Clear cell carcinoma of the ovary
Clinicopathologic features and outcomes in a Chinese cohort

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Abstract
This retrospective analysis aimed to clarify the clinical and pathologic features of ovarian clear cell carcinoma (OCCC), and to determine the factors predictive of survival.

Data waereextracted from OCCC patients who underwent primary surgery followed by adjuvant chemotherapy in Obstetrics & Gynecology Hospital of Fudan University between January2007 and December 2014. Kaplan-Meier survival estimates and Cox proportional hazards model were used for survival analyses.

Of 130 patients (mean age = 56.2 years), 66.2% had stage I disease when the 5-year overall survival and 5-year disease-free survival were 89.2% and 88.1%, respectively. Patients frequently presented with large pelvic mass (>10 cm) and mild-to-moderate elevation of serological CA125 ($\leq$200U/mL). 60.7% of the cases at stage III/IV exhibited resistance to platinum-based chemotherapy; 37.69% of the tumors arose from endometriosis. On multivariate analysis, stage and chemoresistance were independent prognostic factors predictive for poorer survival. Survival at stage IC_1 (surgical rupture) was comparable to that at stage IA (capsule intact), whereas survival at stage IC_2/IC_3 (rupture before surgery) was significantly worse than that at stage IA.

OCCC shows distinct features compared to other epithelial ovarian cancers. FIGO stage and response to chemotherapy affect prognosis independently. Arising from endometriosis is not associated with better survival. Preoperative rupture rather than intraoperative rupture confers an adverse prognosis in otherwise stage IA disease.

Abbreviations: AUC = area under the curve, DFS = disease-free survival, EOC = Epithelial ovarian carcinoma, FIGO = International Federation of Gynecology and Obstetrics, HGSC = high-grade serous carcinoma, OCCC = ovarian clear cell carcinoma, OS = overall survival.

Keywords: chemoresistance, clear cell, ovarian carcinoma, prognosis, stage, survival

1. Introduction

Epithelial ovarian carcinoma (EOC) is the most lethal gynecologic malignancy.[1] It consists of different histologic subtypes including high-grade serous, clear cell, endometrioid, low-grade serous, and mucinous.[2] Ovarian clear cell carcinoma (OCCC) is the second most common subtype after high-grade serous carcinoma (HGSC), representing 5% to 10% of all EOCs in North America, and is even more prevalent in East Asia.[3] The

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biology and clinical behavior of OCCC are distinct from other EOCs. OCCC has a unique genetic profile characterized by frequent ARID1A and PIK3CA mutations, MET amplification, and rare p53 mutation.[4] The association between OCCC and endometriosis has been noted since its first report by Sampson in 1925.[5] Previous studies reported an increased risk of EOC in women with endometriosis, predominantly for clear cell and endometrioid type histology.[2,6] Although it is generally believed that a subset of OCCC develops from ovarian endometriosis, its clinical impact remains unclear.[2,5,7] Unlike HGSC, OCCC frequently presents at an early stage among younger women. When adjusted for stage, women with OCCC had a poorer survival than those with HGSC, but most pronounced in advanced stages.[8] The worse prognosis has been attributed primarily to the relative resistance of OCCC to platinum drugs.[9] An efficacy of 70% to 80% has been demonstrated for platinum-based chemotherapy for the treatment of HGSC; however, the efficacy of these regimens is only 20% to 50% for OCCC.[10] Currently, patients with stage IA OCCC are among the high-risk groups of early-stage EOC defined by the GOG 7601 trial based on 5-year recurrence rates, thus requiring adjuvant chemotherapy.[11] The GOG 157 trial compared 3 versus 6 cycles of adjuvant paclitaxel and carboplatin chemotherapy in patients with high-risk, early-stage EOC.[12] An exploratory analysis broken down by histology suggested that patients with HGSC histology benefit from 6 cycles of chemotherapy but OCCC histology does not.[13] A recent retrospective cohort confirmed this finding,[14] raising the question of the efficacy and optimal number of cycles of upfront chemotherapy for OCCC.

The prognostic significance of several clinical and pathological parameters in OCCC has been investigated; however, the results are discordant, with the exception of stage retaining prognostic significance in all published multivariate analyses.[15,16] The latest FIGO subdivision of stage IC EOC separately identifies intraoperative rupture, ovarian surface involvement, and positive cytology as stage IC_1, IC_2, and IC_3, respectively. In general, stage IC EOC patients have a greater risk of recurrence and poorer survival than those with stage IA despite platinum-based adjuvant chemotherapy. Nevertheless, there is debate as to whether or not intraoperative rupture confers a worse prognosis than that seen in stage IA patients.[17,18] According to a large retrospective multicenter cohort, both pre- and intraoperative capsule rupture had an independent adverse impact on disease-free survival (DFS).[19]

Given that OCCC has a distinct clinical behavior and more knowledge of this rare histologic subtype is needed, we conducted a retrospective analysis of 130 patients with pure OCCC treated at our center during an 8-year period and investigated the prognostic significance of various clinicopathological features.

2. Materials and methods

2.1. Patients

This study was approved by the hospital ethics committee. The medical records of all women treated for OCCC at Obstetrics & Gynecology Hospital of Fudan University (OGHFU) between January 2007 and December 2014 were reviewed. Only primary patients treated at OGHFU with pure OCCC were included. Women with a concurrent malignancy were excluded, and women with lack of sufficient follow-up were excluded from survival analysis. In all, 130 women were enrolled in this study. Data collected included demographic information; clinical, surgical and chemotherapy information; and follow-up information.

2.2. Treatment

Upfront surgery was conducted in all women, either by laparotomy or laparoscopy. In principle, standard primary surgical treatment consisted of hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic $\pm$ para-aortic lymphadenectomy, and debulking procedures such as colon resection. Most women underwent complete surgical staging.

All except 3 women who had no postoperative follow-up received adjuvant chemotherapy. Regimens were as follows: intravenous paclitaxel 175 mg/m^2 over 3 hours plus intravenous carboplatin area under the curve (AUC) 5 over 30 minutes on day 1; every 3 weeks for 3 to 8 cycles.

2.3. Follow-up and statistical analysis

Patients returned for follow-up evaluation every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Survival data were last calculated on November 30, 2015. The endpoints selected for analysis included diseaseDFS and overall survival (OS). DFS was defined as the time from surgery to the date of progression or recurrence, death, or last follow-up. OS was defined as the time from surgery to the date of death or last follow-up. All patients we restaged using the FIGO 2014 staging system. Response to chemotherapy was broken down into refractory (progression within 1 month of chemotherapy), resistant (progression between 1 and 6 months of

chemotherapy), and sensitive (progression after 6 months of chemotherapy).

Statistical analysis was performed using SPSS 20.0 for Windows program. The distributions of clinicopathologic events were evaluated using χ^2 test or Fisher exact test. The univariate survival analysis was based on the Kaplan–Meier method. The survival curves were compared employing the Log-rank test. Multivariable analysis was performed by Cox proportional hazards model to evaluate the independent factors affecting survival. A P value of < .05 was considered significant.

3. Results

3.1. Patient and disease characteristics

A total of 130 women were surgically diagnosed with pure OCCC at OGHFU between January 2007 and December 2014, accounting for 12.32% of all 1055 cases of EOC treated at OGHFU in the same period (Table 1). The mean age at diagnosis was 51.54±7.730 years (range, 31–75 years). The main complaints included: self-sensing abdominal distention/mass (38.5%), abdominal pain/bloating (33.1%), incidental finding during examination (20.7%), and menstrual change (7.7%). Consistent with previous studies,[20] early-stage disease predominated: 86 (66.2%) women had stage I disease; 13 (10.0%) had stage II disease; 29 (21.5%) had stage III disease, and 2 (2.3%) had stage IV disease. 79 (60.77%) women had tumors >10 cm. Baseline CA125 levels were available for 120 women. 90 (75%) women had CA125 levels not exceeding 200 U/mL. A total of 49 (37.69%) tumors arose from endometriosis based on the criteria of Sampson[5] and Scott.[21] Follow-up information was obtained for 127 patients, yielding a follow-up rate of 96.2%. The median follow-up for surviving patients was 47 months (range, 8–106 months).

3.2. Surgery and adjuvant chemotherapy

Initial treatment was surgical for all the patients (Table 2). Lymphadenectomy was omitted in 14 cases because of advanced stage or patient morbidity. Twenty-one women were treated by laparoscopy, among which 19 had stage I disease. 117 women underwent R0 resection. Only 6 women underwent nonoptimal cytoreduction (largest diameter of residual disease >1 cm). Twelve of 116 women had lymph node metastasis.

All the 127 women who had follow-up after surgery received adjuvant chemotherapy. Twenty-six women received >6 cycles of chemotherapy, and the rest received 3 to 6 cycles of chemotherapy. There was no statistically significant difference between the stage and the number of cycles of chemotherapy received. Of 127 women with follow-up, 9 had refractory disease, 21 had resistant disease, and 97 met the criteria for sensitive disease (Table 2).

3.3. Prognostic factors

Survival rates were analyzed by univariate regression regarding age, tumor diameter, tumor origin (of endometriosis or not), residual disease, lymph node status, stage, optimal cytoreduction, chemotherapy cycles, and sensitivity. A subsequent multivariate regression analysis was performed to evaluate the significant survival factors in univariate analysis. As shown in Table 3, only FIGO stage and response to chemotherapy demonstrated an independent significant impact on OS and DFS.

Table 1

Patients and tumors.

	Total n	Percentage (%)	I	II	III	IV	P
Age, y							
≤60	119	(91.5%)	79	12	27	1	.479
>60	11	(8.5%)	7	1	2	1	
Main complaint							
Self-sensing abdominal distention/ mass	50	(38.5%)	41	5	4	0	.28
Abdominal pain /bloating	43	(33.1%)	24	2	15	2	
Incidental findings during examination	27	(20.7%)	17	4	6	0	
Menstrual change	10	(7.7%)	4	2	4	0	
CA125							
≤200 U/mL	90	(75%)	66	8	15	1	.003*
>200 U/mL	30	(25%)	11	5	13	1	
Maximum diameter of the mass, cm							
1–5	12	(9.23%)	7	1	4	0	.17
5–10	39	(30%)	31	5	3	0	
>10	79	(60.77%)	48	7	22	2	
Ascites							
No	78	(60%)	62	5	10	1	.001*
Yes	52	(40%)	24	8	19	1	
Peritoneal cytology							
Unexamined/negative	104	(80%)	78	9	15	2	<.001*
Positive	26	(20%)	8	4	14	0	
Tumor origin							
Endometriosis	49	(37.69%)	44	3	2	0	<.001*
Non-endometriosis origin	81	(62.31%)	42	10	27	2	

* $P < .05$.

Table 2

Surgery and chemotherapy.

	n	I	II	III	IV	P
Surgical approach						
Laparotomy	109	67	12	28	2	.08
Laparoscopy	21	19	1	1	0	
Diameter of residual disease, cm						
0	117	86	12	18	1	<.001*
≤1	7	0	0	7	0	
>1	6	0	1	4	1	
Lymph node metastasis						
No	104	83	12	9	0	<.001*
Yes	12	0		12	0	
Unknown	14	3	0	9	2	
Chemotherapy cycles						
≤6 cycles	101	71	9	20	1	.124
>6 cycles	26	12	4	9	1	
Response to chemotherapy						
Sensitive	97	75	11	11	0	<.001*
Resistant	21	6	2	12	1	
Refractory	9	2	0	6	1	

* $P < .01$.

We subsequently performed multivariate analysis to examine whether tumor capsule status was an independent predictor of survival in stage I OCCC. According to the 2014 FIGO staging, women with stage IC disease were further subdivided into IC_1 (intraoperative rupture) versus IC_2 (surface involvement) versus IC_3 (positive cytology in peritoneal washings or ascites). In this analysis, age, substage, tumor diameter, tumor origin, and response to chemotherapy were entered in the Cox regression model. Given the small sample size of stage IC_3 group, stage IC_2, and IC_3 were combined into one group (rupture before surgery) for analysis. As presented in Table 4, the status of the tumor capsule was a significant outcome predictor for both 5-year OS and DFS in stage I OCCC. Response to chemotherapy retained its significance as an independent prognostic factor for survival among patients with stage I OCCC. Cox regression analysis was then used to further compare survival among stage I stratification. P values between each substage are summarized in Table 5. This examination revealed that the OS of $IC_2 + IC_3$ group was poorer than that of IC_1 group ($P = .025$); however, the OS of IC_1 group did not significantly differ from that of IA group ($P = .623$). The PFS analysis mirrored the OS analysis.

3.4. Patient survival stratified by stage

For the entire cohort, the 3-year and 5-year DFS rates were 80.1% and 72.2%, respectively. The mean DFS was 65.83 months. The 3-year and 5-year OS rates were 86.3% and 81.6%, respectively. The mean OS was 75.8 months. The prognosis for

stage I was excellent, with a 5-year DFS rate of 88.1% and a 5-year OS rate of 89.2%. The 5-year DFS and OS rates at stage II were 56.3% and 85.7%, respectively. The 5-year DFS and OS rates at stage III/IV were of 25.7% and 52.5%, respectively. Stage III and IV were grouped together as there were only 2 cases at stage IV in this study (Table 3 and Fig. 1).

Among the patients with stage I disease, the 5-year DFS and OS rates at stage IC_1 were 89.0% and 91.0%, respectively. The 5-year DFS and OS rates at stage $IC_2 + IC_3$ were 63.3% and 74.3%, respectively, significantly poorer than those at stage IC_1. Patients with stage IA disease had a DFS rate of 92.1% and OS rate of 94.4%, both comparable to those at stage IC_1 (Table 5 and Fig. 2A and B).

4. Discussion

This retrospective 8-year analysis investigated the clinical characteristics and outcomes of pure OCCC cases treated at a large referral center in China. We confirmed that OCCC often presents at an early stage, when it has a good prognosis.[20] FIGO stage and resistance to chemotherapy were independent risk factors affecting the prognosis of patients, while intraoperative tumor rupture was not.

In the present study, OCCC cases accounted for 12.32% of all concurrent EOC cases admitted to the same institution. The geographic prevalence of OCCC is markedly different, representing 5% to 10% of all EOCs in North America, and a higher percentage in East Asia. OCCC constitutes 25% and 10.3% of EOCs in Japan and Korea, respectively.[22,23] No data on OCCC prevalence in Chinese population have been published. The average age at diagnosis in our cohort was early 50s, and nearly two-thirds of the cases were stage I disease. This is consistent with previous studies showing the distinct epidemiology of OCCC from HGSC, which is frequently caught much later in life at an advanced stage.[4,20] The difference may be explained by the indolent nature of OCCC, which is classified as type I EOC.[24,25] OCCC often presents as a large unilateral pelvic mass confined to the ovary, causing symptoms of abdominal pain and distention.[26] This is confirmed by our study, wherein nearly 80%

Table 3

Prognostic factors by univariate and multivariate analyses.

Factors	5-year OS (%)	Univariate P	Multivariate P	5-year DFS (%)	Univariate P	Multivariate P
Age, y		.106			.315	
≤60	81.8			73.8		
>60	47.5			46.4		
Stage		<.001*	.108		<.001*	<.001*
I	89.2			88.1		
II	85.7			56.3		
III/IV	52.5			25.7		
Lymph node metastasis		<.001*	.11		<.001*	.47
Yes	72.2			40.0		
No	87.1			76.3		
Unknown	34.6			33.3		
CA125		.099			.001*	
≤200 U/mL	78.4			71.7		
>200 U/mL	61.3			34.1		
Endometriosis origin		.007*	.292		<.001*	.022
Yes	92.8			93.5		
No	67.8			51.0		
Optimal cytoreduction		<.001*	.912		<.001*	.157
Yes	81.6			70.7		
No	36.7			25.0		
Chemotherapy cycles		.782			.152	
≤6	76.9			67.8		
>6	72.6			51.1		
Response to chemotherapy		<.001*	<.001*		<.001*	<.001*
Sensitive	96.8			87.3		
Resistant	9.5			0.0		
Refractory	0.0			0.0		

DFS = disease-free survival, OS = overall survival.

* $P < .05$.

Table 4

Prognostic factors in patients with stage I OCCC by multivariate analysis.

Factors	n	5-year OS (%)	P	5-year DFS (%)	P
Total	84				
Age, y			.754		.546
≤60	79	92.4		90.0	
>60	5	51.8		48.4	
Stage[†]			.028*		.039*
IA	21	94.4		94.1	
IC$_1$	44	91.0		89.0	
IC$_2$ + IC$_3$	18	74.3		63.3	
Maximum diameter of the mass, cm			.703		.698
1–5	6	92.3		90.2	
5–10	30	88.5		85.6	
>10	48	87.0		85.3	
Endometriosis origin			.292		.332
Yes	44	91.8		89.5	
No	40	86.3		85.1	
Response to chemotherapy			.002*		.001*
Sensitive	75	96.8		87.3	
Resistant	6	9.5		0.0	
Refractory	2	0.0		0.0	

DFS = disease-free survival, OS = overall survival, OCCC = ovarian clear cell carcinoma.

* $P < .05$.

[†] According to the 2014 FIGO staging, women with stage IC disease were further subdivided into IC1 (intraoperative rupture) vs. IC2 (surface involvement) vs. IC3 (positive cytology in peritoneal washings or ascites).

patients were diagnosed because of associated symptoms. Another reason for the earlier age and stage at diagnosis among OCCC cases may lie in the high incidence of endometriosis in this population, which results in a closer follow-up and higher rate of surgery.[27,28] Of our 130 patients, 75% had a CA125 level not exceeding 200 U/mL, although >60% had a large tumor diameter (>10 cm). Considering a frequent mild-to-moderate elevation of serum CA125 level among OCCC cases, CA125 level serves poorly in predicting malignancy in OCCC.[29] Thus, it is necessary to identify novel serological biomarkers for the diagnosis of OCCC.

Table 5

Cox regression analysis for survival stratified by stage I subdivision.

Stage[†]	n	5-year OS (%)	P	5-year DFS (%)	P
IC$_1$ vs. IC$_2$ + IC$_3$			.025*		.039*
IC$_1$	44	91.0		89.0	
IC$_2$ + IC$_3$	18	74.3		63.3	
IA vs. IC$_1$			.623		.785
IA	21	94.4		92.1	
IC$_1$	44	91.0		89.0	

DFS = disease-free survival, OS = overall survival.

* $P < .05$.

[†] According to the 2014 FIGO staging, women with stage IC disease were further subdivided into IC1 (intraoperative rupture) vs. IC2 (surface involvement) vs. IC3 (positive cytology in peritoneal washings or ascites).
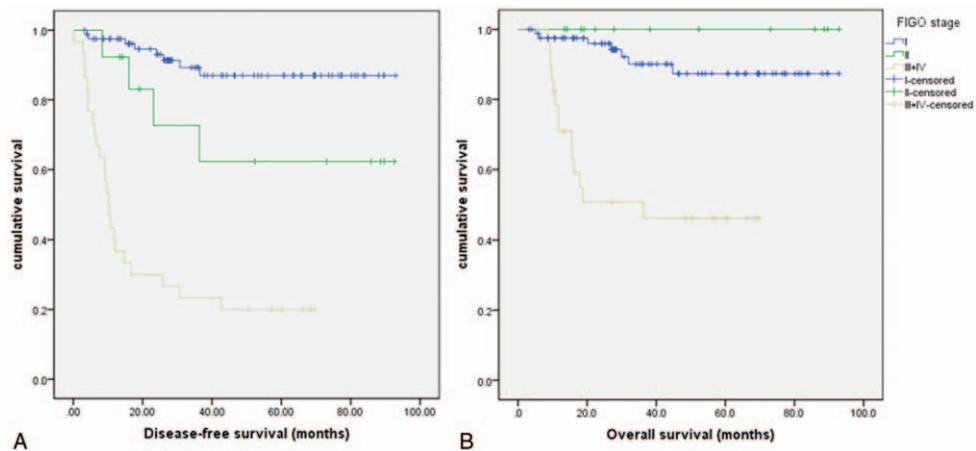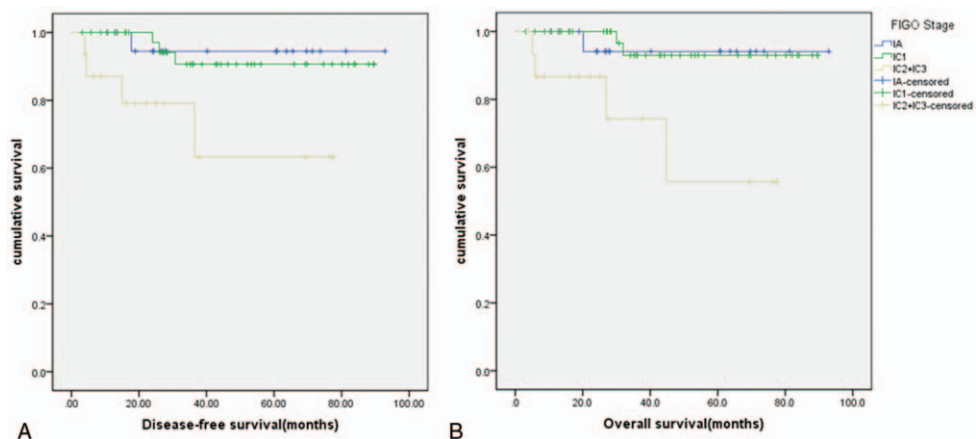
Figure 1. Kaplan-Meier survival analysis stratified by stage. (A) There is significant difference in disease-free survival (A, $P < .05$) and overall survival (B, $P < .05$) among FIGO stages I, II, and III/IV ($P < .05$; $P < .05$).

All except 3 patients at early-stage disease received a complete surgical staging. Patients with advanced disease underwent cytoreduction. Lymphadenectomy was omitted in 14 cases, among which 3 underwent emergent surgeries and patients elected not to have a restaging procedure; 11 were advanced stage disease. A total of 124 (95.4%) cases achieved optimal cytoreduction, with 117 (90%) achieving R0 resection. Lymph node metastasis was found in 12 (10.34%) of the 116 women undergoing lymphadenectomy. Particularly, in cases with disease grossly confined to the ovary, 5.7% (5/88) were found to have positive lymph node. Among these upstaged cases, 60% (3/5) had ovarian surface involvement or positive cytology (data not shown). This was in line with a previous study, showing that 4.4% to 7.4% of all clinically apparent stage I diseases had metastasis to lymph nodes; with positive cytology or ovarian surface involvement, this rate was as high as 37.5%.[30] This may influence clinical decision-making on whether to perform lymphadenectomy in patients with incidental OCCC found after salpingo-oophorectomy. The question remains as to whether a nodal metastasis rate of approximately 5% is clinically relevant given that adjuvant chemotherapy is recommended even for stage IA OCCC by current treatment guidelines for EOC. All 127

women who had follow-up received adjuvant chemotherapy, among which 26 (20.5%) received >6 cycles of chemotherapy. There was no statistically significant difference among the chemotherapy cycles for stages I to IV cases. In this cohort, 23.6% (30/127) patients were refractory or resistant to chemotherapy, consistent with the previously reported platinum-resistance rates by others.[31] The true rate of platinum resistance is better evaluated in advanced disease patients: 64.5% (20/31) women with stage III/IV disease had chemotherapy-refractory or resistant disease, compared to 10.4% (10/96) women with stage I/II disease, largely reflecting the high cure rate in early-stage disease.

Upon survival analysis, we identified FIGO stage and tumor resistance to chemotherapy as independent prognostic factors in OCCC. These features were-well known predictors of survival in EOC.[32] Surprisingly, neither optimal cytoreduction or lymphadenectomy was established as an independent prognostic factor in the present study. This might be related to the small sample size and the fact that detecting nodal disease would not further tailor adjuvant treatment in the present study (all patients received postoperative chemotherapy). The prognostic value of endometriosis in OCCC remains elusive. Although some studies

Figure 2. Survival curves stratified by stage I breakdown. There is no significant difference between stage IA and IC_1 in disease-free survival (A) and overall survival (B); however, there is significant difference between stage IA and stage $IC_2 + IC_3$ in disease-free survival (A, $P < .05$) and overall survival (B, $P < .05$).

concluded that presence of endometriosis was not a prognostic factor,[15,33,34] others reported that endometriosis was an independent predictor of better survival[35] or worse survival.[36] However, one should note that many studies comparing survival of OCCC with or without endometriosis did not draw a clear distinction between cancer with coexisting endometriosis and cancer arising from endometriosis. As these may be 2 different subgroups of OCCC, the results of these studies should be interpreted cautiously. However, in the present study, the strict definition of cancer arising from endometriosis was applied,[5,21] making it possible to reveal the true survival impact of tumor origin. Our finding that endometriosis as tumor origin did not affect prognosis in OCCC was consistent with those of the few reports wherein a clear categorization of OCCC arising from endometriosis was studied.[33,28]

It is generally agreed that rupture before surgery (ovarian surface involvement/asites or positive washings) confers a less favorable outcome for stage IC EOC patients. There is debate though, as to whether surgical rupture worsens prognosis in the absence of surface involvement. Although some studies found that surgical rupture had a significantly negative effect on survival,[19,37] others did not.[37,38] These studies included different histologic subtypes of EOC, and did not compare survival within a single subtype. When confining analysis to clear cell histology, most studies concluded on similar survival of patients between IA and IC with surgical rupture.[9,17,31,39] However, considering that these results were based on retrospective analysis, the prognostic implications of surgical rupture remain unclear. It is highly recommended that every effort be made to remove suspicious adnexal masses intact, whether through laparotomy or minimally invasive approach.

Our study showed that chemoresistance was an independent risk factor for poor survival, verifying the knowledge that poor survival of advanced-stage OCCC is attributed to platinum resistance. At present, stage IA OCCC is treated with adjuvant therapy as clear cell histology is considered a high risk factor partly due to platinum resistance. Paradoxically, these patients are therefore treated with platinum-based chemotherapy because no better alternative exists. There is no straightforward evidence as yet that adjuvant chemotherapy helps prolong survival in women with stage I OCCC. A small series suggested that adjuvant chemotherapy was not necessary for stage IA OCCC patients; for patients with stage IC OCCC, adjuvant chemotherapy seemed to increase PFS, but not with a statistical significance.[40] Recently, studies have shown that molecules such as ADAM9, MICU1, FOXM1, and Annexin A4 are associated with chemoresistance of OCCC, providing possibilities for development of new prognostic biomarkers and potential combinatorial therapeutic target in OCCC.[41–43]

In conclusion, our data confirmed that OCCC often presents at an early stage when it has a favorable prognosis. FIGO stage and response to chemotherapy are 2 independent prognostic factors. Rupture before surgery rather than rupture during surgery confers an adverse effect on survival in otherwise stage IA disease. Our study was limited by its retrospective nature, small sample size, and variable follow-up length. Nevertheless, the present study lends credence to the unique features of OCCC. Further work is required to elucidate the molecular mechanisms behind this distinct entity, and novel targeted therapeutics are needed to improve the current poor outcome of advanced OCCC.

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