Clinical Characteristics and Prognosis of Ovarian Clear Cell Carcinoma: a Retrospective Study of 112 Patients in Beijing

Huimei Zhou
Peking Union Medical College Hospital
Qian Liu
Department of Gynaecologic Oncology, Pekinig Union Medical College Hospital
Xiaohua Shi
Department of Gynaecologic Oncology, Peking Union Medical Hospital
Jiaxin Yang (yangjiaxin@pumch.cn)
Peking Union Medical College Hospital
Dongyan Cao
Peking Union Medical College Hospital
Tao Wang
Peking Union Medical College Hospital
Keng Shen
Peking Union Medical College Hospital

Research

Keywords: Ovarian clear cell carcinoma, Recurrence, Prognosis, Adjuvant chemotherapy, China

Posted Date: December 23rd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-132769/v1

Abstract

Objectives

This retrospective study aimed to evaluate the clinical characteristics and prognosis of ovarian clear cell carcinoma (OCCC) and to further explore the monitoring value of cancer antigen 125 (CA-125).

Methods

The medical records of 112 OCCC patients who were treated in Peking Union Medical College Hospital (PUMCH) between 2014 and 2019 were collected and reviewed, and data such as age, Federation of Gynecology and Obstetrics (FIGO) stage, CA-125 level, treatment, recurrence, and death were extracted.

Outcomes

The median patient age was 50 (45, 57) years. Sixty (53.57%) patients were in stage I, 13 (11.61%) patients were in stage II, 22 (28.57%) patients were in stage III, and 7 (6.25%) patients were in stage IV. In total, 109 (97.32%) patients received adjuvant chemotherapy. The median chemotherapy cycles of CA-125 normalization was 2 (0, 3). The 1-year and 3-year progression-free survival (PFS) rates were 87.85% and 72.90%, respectively. The median PFS1 duration was 19 (11, 35) months, and the median overall survival (OS) duration was 24 (13, 40) months. Recurrence occurred in 32 patients, of whom 7 (21.88%) developed platinum-resistant recurrence. Fifty percent of relapsed patients had a CA-125 level<35 IU/ml at the time of relapse. Nine (28.13%) patients experienced a second recurrence. In the multivariate Cox regression analysis, the Chemotherapy cycles of CA-125 normalization remained nonsignificant for stage I (P=0.003, HR 4.287, 95% CI=1.632–11.258) and stage III (P=0.003, HR 4.287, 95% CI=1.632–11.258) disease. Multivariate Cox regression showed that platinum resistance was an independent factor for PFS2 (*P*=0.008, HR 11.562, 95% CI=1.873–71.353).

Conclusions

FIGO stage and chemotherapy resistance are independent risk factors for prognosis. CA-125 levels following treatment are a valid indicator for treatment monitoring. Regardless of chemosensitivity to CA-125, CA-125 normalization before chemotherapy cycle 2 may not be a distinct inflection point for PFS and OS.

Background

As a form of epithelial ovarian cancer (EOC), ovarian clear cell carcinoma (OCCC) shows distinctive epidemiological and clinical characteristics.[1] In Asia, OCCC accounts for 11.6% (Korea)[2] and 30% (Japan)[3] of all EOCs, surpassing 6% in the United States[4]. In addition, its probability is on the rise, with an observed increase from 3.56% in 1979–1984 to 18.13% in 2005–2008 in Taiwan[5] and from 23.4% in 2010 to 29.1% as of 2010 in Japan[3]. The clinical management of OCCC consists of cytoreductive surgery

followed by platinum- and taxane-based chemotherapy[6]. Compared to other EOCs, due to the relative resistance of OCCC to platinum drugs, the efficacy of platinum-based chemotherapy is less than 40% for patients in stage III/IV.[7] The clinical outcomes of patients with advanced OCCC are dismal. Regarding stage I/II disease, the one-year survival rate of patients with OCCC and other histotypes is no less than 80%, while for stage III/IV disease, the one-year and five-year survival rates of patients with OCCC are 60% and 22%, respectively, which are lower than those of patients with other histotypes (80% and 35%, respectively).[8] For patients who experience recurrence, the 5-year post-recurrence survival rate is only 13.2%.[9] Given the prevalence and poor prognosis of OCCC in Asia, we retrospectively analysed OCCC patients who visited Peking Union Medical College Hospital (PUMCH) between 2015 and 2019, aimed to describe the treatment methods, recurrence rate and survival rate of OCCC patients and to determine risk factors for the recurrence and survival of OCCC patients.

Methods

Patients and data collection

This retrospective single-centre study used essentially the same method as the two-academic-Institute study published in Oncotarget in 2016[10]. We reviewed patients with OCCC (International Federation of Gynecology and Obstetrics [FIGO] stage I – IV) who received treatment at PUMCH (Beijing, China) between 2015 and 2019. We excluded OCCC patients who chose fertility-preserving surgery.

We extracted and evaluated the following information from medical records: demographic and pathological characteristics, immunohistochemistry indicators (Napsin A, HNF1B), stage at diagnosis, surgery, subsequent systemic chemotherapy, recurrence and disease status at last contact. Serum cancer antigen 125 (CA-125) levels were measured using a radioimmunoassay kit (Roche F170 Modular system). The commonly accepted normal upper limit for CA-125 is 35 U/ml. Serum CA-125 levels were measured at the time of the first attack, preoperation and post-operation, at each cycle of chemotherapy, and at each contact during the follow-up period. The need for informed consent was waived because of the retrospective nature of the study. The study protocol was approved by the Ethics Committee of PUMCH.

Main outcome indicators

Progression-free survival 1 (PFS1) and overall survival (OS) were defined as the time intervals from the date of the primary surgery to the date of first recurrence and death or last contact, respectively[11]. Progression-free survival 2 (PFS2) was defined as the time interval from the date of the second surgery or chemotherapy to the date of second recurrence and death or last contact. Patients were considered to have platinum-resistant disease if the interval time was less than 6 months from the completion of the last platinum-based chemotherapy to disease recurrence, and the patients were considered to have platinum-sensitive disease if the time exceeded 6 months.

Statistical analysis

Statistical analysis was performed using SAS V9.3. The distributions of clinicopathologic events were evaluated using the chi-square test or Fisher's exact test. The Wilcoxon rank-sum test or the Kruskal-Wallis H test was used to determine the distribution of continuous variables between groups. The survival curves were compared by employing the log-rank test. A Cox proportional hazards model was used to evaluate the independent factors affecting survival. A *P* value < 0.05 was considered significant.

Outcomes

1. Patient characteristics

The baseline characteristics of the patients are summarized in Table 1. The median patient age was 50 (45, 57) years. Fifty-four (48.21%) patients had a CA-125 level at diagnosis less than 35 IU/ml. Sixteen (14.29%) patients received primary chemotherapy, and 109 (97.32%) patients received chemotherapy. The median chemotherapy cycles of CA-125 normalization was 2 (0, 3). The median follow-up time of 112 patients was 23 months (12.50, 39.50). Napsin A and HNF1B were negative in 9% of patients. The 1-year e and 3-year PFS rates were 87.85% and 72.90%, respectively. The median PFS duration was 19 months (11, 35), and the median OS duration was 24 (13 40) months. Pretreatment CA-125 levels, chemotherapy cycles of CA-125 levels normalization, number of chemotherapy cycles, disease status at the last follow-up, 1-year PFS rate, 3-year PFS rate, 3-year OS rate, and PFS were significantly different according to different FIGO stages.

2. Characteristics of patients who experienced recurrence

Table 2 lists the characteristics of 32 patients who experienced recurrence, of whom 7 (21.88%) had platinum-resistant recurrence. Fifty percent of patients who experienced recurrence had a CA-125 level < 35 U/ml at the time of recurrence. Twenty-one (65.63%) patients underwent a second cytoreductive operation, and 9 (28.13%) patients experienced a second recurrence. The median PFS2 values for stages I, II, III, and IV were 7.00 (3.00, 24.00), 3.00 (2.50, 7.00), 8.50 (3.00, 15.00), and 14.00 (8.00, 36.00), respectively.

3. Survival analysis

Log-rank tests showed that the median PFS1 durations of stage I and stage II-IV disease were significantly different (57 months vs 21 months, P = 0.0003). The median PFS1 durations were also significantly different (17 months vs 54 months, P = 0.0019) between patients who received > 6 and ≤ 6 chemotherapy cycles (supplemental material-Figures 1, 2). Univariate Cox analysis showed that FIGO stage (P = 0.001, HR: 3.57, 95% CI = 1.72–7.41), number of chemotherapy cycles (P = 0.004, HR: 3.23, 95% CI = 1.47–7.08) and chemotherapy cycles of CA-125 normalization (P = 0.004, HR: 3.98, 95% CI = 1.57–7.08) were positive predictors of PFS1. After adjusting for FIGO stage and age, these variables were not significant. In the multivariate Cox regression analysis, chemotherapy cycles of CA-125 normalization remained nonsignificant in patients in stage I (*P* = 0.319, HR 2.26, 95% CI = 0.45–11.27) and stage III (*P* = 0.965, HR 1.03, 95% CI = 0.27–3.89). (supplemental material-Table 4)

Log-rank tests also showed a statistically significant difference in the median PFS2 durations between platinum-resistant relapsed patients and non-platinum-resistant relapsed patients (8 months vs 19 months, P = 0.0020) (supplemental material-Figure 3). Multivariate Cox regression showed that platinum resistance was an independent factor for PFS2 (*P* = 0.008, HR 11.562, 95% CI = 1.873–71.353) (supplemental material-Table 5).

Discussion

This study is one of the largest retrospective series of OCCC patients in which data were collected from patients at diagnosis to second recurrence. We mainly described the stage composition, recurrence status, and PFS of OCCC patients and found that FIGO stage and chemotherapy resistance are independent risk factors for prognosis. We also aimed to explain the limitations associated with CA-125 in the staging and recurrence monitoring of OCCC. The limitations of CA-125 in patients with FIGO stage I and those who experience recurrence are highlighted.

Among the 112 patients included, 53.57% were in stage I and 28.57% were in stage III, which is similar to the results of a national study performed in South Korea[2] but quite different from other single-centre studies[6 7]. All patients underwent staging or cytoreductive surgery. Except for one patient who refused chemotherapy after surgery, all the other patients received platinum chemotherapy drugs. Approximately 1/4 of patients in stage III/IV receive advanced chemotherapy, although we found that advanced chemotherapy is not beneficial to prognosis. It is worth noting that the one-year PFS rate of patients with stage I, II and III disease was approximately 90%, and the three-year PFS rate varied greatly, with 86.44% for patients in stage I, 66.67% for patients in stage II, and 66.67% for patients in stage III 56.67%. These three indicators were slightly higher than the national research data of South Korea. Staging has been confirmed as a risk factor for the prognosis of OCCC in many studies, so I will not repeat it here. OCCC patients with platinum-resistant recurrence had a shorter PFS duration than those with platinum-sensitive recurrence (8 months vs 19 months). The median survival duration with single-agent chemotherapy and bevacizumab does not exceed 16 months[12]. Most other chemotherapy regimens are almost ineffective.[11] A recent study summarized the biological rationale and available clinical data on immunotherapy in platinum-resistant ovarian cancer and discussed the challenges and future areas of research in the field[13].

In contrast to other studies[10 14], we found that the monitoring of CA-125 is of limited significance and has no predictive significance for prognosis.[10 14] We previously published a study in which OCCC patients who visited PUMCH between 1993 and 2013 were analysed and found that CA-125 levels following treatment were a valid indicator for treatment monitoring[10]. Although the same method was used, in the current study, we obtained a negative result, that is, the normalization of CA-125 levels before 2 cycles of chemotherapy does not affect PFS or OS. This may be because the samples we collected are different. In addition, we found that 61.11% of stage I patients had CA-125 levels in the normal range when they first became ill. During treatment, there was no difference in the number of courses of chemotherapy or

prognosis between these patients and other stage I patients, and 72.73% of these patients had normal CA-125 levels after surgery or 1 course of chemotherapy. Therefore, we believe that for patients who are not sensitive to the CA-125 test the first time, ultrasound, CT or MRI should be considered first. Importantly, an examination can reduce the disease burden on patients. In contrast to stage I patients, 76.67% of stage III patients had CA-125 levels greater than 35 IU/ml. We believe these patients are more suitable for CA-125 monitoring. Moreover, 50% of patients who experienced recurrence had CA-125 levels in the normal range, which further showed that monitoring CA-125 levels is of limited significance and may delay the discovery of recurrence.

We verified the value of Napsin A and HNF1B in the diagnosis of OCCC by calculating the false positive rate. In 2013, Skirnisdottir I[15] proposed that the positivity of Napsin A is helpful for the diagnosis of OCCC. In 2020, Fatemeh Nili[16] reported that the sensitivity of Napsin A in the diagnosis of OCCC was 85%. However, we found that 39.62% of patients were still negative for Napsin A. Only 15% of patients were negative for HNF1B, which is consistent with Wenbin Huang's findings[17]. We combined the two indicators and found that the false positive rate was 9%. It is also worth noting that patients who were in remission had a shorter follow-up time than patients who relapsed (22.50 vs 33.00), (not shown in the table due to space reasons). There is no doubt that disease monitoring has been gradually relaxed in these patients. We believe that clinicians should provide patients with continuous follow-up to detect disease recurrence in advance and intervene as soon as possible.

The patients included in the current study were from economically developed areas in China, and they had satisfactory economic and medical conditions, which suggests that in poor areas in China, the accessibility of treatment and prognosis may be worse. Due to the habit of case writing, clinicians are accustomed to recording key CA-125 values, such as preoperative CA-125 values and chemotherapy cycles of CA-125 normalization. CA-125 values that do not exhibit major changes, such as those after each chemotherapy procedure, cannot be obtained and are thus not conducive to our discussion of the monitoring value of CA-125.

Conclusion

FIGO stage and chemotherapy resistance are independent risk factors for prognosis. CA-125 levels following treatment are a valid indicator for treatment monitoring. Regardless of chemosensitivity to CA-125, CA-125 normalization before chemotherapy cycle 2 may not be a distinct inflection point for PFS and OS.

Abbreviations

OCCC: ovarian clear cell carcinoma;

CA-125: cancer antigen 125;

FIGO: International Federation of Obstetrics and Gynecology;

HR: hazardratio;

PFS: progression-free survival;

OS: overall survival

Declarations

Funding Statement

This study was funded by the Chinese Academy of Medical Sciences Initiative of Innovative Medicine (CAMS-2017-I2M-1-002).

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of PUMCH.

Author Contributions

Huimei Zhou designed the study, performed the data analyses and wrote the manuscript. Qian Liu performed the data analyses and revised the manuscript. Jiaxin Yang designed the study, performed the data analyses, revised the manuscript and approved the final version of the manuscript. Xiaohua Shi, Dongyan Cao, Tao Wang and Keng Shen collected and reviewed the data and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

References

1. Fujiwara K, Shintani D, Nishikawa T. Clear-cell carcinoma of the ovary. *Annals of oncology : official journal of the European Society for Medical Oncology* 2016;27 Suppl 1:i50-i52. doi: 10.1093/annonc/mdw086 [published Online First: 2016/05/04]
2. Lee HY, Hong JH, Byun JH, et al. Clinical Characteristics of Clear Cell Ovarian Cancer: A Retrospective Multicenter Experience of 308 Patients in South Korea. *Cancer research and treatment : official journal of Korean Cancer Association* 2020;52(1):277-83. doi: 10.4143/crt.2019.292 [published Online First: 2019/07/20]
3. Machida H, Matsuo K, Yamagami W, et al. Trends and characteristics of epithelial ovarian cancer in Japan between 2002 and 2015: A JSGO-JSOG joint study. *Gynecologic oncology* 2019;153(3):589-96. doi: 10.1016/j.ygyno.2019.03.243 [published Online First: 2019/03/25]
4. Torre LA, Trabert B, DeSantis CE, et al. Ovarian cancer statistics, 2018. *CA: a cancer journal for clinicians* 2018;68(4):284-96. doi: 10.3322/caac.21456 [published Online First: 2018/05/29]

5. Chiang YC, Chen CA, Chiang CJ, et al. Trends in incidence and survival outcome of epithelial ovarian cancer: 30-year national population-based registry in Taiwan. *Journal of gynecologic oncology* 2013;24(4):342-51. doi: 10.3802/jgo.2013.24.4.342 [published Online First: 2013/10/30]
6. Huang HJ, Yang LY, Tung HJ, et al. Management and clinical outcomes of patients with recurrent/progressive ovarian clear cell carcinoma. *Journal of the Formosan Medical Association = Taiwan yi zhi* 2020;119(4):793-804. doi: 10.1016/j.jfma.2019.11.018 [published Online First: 2019/12/11]
7. Tang H, Liu Y, Wang X, et al. Clear cell carcinoma of the ovary: Clinicopathologic features and outcomes in a Chinese cohort. *Medicine* 2018;97(21):e10881. doi: 10.1097/md.0000000000010881 [published Online First: 2018/05/26]
8. Peres LC, Cushing-Haugen KL, Köbel M, et al. Invasive Epithelial Ovarian Cancer Survival by Histotype and Disease Stage. *Journal of the National Cancer Institute* 2019;111(1):60-68. doi: 10.1093/jnci/djy071 [published Online First: 2018/05/03]
9. Kajiyama H, Shibata K, Mizuno M, et al. Postrecurrent oncologic outcome of patients with ovarian clear cell carcinoma. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* 2012;22(5):801-6. doi: 10.1097/IGC.0b013e3182540145 [published Online First: 2012/05/24]
10. Bai H, Sha G, Xiao M, et al. The prognostic value of pretreatment CA-125 levels and CA-125 normalization in ovarian clear cell carcinoma: a two-academic-institute study. *Oncotarget* 2016;7(13):15566-76. doi: 10.18632/oncotarget.7216 [published Online First: 2016/02/11]
11. Ye S, Zhou S, Chen W, et al. Recurrence Patterns and Survival Outcomes in Chinese Patients with Surgically Treated Recurrent Ovarian Clear Cell Carcinoma: A Single Institutional Analysis of 45 Cases. *Cancer management and research* 2020;12:913-19. doi: 10.2147/cmar.s242129 [published Online First: 2020/02/28]
12. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2014;32(13):1302-8. doi: 10.1200/jco.2013.51.4489 [published Online First: 2014/03/19]
13. Le Saux O, Ray-Coquard I, Labidi-Galy SI. Challenges for immunotherapy for the treatment of platinum resistant ovarian cancer. *Seminars in cancer biology* 2020 doi: 10.1016/j.semcancer.2020.08.017 [published Online First: 2020/09/16]
14. Gadducci A, Notarnicola M, Menichetti A, et al. Has serum CA 125 assay at the time of relapse a prognostic relevance for patients with recurrent ovarian carcinoma after primary cytoreduction and platinum- and paclitaxel-based chemotherapy? *European journal of gynaecological oncology* 2016;37(2):182-8. [published Online First: 2016/05/14]
15. Skirnisdottir I, Bjersand K, Akerud H, et al. Napsin A as a marker of clear cell ovarian carcinoma. *BMC cancer* 2013;13:524. doi: 10.1186/1471-2407-13-524 [published Online First: 2013/11/07]

16. Nili F, Tavakoli M, Izadi Mood N, et al. Napsin-A Expression, a Reliable Immunohistochemical Marker for Diagnosis of Ovarian and Endometrial Clear Cell Carcinomas. *Iranian journal of pathology* 2020;15(2):81-85. doi: 10.30699/ijp.2020.106598.2222 [published Online First: 2020/03/28]
17. Huang W, Cheng X, Ji J, et al. The Application Value of HNF-1β Transcription Factor in the Diagnosis of Ovarian Clear Cell Carcinoma. *International journal of gynecological pathology : official journal of the International Society of Gynecological Pathologists* 2016;35(1):66-71. doi: 10.1097/pgp.0000000000000213 [published Online First: 2015/07/15]

Tables

Table 1
Patient characteristics

Characteristic	Stage I (N = 60)	Stage II (N = 13)	Stage III (N = 32)	Stage IV (N = 7)	All (N = 112)	Statistics	P-value
Age at diagnosis, years, median (range)	49 (42.50, 56)	52.50 (45.50, 56.50)	49.50 (46.50, 57.50)	59 (47, 64)	50 (45, 57)	3.47*	0.3245
Pretreatment CA-125 level, IU/ml						22.23#	< 0.0001
<35, n (%)	36 (66.67)	3 (25.00)	5 (16.67)	2 (33.33)	46 (45.10)		
≥35, n (%)	18 (33.33)	9 (75.00)	25 (83.33)	4 (66.67)	56 (54.90)		
Primary chemotherapy						7.23#	0.0648
No, n (%)	54 (90)	13 (100.0)	24 (75)	5 (71.43)	96 (85.71)		
Yes, n (%)	6 (10)	0 (0)	8 (25)	2 (28.57)	16 (14.29)		
Chemotherapy cycles of CA-125 normalization, median (range, cycles)	1 (0, 2)	2 (2, 3)	2 (2, 4)	1.50 (0, 3)	2 (0, 3)	14.67*	0.0021
Received chemotherapy						1.71*	0.6355
Yes, n (%)	59 (98.33)	12 (92.31)	31 (96.88)	7 (100.0)	109 (97.32)		
No, n (%)	1 (1.67)	1 (7.69)	1 (3.13)	0 (0.00)	3 (2.68)		
Number of chemotherapy cycles, median (range)	6 (3.50,6)	5 (5, 6)	6 (5.50, 8)	5 (5, 8)	6 (4, 6)	11.23*	0.0105
Napsin A						0.22#	0.9739
+, n (%)	16 (61.54)	5 (55.56)	10 (62.50)	1 (50)	32 (60.38)		

*: Kruskal-Wallis H test; #: chi-square test

Characteristic	Stage I	Stage II	Stage III	Stage IV	All	Statistics	P-value
	(N = 60)	(N = 13)	(N = 32)	(N = 7)	(N = 112)		
-, n (%)	10 (38.46)	4 (44.44)	6 (37.50)	1 (50)	21 (39.62)		
HNF1B						0.52#	0.9138
+, n (%)	15 (83.33)	4 (80)	13 (86.67)	2 (100.0)	34 (85)		
-, n (%)	3 (16.67)	1 (20)	2 (13.33)	0 (0)	6 (15)		
Napsin A and HNF1B						4.97#	0.5473
++, n (%)	10 (62.50)	3 (75.00)	7 (58.33)	0 (0.00)	20 (60.61)		
+-, n (%)	5 (31.25)	0 (0.00)	4 (33.33)	1 (100.0)	10 (30.30)		
–, n (%)	1 (6.25)	1 (25.00)	1 (8.33)	0 (0.00)	3 (9.09)		
Disease status at the last follow-up						32.22#	< 0.0010
Alive with disease, n (%)	7 (11.67)	4 (30.77)	16 (50)	2 (28.57)	29 (25.89)		
Alive, n (%)	51 (85)	8 (61.54)	13 (40.63)	2 (28.57)	74 (66.07)		
Dead, n (%)	2 (3.33)	1 (7.69)	3 (9.38)	3 (42.86)	9 (8.04)		
Follow-up time (months), median (range)	27.50 (14, 41)	20 (11, 35)	18.50 (7.50, 38.50)	19 (13, 51)	23 (12.50, 39.50)	2.76*	0.4304
1-year PFS rate, n (%)	53 (89.83)	11 (91.67)	27 (90)	3 (50)	94 (87.85)	8.56#	0.0357
3-year PFS rate, n (%)	51 (c	8 (66.67)	17 (56.67)	2 (33.33)	78 (72.90)	14.47#	0.0023
1-year OS rate, n (%)	58 (98.31)	12 (100.0)	29 (96.67)	5 (83.33)	104 (97.20)	4.87#	0.1812
3-year OS rate, n (%)	57 (96.61)	12 (100.0)	28 (93.33)	3 (50)	100 (93.46)	20.33#	0.0010

*: Kruskal-Wallis H test; #: chi-square test

Characteristic	Stage I	Stage II	Stage III	Stage IV	All	Statistics	P-value
	(N = 60)	(N = 13)	(N = 32)	(N = 7)	(N = 112)		
PFS, median (range)	26 (11, 38)	23 (12, 32.50)	14 (8, 20)	12 (10, 16)	19 (11, 35)	8.06*	0.0449
OS, median (range)	26 (14, 41)	23 (13.50, 37)	19.50 (9, 40)	19 (13, 51)	24 (13, 40)	1.24*	0.7443
*: Kruskal-Wallis H test; #: chi-square test							

Table 2
Characteristics of patients who experienced recurrence

Characteristic	Stage I	Stage II	Stage III	Stage IV	All	Statistics	P-value
	(N = 11)	(N = 4)	(N = 14)	(N = 3)	(N = 32)		
Platinum resistance						3.38#	0.3363
Yes, n (%)	4 (36.36)	1 (25.00)	1 (7.14)	1 (33.33)	7 (21.88)		
No, n (%)	7 (63.64)	3 (75.00)	13 (92.86)	2 (66.67)	25 (78.13)		
CA-125 level at recurrence						2.44#	0.4867
<35, n (%)	7 (63.64)	1 (25.00)	6 (42.86)	2 (66.67)	16 (50.00)		
≥35, n (%)	4 (36.36)	3 (75.00)	8 (57.14)	1 (33.33)	16 (50.00)		
Second cytoreductive operation						5.07#	0.167
Yes, n (%)	10 (90.91)	2 (50.00)	7 (50.00)	2 (66.67)	21 (65.63)		
No, n (%)	1 (9.09)	2 (50.00)	7 (50.00)	1 (33.33)	11 (34.38)		
Second recurrence						6.89#	0.0755
Yes, n (%)	1 (9.09)	0 (0.00)	7 (50.00)	1 (33.33)	9 (28.13)		
No, n (%)	10 (90.91)	4 (100.0)	7 (50.00)	2 (66.67)	23 (71.88)		
PFS2	7.00 (3.00, 24.00)	3.00 (2.50, 7.00)	8.50 (3.00, 15.00)	14.00 (8.00, 36.00)	8.00 (3.00, 14.50)	3.26*	0.3531

*: Kruskal-Wallis H test; #: chi-square test

Table 3
Survival analyses of PFS1

Parameter	Univariate		Multivariate*	
	HR	P-value	HR	P-value
FIGO stage (II-IV vs I)	3.57 (1.72, 7.41)	0.001	——	——
Age at diagnosis (> 50 vs ≤ 50)	0.88 (0.44, 1.76)	0.717	——	——
CA-125 level at diagnosis (≥ 35 vs < 35)	2.56 (0.76, 8.7)	0.131	1.23 (0.6, 2.51)	0.567
Primary chemotherapy (Yes vs No)	1.04 (0.41, 2.6)	0.941	0.6 (0.22, 1.65)	0.319
Number of chemotherapy cycles (> 6 vs ≤ 6)	3.23 (1.47, 7.08)	0.004	2.1 (0.91, 4.84)	0.080
chemotherapy cycles of CA-125 normalization (> 1 vs ≤ 1)	3.98 (1.57, 10.09)	0.004	2.71 (0.99, 7.38)	0.052
* Multivariate Cox regression adjusted for FIGO stage and age; HR: hazard ratio				

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementalmaterial3figures.docx