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Original Article

An exploratory analysis about cycles of adjuvant chemotherapy and outcomes by substage for stage I ovarian clear cell carcinoma: a single institution retrospective study

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Abstract: This retrospective cohort study was designed to explore the prognostic impact of adjuvant chemotherapy and tumor substage on stage I ovarian clear cell carcinoma (OCCC). Data of 102 patients with stage I OCCC who underwent surgery at the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College from February 1999 to December 2018 was retrospectively analyzed. Prognostic factors were evaluated using the Cox Regression Model. The disease-free survival (DFS) and overall survival (OS) were assessed by the Kaplan-Meier method and compared between different groups with the log-rank test. $P < 0.05$ was considered statistically significant. The median follow-up duration was 40.5 months. Thirty-one (30.4%) patients were at stage IA, and 17 (16.7%), 5 (24.5%) and 17 (16.7%) patients were at stage IC1, IC2 and IC3 respectively. The 5-year and 10-year DFS rates of the entire cohort were 82.8% and 78.8% respectively, and the 5-year OS was 97.9%. Patients at stages ICl (intraoperatively ruptured tumor) and IA had similar DFS (P=0.538, OR=0.024), and that of patients at stages IC2 (tumor ruptured preoperatively or tumor on ovarian surface) or IC3 (ascites or peritoneal washings with positive cytology) was significantly lower (72.6% vs. 95.1%, P=0.039, OR=5.051). The 5-year DFS of patients receiving four (83.9%) and more than four (81.7%) cycles adjuvant chemotherapy were similar. Furthermore, univariate analysis showed that age, tumor size and CA199 levels were significantly correlated with DFS, although none of these variables were identified as independent prognostic factors in the multivariate analysis. In summary, our results suggest that patients with stage I OCCC have overall good prognosis. However, tumor surface involvement or positive cytology can worsen prognosis, and the prognosis may not be improved by more than four cycles chemotherapy following surgery. The remarkable increased CA199 may be a potential indicator of poor prognosis in stage I OCCC.

Keywords: Ovarian clear cell cancer, stage I, clinicopathologic variables, prognosis

Epithelial ovarian cancer is classified into the high grade serous (HGSC), endometrioid, clear cell, mucinous, low grade serous, and other rare subtypes based on histopathological characteristics. Ovarian clear cell cancer (OCCC) is the third most common epithelial ovarian cancer, accounting for approximately 5~25% of all cases worldwide [1], 5~10% of the cases in North America and a higher percentage in East Asia. Compared to HGSC, OCCC is usually seen in younger women with endometriosis, and diagnosed at early stages (FIGO stage I or II). OCCC is also more invasive compared to HGSC, and its prognosis is affected by the tumor stage [2]. Although advanced OCCC is associated with significantly worse prognosis [3], the prognostic relevance of the different substages in early stage OCCC remains controversial.

Ovarian cancer is primarily treated with surgery and adjuvant chemotherapy. Surgical resection is the only curative option for some patients at stage I, and subsequent chemotherapy cycles can improve recurrence-free survival but have no significant effect on the overall survival [4-6]. However, the results of the prospective multicenter ICON1 trial suggest that platinum-based adjuvant chemotherapy can improve sur-

vival and delay recurrence in patients with early-stage ovarian cancer [7]. Despite lack of convincing data, the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) guidelines recommend chemotherapy for all OCCC patients regardless of stage. However, the optimal duration of adjuvant chemotherapy for early stage ovarian cancer is unclear.

In view of these gaps in our knowledge, we conducted a single-center retrospective study to assess the outcome of the different substages of stage I OCCC, and the prognostic impact of chemotherapy.

Materials and methods

Patients and materials

A total of 378 women were diagnosed with OCCC between February 1999 and December 2018 at the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, of which 214 (56.6%) were at FIGO stage I. The retrospective analysis was performed on 102 patients with histologically confirmed stage I OCCC who underwent surgery. Data including age, primary symptoms, endometriosis or dysmenorrhea, CA125 and CA199 expression status, surgery, stage, regimens and cycles of adjuvant chemotherapy, and time to recurrence were retrieved from the medical records. Endometriosis was diagnosed on the basis of the primary symptoms and post-operation pathology. Surgical staging included hysterectomy, bilateral salpingo-oophorectomy, omentum resection and pelvic lymphadenectomy (resection of $\geq$ 10 lymph nodes). All patients were restaged according to the International Federation of Gynecology and Obstetrics (FIGO) 2014 staging system, and stage IC was further classified into the following substages: intraoperative rupture (IC1), preoperative rupture or surface involvement (IC2), and positive cytology in ascites or peritoneal washing (IC3). Time to recurrence or disease free survival (DFS) was defined as the time from histological diagnosis to the last follow-up or tumor recurrence as confirmed by histology or radiological imaging. Patents were followed up by telephone interviews and outpatient service till December 2019.

Statistical analysis

The significant prognostic factors were identified by univariate and multivariate analysis using the Cox Regression Model. The relationship between tumor stage and adjuvant chemotherapy cycles was analyzed by Fisher exact test. DFS was evaluated by the Kaplan-Meier method and compared between different groups using the log-rank test. All statistical analyses were performed using SPSS 26.0 version, and $P < 0.05$ was considered statistically significant.

Results

Clinicopathologic features

The median age at diagnosis was 51 years (29-76 years). In addition, 62.7% (64/102) of the patients presented with pelvic or adnexal mass as the primary symptom, and 54.9% (56/96) with endometriosis. Pre-treatment CA125 levels were tested in 68 patients, of which 44 (64.7%) showed levels higher than the median value (50.76 U/ml), and 12 patients had an aberrantly high amount of 200 U/ml. CA199 was detected in 55 patients before treatment, and was elevated in 47.3% (26) patients (higher than the median cut-off of 24.8 U/ml), of which 10 had level higher than 100 U/ml. The median tumor diameter was 12 cm (4.9 cm~29.3 cm). Thirty-three patients underwent oophorocystectomy or salpingo-oophorectomy at other hospitals and received supplementary full surgery staging. Oophorocystectomy was performed in 6 patients, of which one had tumor rupture and one had intact resection, while complete details of the surgery were not available for the remaining patients. Of the 69 patients that underwent primary surgery at our hospital, 63 received the full surgery staging. Lymphadenectomy was performed all but 6 patients. In addition, 92/102 (90.2%) patients received paclitaxel and platinum-based adjuvant chemotherapy, and 8 patients received other chemotherapy regimens such as irinotecan, mitomycin or VP-16. The median interval between surgery and chemotherapy was 13 days. Twenty patients had 4 cycles adjuvant chemotherapy and 65 patients received more than 4 cycles, of which 52 received 6 cycles. The clinicopathological features are summarized in **Table 1**.

Table 1. Clinicopathological features of patients with stage I OCCC (n=102)

	Parameters	N/Percentage
Age	≤ 50	50 (49.0%)
	50~60	37 (36.3%)
	> 60	15 (14.7%)
Primary symptom	Pelvic mass	64 (62.7%)
	Abdominal pain	13 (12.7%)
	Abdominal distension	12 (11.8%)
	Increased abdominal girth	2 (2.0%)
	Other	11 (10.8%)
endometriosis	Yes	56 (54.9%)
	No	40 (39.2%)
	Unknown	6 (5.9%)
CA125	< 35	24 (23.5%)
	35~200	32 (31.4%)
	> 200	12 (11.8%)
	Unknown	34 (33.3%)
CA199	< 37	29 (28.4%)
	37~100	16 (15.7%)
	> 100	10 (9.8%)
	Unknown	47 (46.1%)
Tumor size (cm)	≤ 10 cm	38 (37.3%)
	> 10 cm	51 (50.0%)
	Unknown	13 (12.7%)
lymphadenectomy	Yes	96 (94.1%)
	No	6 (5.9%)
substage	IA	31 (30.4%)
	IB	0
	IC1	17 (16.7%)
	IC2	25 (24.5%)
	IC3	17 (16.7%)
	Unknown	10 (11.8%)
Chemotherapy regimen	Paclitaxel and platinum	92 (90.2%)
	Other*	8 (7.8%)
	Unknown	2 (2.0%)
Chemotherapy cycle	1~3	15 (14.7%)
	4	20 (19.6%)
	> 4	65 (63.7%)
	Unknown	2 (2.0%)

*Other chemotherapy regimens including mitomycin combined with irinotecan or VP-16, irinotecan combined with 5-Fu or platinum, and cyclophosphamide combined with pharmorubicin.

Survival by tumor substage and chemotherapy

The median follow-up duration was 40.5 months (3~212 months), and seven patients were lost in that period. In addition, 2 patients died and 15 had recurrence, and the disease recurred within two years in 12 patients. The 5-year and 10-year DFS were 82.8% and 78.8% respectively, and the 5-year OS was 97.9%. Furthermore, the 5-year DFS rates of the IA, IC1, IC2 and IC3 patients were 92.3%, 100%, 78.0% and 66.7% respectively, and not significantly different across all substages (P=0.076). The DFS of the IA and ICI stage patients were statistically similar (P=0.538, OR=0.024), as were that of stage IC2 and IC3 patients (P=0.143). However, the IC stage was associated with a lower 5-DFS compared to stage IA (81% vs. 92.3%, P=0.359, OR=2.050), and patients at the IC2 and IC3 substages in particular had the significant decrement in DFS compared to patients at IA and IC1 (72.6% vs. 95.1%, P=0.039, OR=5.051) (**Table 3**, **Figure 1**). Furthermore, no significant difference was seen between the DFS of patients treated with paclitaxel, platinum-based regimen and other non-platinum regimens (P=0.441), or between patients that received 4 (83.9%) and > 4 (81.7%) cycles of adjuvant chemotherapy. Similar number of patients received four or more cycles of chemotherapy in substages IA (P=0.952) and IC (P=0.706).

Univariate and multivariate analysis for DFS

Univariate analysis showed that age, tumor size and CA199 levels were significantly correlated to DFS. The 5-year DFS rate was significantly lower for patients older than 50 years compared to the younger patients (75.5% vs. 91.2%, P=0.048, HR: 3.633). In addition, tumors larger than 10 cm significantly increased the risk of recurrence (HR: 4.678, P=0.045) and decreased the 5-year DFS (74.4%) compared to that of patients harboring smaller tumors (≤ 10 cm; 92.7%). Furthermore, CA199 levels higher than 100 U/ml were also significantly correlated to inferior DFS (43.8% vs. 82.8%, P=0.025, HR: 4.024) (**Figure 2**). Endometriosis, CA125 levels and

Table 2. Univariate analysis of factors influencing DFS among patients with stage I OCCC

Factors	Univariate analysis				
	β	$S_{\bar{x}}$	Wald	*P*-vaule	OR
Age	1.290	0.652	3.915	0.048	3.633
Endometriosis	-0.131	0.557	0.055	0.814	0.877
CA125	0.001	0.001	2.859	0.091	1.001
CA199	1.405	0.619	5.148	0.025	4.024
Tumour size	1.526	0.771	3.920	0.045	4.678
Lymphadenectomy	3.128	4.528	0.477	0.490	22.834
Substage					
IA			3.730	0.337	
IC1	-1.564	0.839	3.473	0.971	0.209
IC2	-13.530	338.880	0.002	0.383	0.000
IC3	-0.774	0.676	1.312	0.076	0.461
Chemo regimen	3.193	4.148	0.592	0.441	24.357
Chemo cycle					
1~3			0.316	0.854	
4	0.374	0.786	0.227	0.634	1.454
> 4	-0.161	0.783	0.042	0.837	0.851

Table 3. Cox regression analysis of survival in patients stratified by stage I subdivision

Substage	Univariate				
	β	$S_{\bar{x}}$	Wald	P	OR
IA vs. IC	0.717	0.782	0.841	0.359	2.050
IA vs. IC1	-3.723	6.129	0.369	0.538	0.024
IA+IC1 vs. IC2+IC3	1.659	0.783	4.492	0.039	5.051

lymphadenectomy were not significantly correlated with DFS. The results are summarized in **Table 2**. Multivariate analysis did not reveal any independent prognostic factor.

Discussion

OCCC has distinct clinical and oncogenic characteristics compared to HGSC, such as younger age at diagnosis, early stage and unilateral ovary involvement [8, 9]. The median age of OCCC patients in our cohort was 51 years, and 56.6% of the patients were at stage I of the disease. In addition, 62.7% of the patients presented with pelvic mass or adnexal mass as the primary symptom, which may cause abdominal distension, pain and increased girth. Given the palpable nature of these symptoms, OCCC is often diagnosed early.

There is no consensus at present regarding the prognostic relevance of pre- or intraoperative tumor rupture and positive cytology. We found that the substages IC2 and IC3 were associated with a significantly worse DFS compared to IA and IC1 (72.6% vs. 95.1%, P=0.039). But there was no significant difference between stage IA and stage IC1 (P=0.538). Consistent with this, Shu CA reported significantly lower 3-year DFS (92.9% vs. 75.7%) and 3-year OS (93.5% vs. 85.9%) among stage IA versus IC patients in a retrospective study of 177 OCCC patients. Subgroup analysis further revealed similar DFS and OS in IA and IC1 patients (92.9% vs. 89.8%, 93.5% vs. 96.2%), whereas both DFS and OS were significantly decreased in patients with stage IC2 and IC3 tumors (HR: 10.38, 95% CI: 3.34-32.2; HR: 7.56, 95% CI: 1.95-29.3) [10]. Hoskins PJ performed a retrospective cohort study of 241 stage I/II OCCC patients, and found that the 5-year DFS rate among stage IC1 was similar to that among stage IA (88% vs. 84%). The patients with stage IC2 and IC3 had 41% 5-year DFS [11]. In contrast, Yamagami W reported significant differences in the 5-year survival rates between stages IA and IC1 (P=0.003), and between IC1 and IC2 (P < 0.001) clear cell and mucinous carcinoma [12].

Due to frequent chemoresistance, the benefit of extending postoperative chemotherapy in OCCC is ambiguous. NCCN recommends 6 cycles of chemotherapy for stage I high-grade serous ovarian cancer, and 3-6 cycles for all other ovarian cancer types at the same stage. In our study, the 5-year DFS rates for 4 cycles and more cycles were 83.9%, 81.7%, respectively. We did not observe any significant correlation between the number of chemotherapy cycles and DFS in any of the stage I subgroups. Likewise, Prendergast EN reported similar recurrence rates among stage I and II OCCC patients that received 3 or 6 cycles of chemotherapy (18.4% vs. 27.3% for 3 vs. 6 cycles, P=0.4). The number of chemotherapy cycles also had no impact on the progression free survival (PFS; HR: 1.4; 95% CI: 0.63-3.12, P=

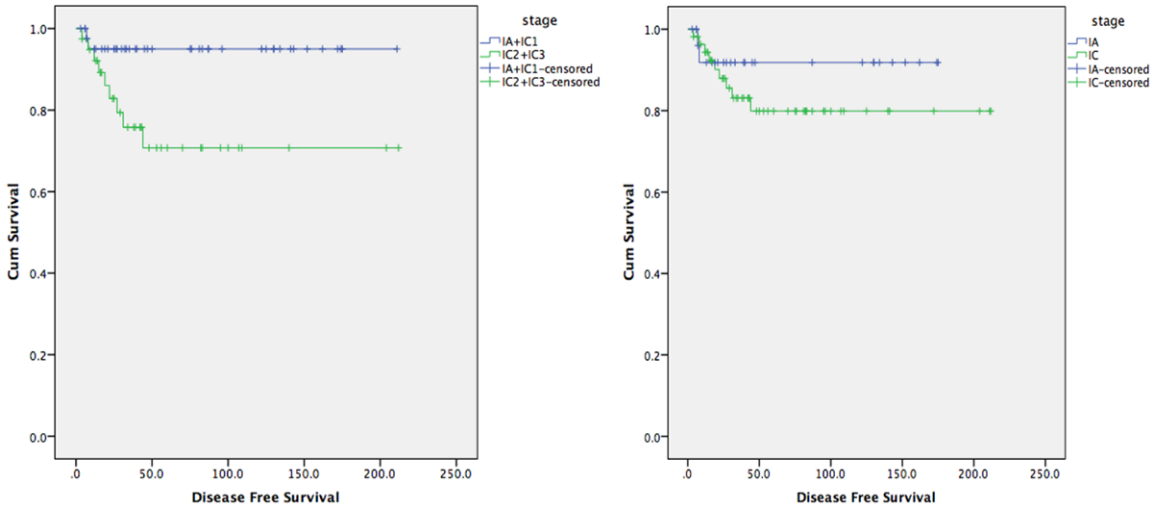

Figure 1. Kaplan-Meier survival analysis of DFS with substage.

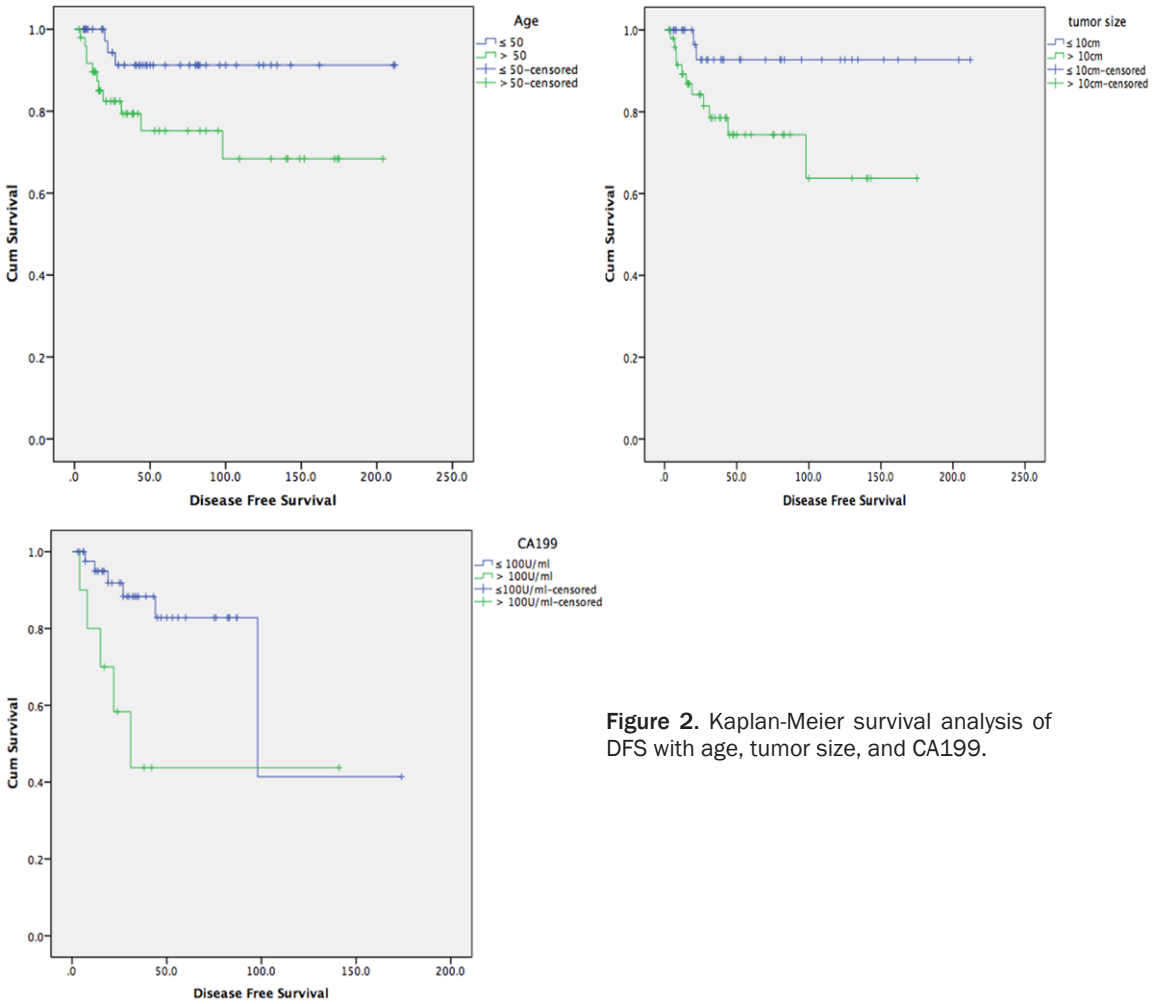

Figure 2. Kaplan-Meier survival analysis of DFS with age, tumor size, and CA199.

0.4) or OS (HR: 1.65; 95% CI: 0.59-4.65, P=0.3), and there was no benefit of increasing chemotherapy even after adjusting for stage [13]. In the GOG 157 phase III trial, the 5-year recur-

rence rates in high risk early stage EOC patients receiving 3 or 6 cycles of carboplatin and paclitaxel chemotherapy were 25.4% and 20.1% respectively [14]. However, 6 cycles of chemotherapy significantly lowered the risk of recurrence in patients with serous tumors compared to 3 cycles of chemotherapy (HR=0.33, CI=0.14-0.77; P=0.04), whereas no such benefit was seen with non-serous tumors [15]. On the whole, the existing studies have the limitations of small sample sizes and/or retrospective design, and therefore they were underpowered to effectively recommend the optimal duration of postoperative chemotherapy for stage I OCCC.

We also identified CA199 level as a potential prognostic factor of OCCC. While CA199 levels are usually high in mucinous ovarian cancer patients, few studies have reported aberrant CA199 in OCCC patients. In our study, 47.3% of the patients had moderately elevated levels, and > 100 U/ml portended worse prognosis. However, no mucinous or other tissue types were detected in the tumor tissues of patient with elevated CA199. Toshihiko T reported high preoperative serum levels of CA199 in 21/45 patients diagnosed with endometriosis [16], which can be partly explained by evidence indicating that OCCCs are derived from endometriosis [17-19]. Therefore, an aberrant increase in CA199 may be indicative of poor prognosis in OCCC patients.

The strengths of our study included: patients had underwent optimal staging surgery by experienced gynecologic oncologists; and all pathologic specimens were reviewed by expert pathologists with a focus on gynecologic oncology. All patients have received standard treatment according to NCCN practical guidelines. But this study is retrospective and had small sample size. It is not adequately powered to effectively answer the question regarding the non-inferiority of 4 versus more cycles of adjuvant chemotherapy. Nevertheless, we feel our study provides an important contribution as we found no separation in survival curves to favor the administration of more chemotherapy.

In conclusion, the overall prognosis of OCCC patients at stage I is good, although tumor surface involvement or positive cytology can worsen the prognosis. Furthermore, more than four cycles adjuvant chemotherapy does not seem to improve the clinical outcomes, although this will have to be validated. The prognostic impact of age, tumor size and CA199 levels were also not significant. The pathogenesis of OCCC needs to study further at the molecular level in order to identify novel biomarkers and therapeutic targets.

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Disclosure of conflict of interest

None.

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