant spread.[1,4] Previous studies have demonstrated an increased epithelial ovarian cancer incidence in women with endometriosis.[5,6] The longer the duration of endometriosis, the larger the size of endometrioma, the greater is the risk for developing ovarian cancer.[7] The risk of endometriosis-associated ovarian cancer (EAOC) varies by histological subtypes and the greatest risk is associated with ovarian endometrioid (EC) and clear cell carcinoma (CCC).[8] Although endometriosis has not been considered to be a precancerous lesion, several studies have provided unequivocal evidence that atypical endometriosis is in fact an intermediate lesion between endometriosis and ovarian cancer.[9] However, definite mechanisms involved in the malignant transformation remain not entirely understood. In recent years, novel evidences have emerged, improving our understanding of this entity. Many gene mutations including ARID1A, PIK3CA, MET, and HNF1β may contribute to the malignant transformation of endometriosis.[10-13] Oxidative stress, inflammation and steroid hormones also participate in the process. Nowadays, a highly controversial issue is whether EAOC is a different disease or whether it is similar to non-endometriosis associated ovarian cancer (non-EAOC). Some studies have showed that EAOC seems to represent a distinct disease entity with different histological subtypes, early presentation and a relatively favorable outcome, whereas others have failed to find such a difference.[7,14-16]

In this study, 128 patients diagnosed with CCC and EC in our hospital were divided into EAOC group and non-EAOC group according to Sampson's and Scott's criteria.[17,18] This study aims at analyzing the clinicopathological features and chemotherapy response of EAOC compared with non-EAOC.

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Table 1. Clinicopathological features in patients with CCC and EC associated or not with endometriosis.

Clinicopathological features	EAOC (n = 34) N(%)/**x**(_±s/M	Non-EAOC (n = 94) N(%)/**x**(_±s/M	p
Age			
Mean ± SD	48.65 ± 8.98 (32–63)	54.39 ± 9.05 (31–74)	0.002*
Median age of menarche	13	14	0.001*
Menopausal status			0.211
Premenopausal	11 (32.36%)	42(44.68%)	
Postmenopausal	23 (67.64%)	52 (55.32%)	
Personal history			
Infertility	9 (26.47%)	10 (10.64%)	0.026*
Symptoms			
Dysmenorrhea	15 (44.12%)	22 (23.40%)	0.022*
Pelvic pain	18 (52.94%)	42 (44.68%)	0.408
Abdominal distension	14 (41.18%)	31 (32.40%)	0.391
Menstrual disorder	12 (35.29%)	17 (18.09%)	0.040*
Vaginal bleeding	6 (17.65%)	24 (25.53%)	0.352
Tumor diameter (cm)	12.15	10.00	0.100
Histology			0.207
EC	16 (47.06%)	56(59.57%)	
CCC	18 (52.94%)	38(40.43%)	
FIGO stage			0.032*
I–II	31 (91.18%)	69 (73.40%)	
III–IV	3 (8.82%)	25 (26.60%)	
EC grade			0.228
Low grade	11(68.75%)	29 (51.79%)	
High grade	5(31.25%)	27 (48.21%)	
Ascites	15 (44.12%)	60 (63.83%)	0.046*
Tumor markers			
CA125			0.105
<35 U/mL	11(32.35%)	24 (25.53%)	
35–600 U/mL	18 (52.94%)	38 (40.43%)	
>600 U/mL	5(14.71%)	32 (34.04%)	
CA199 (U/mL)	131.21	49.86	0.520
HE4 (pmol/L)	152.00	152.00	0.369

*p < 0.05. EAOC, endometriosis-associated ovarian cancer; non-EAOC, non-endometriosis-associated ovarian cancer; M, median.

Results

According to Sampson's and Scott's criteria,[17,18] 34 were EAOC and 94 patients were non-EAOC. Table 1 summarizes clinicopathological features for both groups. The mean age of patients in EAOC group was 48.65 ± 8.98 years, whereas it was 54.39 ± 9.05 years in non-EAOC group (p = 0.002). The EAOC patients were more likely to have an earlier menarche age (p = 0.001), a higher incidence of infertility (p = 0.026) and a lower incidence of ascites (p = 0.046) than the non-EAOC patients. We also observed significant differences in dysmenorrhea (p = 0.022) and menstrual disorder (p = 0.040) between the two groups, which may explain the reason for earlier diagnosis in EAOC group. There was no obvious difference in pelvic pain (p = 0.408), abdominal distension (p = 0.391), and vaginal bleeding (p = 0.352). The majority of patients (91.18%) in EAOC group presented at earlier stage (p = 0.032) compared with those in non-EAOC group. As the pathological grade of CCC is generally regarded as high grade in the pathological results, we only compared the EC grade in two groups. Low grade tumor (G1) was more common in EAOC group (68.75%) than in non-EAOC group (51.79%), although the difference was not significant (p = 0.228).

Tumor markers in ovarian cancer mainly included serum CA125, CA199, and HE4. Serum CA125 were divided into low (<35 U/mL), middle (35–600 U/mL) and high (>600 U/mL) level. Among 128 patients, the proportion of low and middle level CA125 was higher in EAOC group than in non-EAOC group, whereas it did not show a significant difference (p = 0.105). There was also no difference in CA199 (p = 0.520) and HE4 (p = 0.369) level between the two groups.

After a median follow-up of 32.9 months (range, 0.2–-164.7 months), 10 patients (29.41%) in EAOC group versus 31 patients (32.98%) in non-EAOC group died from tumor recurrence or distant metastasis (p = 0.702). Patients with EAOC had longer overall survival time, 109.8 months (95% CI 77.085–-142.515) versus 47.4 months (95% CI 39.540–55.260) in non-EAOC patients (p = 0.011). Furthermore, the 5 year Kaplan-Meier estimate of survival rate was 67.8% in 34 patients of EAOC group and was 34.3% in 94 patients of non-EAOC group (Figure 1A, p = 0.009).

The Kaplan-Meier survival analysis showed that CA125 > 600 U/mL, presence of ascites, advanced stage (III–IV), residual tumor>1cm, and chemo-resistance were risk factors for survival, whereas association with endometriosis was a protective factor for survival (Figure 1). Cox regression analysis further confirmed that ascites (p = 0.045, HR = 2.274, 95%CI 1.020–5.069), stages III–IV (p = 0.001, HR = 3.743, 95%CI 1.683–8.327), residual tumor≥1cm (p = 0.004, HR = 3.423, 95% CI 1.470–7.970), and chemo-resistance (p = 0.000, HR = 4.300, 95% CI 1.932–9.570) could increase the death hazard ratio, but association with endometriosis (p = 0.033, HR = 0.423, 95%CI 0.192–0.933) could decrease the death hazard ratio (Table 2). The potential bias should not be ignored because early stage tumor (stages I–II) was more common in EAOC group. We further performed multi-variable Cox regression analysis after stratifying by stage, and then found association with endometriosis had no statistically significant impact on the survival (Table 3). Association with endometriosis was not an independent predictor of better survival in ovarian cancer. Chemo-resistance is related to poor prognosis of ovarian cancer patients. Next, multi-variable analysis was performed to seek factors affecting chemo-resistance. Histological type of CCC (p = 0.016, OR = 4.364, 95%CI 1.312–14.523), CA125 > 600 U/mL (p = 0.038, OR = 3.782, 95%CI 1.078–13.274), and residual tumor > 1cm (p = 0.008, OR = 8.262, 95%CI 1.743–39.155) might be high risk factors for chemo-resistance. Association with endometriosis (p = 0.535) and advanced stage (p = 0.211) seemed not relevant with chemo-resistance (Table 4).

Discussion

CCC and EC were considered as "EAOC", and thus our study mainly focused on the two histologic sub-types. In our series, the proportion of EAOC was 26.6% which is lower than that reported (33.3%) in the literature. Due to limited sampling for pathologic evaluation, it is not extensive enough to detect all foci of endometriosis adjacent to tumors. Furthermore, some ovarian tumors overgrow rapidly and replaced the original ectopic endometrium, which may lead to the disappearance of histological transition region from endometriosis into ovarian cancer.

Many studies have been performed in order to understand whether EAOC is a clinically distinct entity from non-EAOC. According to the currently accepted dualistic model of Kurman and Shih for the pathogenesis of epithelial ovarian cancer,[19] type-I tumors comprise low-grade serous, low-grade

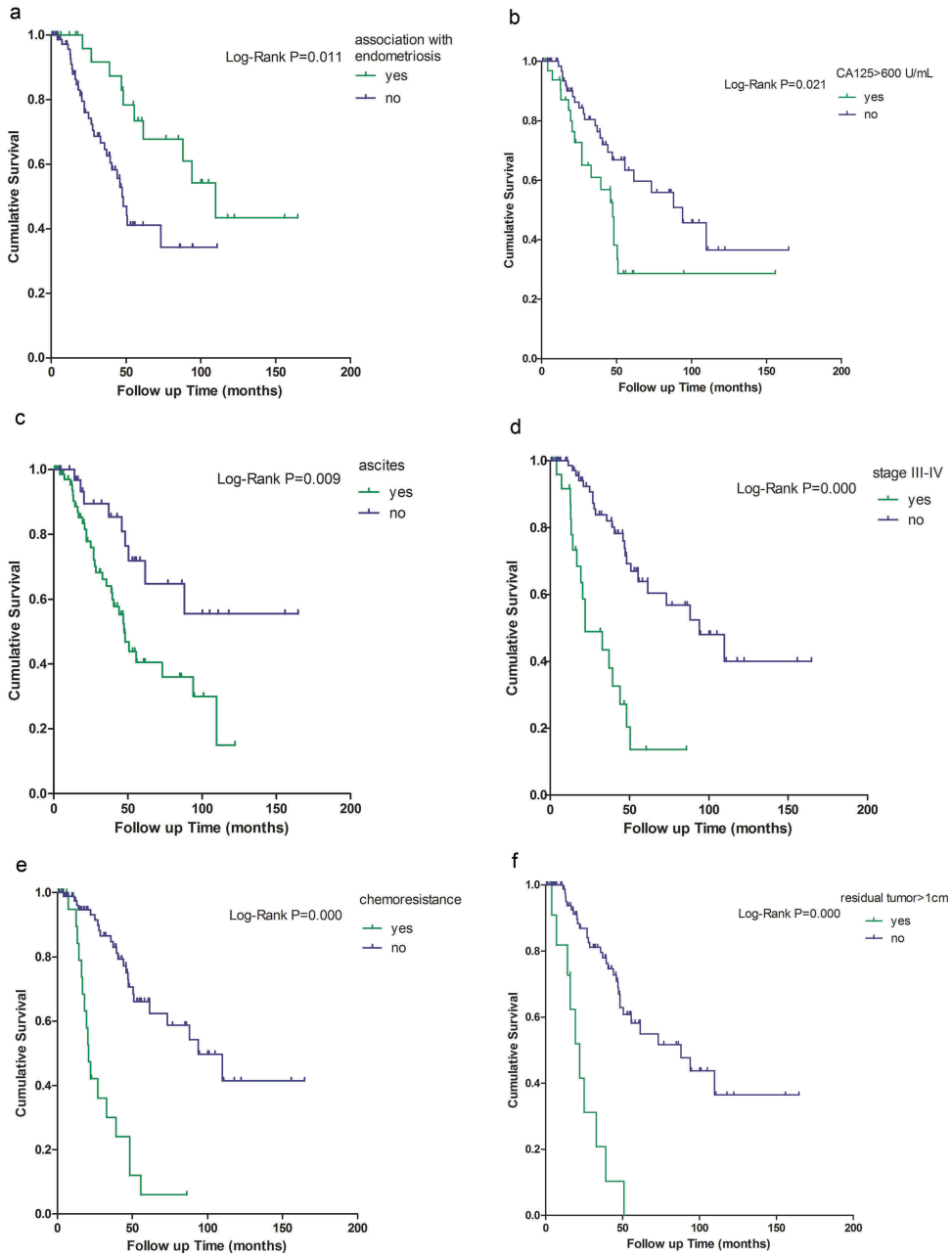

Figure 1. Multi-variable analysis of overall survival.

Kaplan-Meier survival functions in ovarian cancer associated with (A) endometriosis, (B) CA125 > 600 U/mL, (C) ascites, (D) at stage III–IV, (E) chemo-resistance, and (F) residual tumor>1cm. Log-rank $p < 0.05$ makes a significant difference at five-year survival. The censored cases precludes unequivocal conclusion.

Table 2. Variable analysis of overall survival.

	Kaplan–Meier test		Cox-regression Analysis	
variable	Log-rank *p* value	*p* value	HR	95%CI
Association with endometriosis	0.011*	0.033*	0.423	0.192–0.933
Serum CA125 > 600 U/mL	0.021*	0.346	0.702	0.337–1.464
Ascites	0.009*	0.045*	2.274	1.020–5.069
Stages III–IV	0.000*	0.001*	3.743	1.683–8.327
Chemo-resistance	0.000*	0.000*	4.300	1.932–9.570
Residual tumor > 1 cm	0.000*	0.004*	3.423	1.470–7.970
Histological type of CCC	0.610	–	–	–

*$p < 0.05$. HR, hazard ratio; CI, confidence interval.

endometrioid, clear cell, mucinous carcinomas and malignant Brenner tumors, which are usually developed in a stepwise fashion from well-established precursor lesions such as cystadenofibroma, borderline tumors, and endometriosis. Type-I tumors typically present as large masses confined to one ovary, with low stage, and have a good prognosis. Tumor cells are characterized by mutations of KRAS, BRAF, PTEN, PIK3A, ARID1A, CTNNB1 and microsatellite instability, but rare p53 activation and low chromosomal instability.[20,21] In contrast, type-II tumors comprise high-grade serous, high-grade endometrioid, malignant mixed mesodermal tumors

Table 3. Variable analysis of overall survival after stratifying for stage.

	Cox-regression analysis		
Variable	*p* value	HR	95%CI
Stages I–II			
Association with endometriosis	0.162	0.504	0.193–1.318
Serum CA125 > 600 U/mL	0.725	0.834	0.304–2.291
Ascites	0.063	2.731	0.945–7.889
Chemo-resistance	0.003*	4.300	1.633–11.323
Residual tumor > 1 cm	0.040*	3.479	1.062–11.400
Stages III–IV			
Association with endometriosis	0.037*	0.068	0.005–0.848
Serum CA125 > 600 U/mL	0.527	0.656	0.178–2.417
Ascites	0.481	1.779	0.359–8.822
Chemo-resistance	0.007*	10.120	1.882–54.415
Residual tumor > 1 cm	0.027*	3.653	1.156–11.539

*$p < 0.05$. HR, hazard ratio; CI, confidence interval.

Table 4. Variable analysis of chemo-resistance.

	Logistic regression analysis		
variable	*p*	OR	95%CI
Association with endometriosis	0.535	1.494	0.421–5.299
Histological type of CCC	0.016*	4.364	1.312–14.523
Serum CA125 > 600 U/mL	0.038*	3.782	1.078–13.274
Residual tumors>1 cm	0.008*	8.262	1.743–39.155
Stages III–IV	0.211	2.277	0.628–8.260

*$p < 0.05$. OR, odds ratio; CI, confidence interval.

(carcinosarcomas), and undifferentiated carcinomas. They are not associated with the morphologically detectable precursor lesions but highly aggressive present in advanced stage.

The EAOC patients were more likely to exhibit the favorable features of type I tumors, often being diagnosed at a younger age, an earlier stage, a better prognosis, and are related to nulliparity and infertility.[22,23] Although there was no significant difference in EC grade between the two groups due to small sample size, the trend could be observed from lower grade tumors in EAOC that type-I tumors were more frequent among those with EAOC; on the contrary, type-II tumors were more frequent high-grade in the non-EAOC group. The interpretation of these potential observations on clinicopathological features was that EAOC might represent a single entity distinct from ovarian cancer without endometriosis.

In this study, EAOC was significantly more frequently diagnosed at an early stage, consistent with previous findings. As one typical symptom of patients with endometriosis, the incidence of dysmenorrhea in the group of EAOC was higher than non-EAOC. It is possible that women with associated endometriosis seek medical help because of their symptoms and were incidentally found to have ovarian cancer; on the other hand, patients without associated endometriosis may have significant symptoms only in later stages. That could explain why most EAOC patients were diagnosed at an earlier stage. We also found menarche age in females of EAOC group was earlier than that of non-EAOC group. A meta-analysis suggested that early age at menarche was associated with a very modest increase in endometriosis risk.[24] Earlier menarche age may increase opportunities for retrograde menstruation, resulting in the increased incidence of endometriosis and thus EAOC. Infertility was another symptom of endometriosis and infertility rate in ovarian cancer with endometriosis was significantly higher than the group without endometriosis.[25] Brinton found that among infertile women, a significantly higher prevalence of ovarian cancer in these patients with endometriosis than the general population without endometriosis.[26] Stewart further reported that the risk of ovarian cancer was decreased if women diagnosed with endometriosis had children.[27]

Serum CA125 is the most commonly measured tumor marker for epithelial ovarian cancers. It is also elevated in conditions of endometriosis, uterine adenomyosis, pelvic inflammatory disease. We recorded no statistically significant difference in the preoperative serum CA125 between the EAOC and non-EAOC groups. This is consistent with previous studies.[28,29] While Wang and Lim found that patients with EAOCs had significantly lower levels of CA125,[30,31] a high level (over 200 U/mL) and/or rapid rise of serum CA125 levels should make one highly suspicious of the eventual development of EAOC in a woman with endometriosis.[32] In addition to CA125, human epididymis protein 4 (HE4) is also used in ovarian cancer screening. HE4 is highly elevated in specific subtypes of ovarian cancers.[33] In our study, no significant differences of HE4 level were observed in the two groups. One possible reason is that serum HE4 is elevated in malignant ovarian diseases, whereas it remains normal in all benign lesions, including endometriosis.[33]

In patients with EAOCs, a significantly longer overall survival was recorded, both in our and in other studies.[1,22] Meanwhile, we observed a higher 5-year survival rate for EAOC compared with the non-EAOC group. In multi-variable analysis of overall survival, association with endometriosis and advanced stages (III–IV) had a statistically significant impact on the survival. To understood further whether the impact of association with endometriosis on the survival was unexpected due to stage variance, multi-variable Cox regression analysis of survival after stratifying for stage was chosen. We had not found survival difference at both early and advanced stage. The best explanation for this is that association with endometriosis leads to a higher prevalence of early-stage and low-grade tumors, and thus a much better survival rate than non-EAOC. These survival analysis findings showed that stage at diagnosis seems to be more important to prognosis than association with endometriosis alone, which is consistent with findings of previous studies.[34]

Poor prognosis of epithelial ovarian cancers is closely related to chemo-resistance. In our study, we found that chemo-resistance is a risk factor for overall survival. For patients with epithelial ovarian cancer, recommended postoperative treatment is still the standard intravenous taxane-carboplatin regimens (with paclitaxel or docetaxel).[35] Most CCC patients are resistant to taxane, or platinum-based chemotherapy, which may be associated with decreased drug accumulation, increased drug detoxification, an increased DNA repair activity, and low cell proliferation.[36] As endometriosis develops to EAOC, many resistance-related protein expressions such as mismatch repair protein, hMLH1 protein, and XRCC5 may change, and thus decrease drug resistance.[37-39] However, no significant difference in chemo-resistance was observed between EAOC and non-EAOC groups as to parity via logistic regression analysis in our study (Table 4). One possible reason is the small sample size. The other possible

reason is that we may actually have missed some cases of EAOC because of lacking malignant transformation point. The relationship of association with endometriosis in ovarian cancers and chemo-resistance needs to be further explored to look for potential molecular targets for decreasing clinical drug resistance.

In conclusion, EAOC has different clinicopathological features compared to non-EAOC. EAOC appears to confer a better overall survival which may be related to the earlier stage. Despite the fact that no differences in chemo-resistance are observed, detection of the resistance-related proteins may be a basis for a targeted therapy, and the clinical and therapeutic significance of these findings need be supported by further research.

Patients and methods

The study includes patients with CCC and EC diagnosed in the department of obstetrics and gynecology of Tianjin Medical University General Hospital between 2002 and 2017. All patients underwent hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymph node resection at our center according to national comprehensive cancer network (NCCN) guideline. Most patients received platinum-based chemotherapy after surgery. Patients were considered to be chemotherapy-resistant if the duration from completion of the last regimen to tumor recurrence was less than 6 months or tumor progressed during chemotherapy. Patients receiving neoadjuvant chemotherapy were excluded. The study was approved by the Institute Research Ethics Committee of Tianjin Medical University General Hospital.

A histologic review of all cases was performed by experienced gynecologic pathologists at our institution. The criteria defined cases associated with endometriosis which included that: (1) tumor is adjacent to unequivocal foci of endometriosis, (2) absence of any other primary tumor, (3) the presence of tissue resembling endometrial stroma surrounding epithelial glands.[17] Scott added a transition from endometriosis to neoplastic epithelium (or stromal component) to the criteria.[18] According to Sampson's and Scott's criteria, cases were divided into two groups. Thirty-four of the patients were found to be associated with endometriosis, the remaining ninety-four patients were considered as ovarian cancer not associated with endometriosis. All patients were followed up to December 2017.

The following data were collected in a tabulated manner: age, personal history, symptoms, presence or absence of ascites, diameter of tumor, pathological type, grade, and stage of the tumor, and preoperative level of serum CA125 and HE4.

Statistical analysis was performed for determining the significance values using SPSS 21.0 (IBM Corp.,Armonk,NY, USA). A descriptive analysis was performed to describe the two groups. Differences in means for age were evaluated for significance using two independent sample t tests. The non-normal distribution data such as menarche, tumor diameter, CA199, and HE4 level, was evaluated for significance using the Mann-Whitney test. The difference in proportions for categorical variables, including menopausal status, infertility, dysmenorrhea, pelvic pain, abdominal distension, menstrual disorder, vaginal bleeding, histology, FIGO stage, EC grade, and ascites were evaluated for significance using $\chi 2$ test or Fisher exact test. Differences for ranked data like CA125 level were evaluated for significance using the rank-sum test. Kaplan–Meier test and Cox regression analysis were used to determine survival prognostic factors. Multiple factors of chemotherapy response were analyzed using logistic regression model. A p value <0.05 was accepted as statistically significant.

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Conflict of interest

The authors are financially independent and have no potential conflict of interest.

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