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Recurrent ovarian clear cell carcinoma: a retrospective evaluation of the efficacy and prognostic factors

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Summary

Purpose: The aim of this study was to investigate the effectiveness of treatment and prognostic factors in patients with recurrent ovarian clear cell carcinoma. *Materials and Methods:* The 78 patients with ovarian clear cell carcinoma (CCC) in Peking University Cancer Hospital from 1996 to 2015 received laparotomy and initial chemotherapy. The efficacy of surgery, chemotherapy, and prognosis of patients with recurrent CCC were evaluated. *Results:* The overall response rate (RR) to platinum based chemotherapy of PTX + platinum regimen showed no significant correlation with PFI in this study ($p = 0.683$). According to non-platinum regimen, irinotecan + mitomycin C regimen had a higher activity (RR = 41.7%) compared with topotecan regimen (RR = 20%). The overall survival (OS) had a marked correlation with tumor staging ($p = 0.027$), residuals ($p = 0.019$), second-line chemotherapy response ($p = 0.003$), and progression free survival (PFS, $p = 0.014$). *Conclusions:* No residual tumor in initial surgery is critical for the prognosis of patients with CCC, even in optimal cytoreductive surgery. Irinotecan, as one kind of effective chemotherapy regimen, is preferred to be conducted in patients with recurrent CCC.

Key words: Clear cell carcinoma; Recurrence; Second-line chemotherapy; Irinotecan.

Introduction

Ovarian cancer is the second most common disease among gynecologic malignancies, leading to a high mortality every year. It could be divided into epithelial, mesenchymal, sex cord-stromal, or germ cell origin [1, 2]. Ovarian clear-cell carcinoma (CCC), was first reported by the World Health Organization in 1973 as a distinct entity of epithelial ovarian cancer (EOC) in terms of clinical, histopathological, or genetic features.

CCC is rare, accounting for different rate of death with different geography [3]. The incidence of CCC in America and Europe were 1–12% for ovarian cancer, whereas it was as high as 15–25% in Japan [4-7]. The reason for this disparity is not well known [8, 9]. CCC has unique clinical features including a high incidence of Stage I disease, vascular thromboembolic complications, hypercalcemia, and is frequently characterized by chemoresistances and recurrences resulting in a poor prognosis [10].

Survival rate of patients with ovarian cancer has dramatically improved after introduction of platinum-based chemotherapy, but there still exists a large number of patients with no response to the treatments or with recurrence after treatment. Standard treatments for patients with recurrent CCC have not been well established. So the aim of this study was to investigate the characteristics of clinical treatment and prognosis in patients with recurrent CCC.

Materials and Methods

The study was approved by the institutional review board of Peking University Cancer Hospital and all of the patients agreed to participate in this clinical trial and signed a written informed consent. A total of 78 patients with CCC accounted for 7.4% of the EOC (78/1049) incidence in Peking University Cancer Hospital between 1996 and 2015. All the 78 patients underwent laparotomy including hysterectomy, omentectomy, bilateral salpingo-oophorectomy, peritoneal washing, pelvic abdominal aorta lymphadenenctomy, and cytoreductive surgery.

Initial adjuvant chemotherapy was selected with platinum-based drugs. Paclitaxel (PTX) plus carboplatin treatment: an infusion of PTX (175 mg/m^2) + carboplatin (AUC 5) on day 1, every three weeks. Cyclophosphamide plus cis-platinum treatment: an infusion of 600 mg/m^2 cyclophosphamide and 60 mg/m^2 cis-platinum on day 1, every three weeks.

Out of the 78 patients with CCC treated in these hospitals, the authors identified 53 patients with recurrent disease. Stages of the disease at diagnosis were based on the International Federation of Gynecology and Obstetrics (FIGO) stage [11]. The response rate (RR) was evaluated by revised RECIST guideline [12] or CA125 criteria [13]. Complete remission (CR) was defined with disappearance of all target lesions. Partial remission (PR) was defined with at least a 30% decrease in the sum of diameters of target lesions. Progressive disease (PD) was defined with at least a 20% increase in the sum of diameters of target lesions. Stable disease (SD) was defined with neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Patients with CR and PR after chemotherapy were defined as responders.

The recurrent CCC was classified as either platinum-sensitive CCC or platinum-resistant CCC. Tumors recurring in less than six

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Table 1. — *The clinical characteristics of the 53 patients with recurrent or refractory CCC.*

Characteristics	Number of patients	(%)
Total	53	
Median age, range	55, 32-76	
Stages		
I	4	7.5
II	5	9.4
III	40	75.5
IV	4	7.5
Histology		
Complete CCC	47	88.7
Mixed CCC	6	11.3
Residuals		
No visible residuals	11	20.8
Residual tumor≤1cm	31	58.5
Residual tumor >1cm	11	20.8
Family history		
Breast cancer or ovarian cancer	1	1.9
Other cancers	15	28.3
No cancer	37	69.8

Data are presented as number (percentage) as appropriate. CCC: ovarian clear cell carcinoma.

months or with PD, SD after chemotherapy, were defined as platinum-resistant CCC and recurring in more than six months were defined as platinum-sensitive CCC [14].

Platinum-free intervals (PFI) [15] of one to six months, six to 12 months, and over one year were used to evaluate the RR to platinum based chemotherapy in patients. Overall survival (OS) was observed from the start of the surgery to the end of the time of death or last follow-up observation.

Patients received regular follow-up reexamination with carbohydrate antigen (CA) 125, chest radiograph, abdominal ultrasound, abdominal and pelvic enhanced CT or enhanced MRI every three to six months. Bone scintigraphy or targeted biopsy would be conducted when necessary. The follow-up ending time was the time of death or December 1, 2015.

The data were analysed by SPSS software (version 16.0). Kaplan–Meier method and COX regression analysis were used for calculating the survival distribution. Mann-Whitney U test was used to compare the differences of therapic efficacy. A p-value of < 0.05 was considered statistically significant.

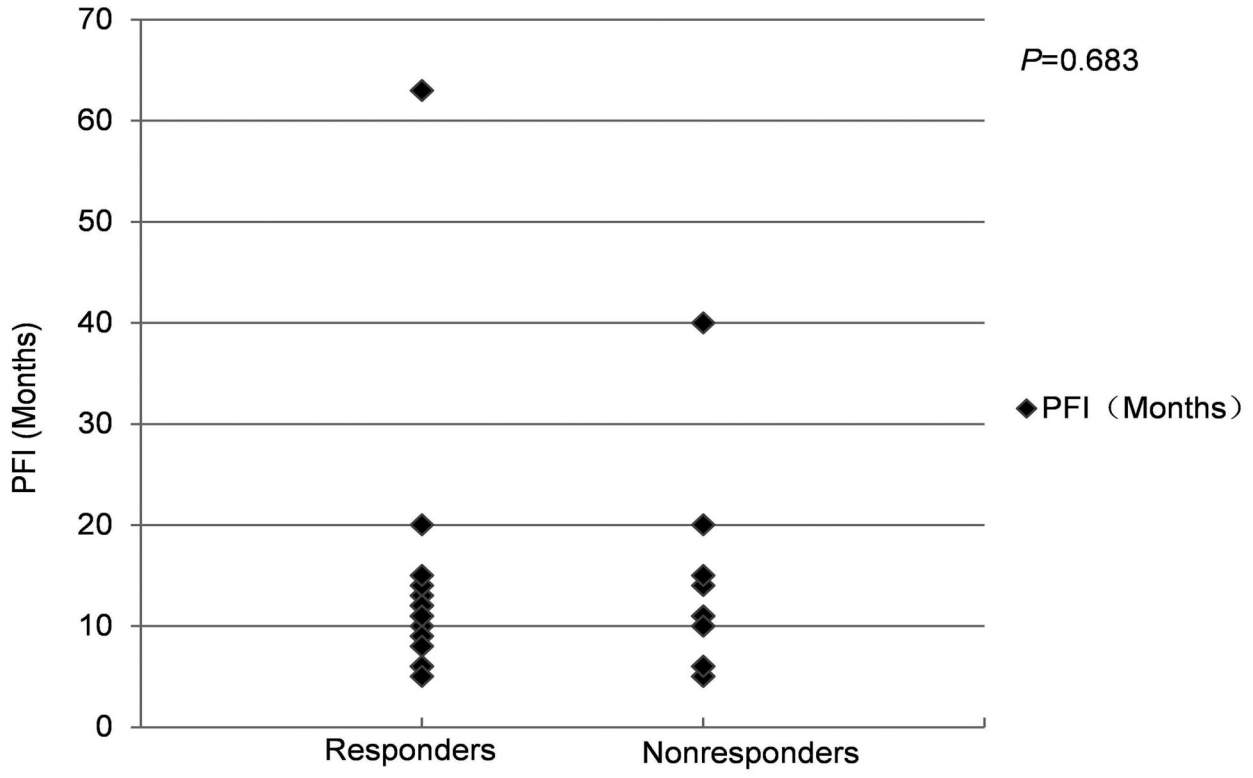

Figure 1. — The relationship of the response to platinum-based chemotherapy and progression free survival (PFS) in patients with recurrent CCC by scatter diagram.

Table 2. — *The efficacy of the 27 patients with recurrence according to PFI scale.*

RR	1-6 months (n=7)	6-12 months (n=9)	> 12 months (n=11)	All (n=27)
CR	0 (0 %)	2 (22.2 %)	4 (36.4 %)	6 (22.2 %)
PR	3 (42.9 %)	3 (33.3 %)	3 (27.3 %)	9 (33.3 %)
SD	2 (28.6 %)	1 (11.1 %)	2 (18.2 %)	5 (18.5 %)
PD	2 (28.6 %)	3 (33.3 %)	2 (18.2 %)	7 (25.9 %)

Data are expressed as number (percentage) as appropriate. RR: response rate; CR: complete remission; PR: partial remission; SD: stable disease; PD: partial disease.

Table 3. — *The efficacy of non-platinum regimen in patients with recurrent and resistant CCC.*

RR	Irinotecan+ mitomycin C (n=24)	Topotecan (n=10)	Gemcitabine (n=4)
CR	2 (8%)	0 (0%)	0(0%)
PR	8 (33.3%)	2 (20%)	1(25%)
SD	8 (33.3%)	5 (50%)	2(50%)
PD	6 (25%)	3 (30%)	1(25%)

Data are expressed as number (percentage) as appropriate. RR: response rate; CR: complete remission; PR: partial remission; SD: stable disease; PD: partial disease.

Table 4. — *The survival distribution of the 53 patients with recurrent CCC by COX regression analysis.*

Factors	*Wald* value	RR	95.0% CI Lower	Upper	*p* value
Tumor staging	4.898	5.943	1.226	28.805	0.027
Residual tumor	5.528	5.760	1.338	24.794	0.019
Response to second-line chemotherapy	8.594	0.166	0.050	0.552	0.003
PFS	5.987	0.803	0.673	0.957	0.014

CCC: ovarian clear cell carcinoma; RR: relative risk; CI: confidence interval; PFS: progression free survival.

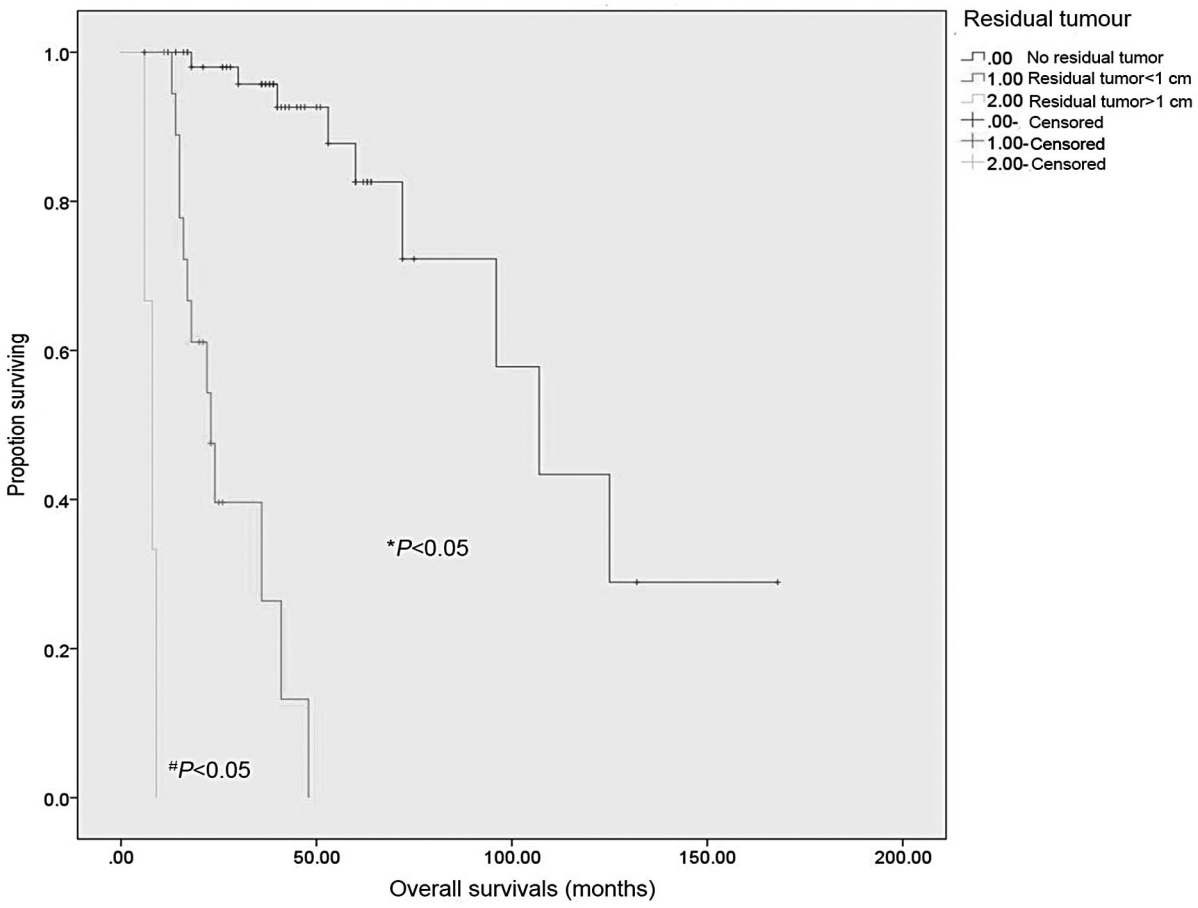

Figure 2. — The survivorship curve with residual tumor in patients with recurrent disease. The proportion surviving in patients with residual tumor < 1cm *vs*. patients with no residual tumor, $^{*}p < 0.05$. The proportion surviving in patients with residual tumor < 1 cm *vs.* patients with residual tumor > 1 cm, $^{\#}p < 0.05$.

Results

The 53 patients with the mean age of 53 (range: 32-76) years were investigated (Table 1). Four (7.5%) cases were in Stage I, five (9.4%) cases were in Stage II, 40 (75.5%) cases were in Stage III, and four (7.5%) cases were in Stage IV. At histological analysis, six (11.3%) cases were mixed cancer (CCC element ≥ 80%) and 47 (88.7%) cases were complete cancer. There were 11 (20.8%) cases with no visible residual tumor, 11 (20.8%) cases with residual tumor with a diameter less than 1 cm, and 31 (58.5%) cases with residual tumor diameter more than 1 cm after the initial surgery. All patients received postoperative adjuvant chemotherapy. Forty-six patients received PTX plus carboplatin regimen and seven patients received cyclophosphamide plus cis-platinum regimen. According to PFI, 33 of the patients were platinum-resistant (seven tumors recurred in less than six months, 26 tumors with refractory CCC) and 20 of the patients were platinum-sensitive.

Among the 53 patients with recurrent disease by December 1, 2015, 24 patients had metastasis in parenchymal organs including spine in four cases, liver in 11 cases, lung in seven cases, and brain in two cases. Lymph node in abdominopelvic cavity occurred in 17 cases and pelvic cavity or residual vagina occurred in 12 cases. Second-line chemotherapy was not delivered in all patients according to the PFI. Among the 53 patients, 27 patients received platinum based regimen, 12 non-responders of the 27 patients, and the other 26 patients with platinum resistance received non-platinum regimen.

The 27 patients with recurrent CCC received PTX + platinum regimen consisting in an infusion of PTX (80 mg/m^2) on days 1, 8, and 15 and carboplatin (AUC 5) on day 1 for four weeks. According to PFI, the overall RR to platinum based chemotherapy was 55.5%, and the RR was 42.9%, 55.5%, 63.7% respectively, in patients at one to six months, six to 12 months, and >12 months (Table 2), showing no significant correlation with PFI ($p = 0.683$, Figure 1).

Twelve non-responders to PTX + platinum regimen and the other 26 patients with platinum resistance received non-platinum drugs treatment including gemcitabine in four patients, topotecan in ten patients, and irinotecan plus mitomycin C in 24 patients. The gemcitabine therapy consisted in an infusion of gemcitabine (1000 mg/m^2) on days 1, 8, and 15 for four weeks. The topotecan therapy consisted in an infusion of topotecan (4 mg/m^2) on days 1, 8, and 15 for four weeks. The irinotecan plus mitomycin C therapy consisted in an infusion of irinotecan (120 mg/m^2) and mitomycin C (7mg/m^2) on days 1 and 15 for two cycles, every four weeks. The RR to gemcitabine, topotecan, irinotecan plus mitomycin C were 25%, 20%, 41.7%, (Table 3).

The one-, three-, and five-year survival rates were 94.1%, 59.5%, and 26.9%, respectively, and the median survival time was 26 (6~132) months in the 53 patients. The overall survival had significant correlation with the factors of tumor staging ($p < 0.05$), residual tumor ($p < 0.05$), response to initial chemotherapy ($p < 0.05$), response to second-line chemotherapy ($p < 0.05$), and PFS ($p < 0.05$) by single factor analysis. Then the authors evaluated the single factors by COX regression analysis. As shown in Table 4 , the OS is markedly correlated with tumor staging ($p = 0.027$), response to second chemotherapy ($p = 0.003$), PFS ($p = 0.014$), and residuals ($p = 0.019$). As the Kaplan–Meier survival analysis showed, a significant difference of proportion survival was seen in patients between no visible residual tumor and residual less than 1 cm ($p < 0.05$, Figure 2); the median survival times were 72, 26, and 15 months in patients with no residual, residual with a diameter less than 1 cm, and residual with a diameter more than 1 cm, respectively.

Discussion

Advanced CCC is associated with a very poor prognosis and resistance to standard treatment [16]. In the present study, patients with recurrent CCC from Stage III to IV accounted for 83% of the total 53 patients. Previous study displayed that the five-year survival rate of recurrent CCC was lower than recurrent serous adenocarcinoma (22.5% *vs*. 32.4%) and recurrent CCC had a higher rate of relapse in the lymph nodes (pelvic, para-aortic, and other lymph nodes) and parenchymal organs (liver, lung, bone, spleen, brain, and others), compared with high-grade serous ovarian cancer (40% *vs*. 7%, 40% *vs*. 13%) [17]. The present study showed similar results of five-year survival rate with 26.9% and 45.3% (24/53) of relapse sites with parenchymal organs and 32.1% (17/53) of relapse sites with lymph node in abdominopelvic cavity, indicated that the recurrent CCC were more likely to occur in advanced stages with parenchymal organs metastasis and with much lower long-term survival rates.

One indicator widely used in response to prognosis and chemotherapy of recurrent CCC is PFI. However the present study did not fully comply with PFI. Takano *et al.* [18] reported that PFI had no predictive value for long-term chemosensitivity in recurrent CCC patients and Esposito *et al.* [14] showed no obvious relationship between the RR and PFI in the study of platinum-based chemotherapy in patients with recurrent disease. The present study showing no relationship between the RR and PFI in patients with recurrent disease was in accordance with these studies, which may be related with the less recurrent cases. More research must be done to verify the relationship between PFI and RR.

Non-platinum regimen was chosen in the present study as second-line therapy. Esposito *et al.* [14] showed that the RR to non-platinum regimen (primary medicine: gemcitabine, topotecan, and caelyx) was 32% in 50 platinum-resistant patients with recurrent CCC. Furthermore, the

RR to gemcitabine therapy was as high as 66%. In the present study, the authors chose gemcitabine, topotecan, and irinotecan plus mitomycin C for recurrent CCC. Irinotecan + mitomycin C, administered in 24 cases, showed a higher activity (RR=41.7%) compared with topotecan (RR=20%) and gemcitabine (RR=25%). Irinotecan, as a DNA topoisomerase-I (TOPO-I) inhibitior, demonstrated potent antitumor activity against ovarian cancer. Kunito *et al.* [19] reported that a combination of irinotecan and cis-platinum had the potential therapic effect on CCC and had similar disease-free survival with the combination of PTX and carboplatin. A combination of irinotecan and mitomycin C, which could improve the efficacy of irinotecan [20], was found to be an effective treatment in CCC in the study by Shimizu *et al.* [21]. The positive efficacy of irinotecan has been showed in the present study. Due to these patients with platinum resistance, irinotecan was not combined with platinum-based drugs.

In the present study, COX regression analysis showed that OS had significant correlation with tumor staging ($p = 0.027$), residuals ($p = 0.019$), response to second-line chemotherapy ($p = 0.003$), and PFS ($p = 0.014$). Takano *et al.* [22] observed that no visible residual tumor was the only independent factor for prognosis. In the present study, the factor of no visible residual could improve the OS of patients with recurrent CCC, and the OS was shown with a marked difference between patients with no residual and residuals, even with optimal cytoreductive surgery (residual diameter <1 cm, $p < 0.05$), indicating that no visible residual is a critical factor in the prognosis of patients with recurrent CCC.

The present study has some limitations. It was a retrospective analysis which may have affected the results due to unmeasured confounder. Furthermore, the authors failed to reach the significant difference of the efficacy between irinotecan and topotecan, which may due to the less cases for the two groups. Lesser samples in this study was the main impediment in the investigation.

Conclusion

Initial surgery with no residual is critical in the prognosis of CCC patients, even with optimal cytoreductive surgery. Furthermore, CCC with recurrence is more likely to occur in a parenchymal organ. Irinotecan, as one kind of effective chemotherapy regimen, is preferred to be conducted in patients with recurrent CCC.

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