

Original Article



The post-progression survival of patients with recurrent or persistent ovarian clear cell carcinoma: results from a randomized phase III study in JGOG3017/GCIG

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ABSTRACT

Objective: In this study we sought to investigate the clinical factors that affect post-progression survival (PPS) in patients with recurrent or persistent clear cell carcinoma (CCC).

We utilized the JGOG3017/Gynecological Cancer InterGroup data to compare paclitaxel plus carboplatin (TC) and irinotecan plus cisplatin (CPT-P) in the treatment of stages I to IV CCC.

Methods: We enrolled 166 patients with recurrent or persistent CCC and assessed the impact of variables, including platinum sensitivity, treatment arm, crossover chemotherapy, primary stage, residual tumor at primary surgery, performance status, ethnicity, and tumor reduction surgery at recurrence on the median of PPS in patients with recurrent or persistent CCC.

Results: A total of 77 patients received TC, and 89 patients received CPT-P. The median PPS for patients with platinum-resistant disease was 10.9 months, compared with 18.8 months for patients with platinum-sensitive disease (hazard ratio [HR]=1.88; 95% confidence interval [CI]=1.30–2.72; log-rank $p < 0.001$). In the multivariate analysis, the platinum sensitivity (resistant vs. sensitivity; HR=1.60; $p = 0.027$) and primary stage ($p = 0.009$) were identified as independent predictors of prognosis factors for PPS in recurrent or persistent CCC.

Conclusions: Our findings revealed that platinum sensitivity and primary stage are clinical factors that significantly affect PPS in patients with recurrent or persistent CCC as well

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Presentation

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Conflict of Interest

K.E., T.T., S.N., Y.H., K.Y., T.F., S.T., Y.N., and S.T. have nothing to conflict of interest.

Dr. Aoki (A.D.) reports personal fees from Daiichi Sankyo Co., Ltd., Yakult Honsha Co., Ltd., and Nippon Kayaku Co., Ltd., for the outside the submitted work.

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Author Contributions

Data curation: K.E., T.T., S.N.; Formal analysis: K.E., T.T.; Investigation: A.D., Y.H., K.Y., T.O., F.K., K.E., T.F., S.T., O.A., Y.N., E.T., S.T.; Writing - original draft: K.E., T.T.

as other histologic subtypes of ovarian cancer. PPS in patients with recurrent CCC should establish the basis for future clinical trials in this population.

Keywords: Recurrence; Platinum; Ovarian Cancer; Survival

INTRODUCTION

The number of patients with ovarian cancer is increasing, with current rates approximately 1.3 times higher than they were 10 years ago [1]. In 2018, 295,414 new cases of ovarian cancer and 184,799 deaths were reported worldwide. Clear cell carcinoma (CCC) is a histologic subtype of epithelial ovarian cancers (EOC). It has been defined by the World Health Organization as lesions characterized by clear cells growing in solid/tubular or glandular patterns as well as hobnail cells [2]. The prevalence of CCC is higher in Asian women, particularly in the Japanese population, where it accounts for 24%–26.9% of all EOCs [3–5].

CCC is associated with poor patient outcomes and has previously demonstrated resistance to chemotherapy [3,6–10]. CCC has also been identified as an independent predictor of prognosis in stage III/IV EOC. Furthermore, CCC is associated with a higher incidence of recurrence in the early stages (I & II) than other subtypes [3,6,9,11,12]. Therefore, we formed the Japanese Gynecologic Oncology Group (JGOG) 3017/Gynecological Cancer InterGroup (GCIG) Trial, which is a randomized phase III study designed to compare paclitaxel plus carboplatin (TC) and irinotecan plus cisplatin (CPT-P) in the treatment of stages I to IV CCC. Over a median follow-up period of 44.3 months, we did not observe a significant difference in efficacy between the 2 treatment arms [13]. Of the 619 patients with CCC, 166, excluding those who died of the disease without recurrence, had recurrent or persistent CCC. The 2-year progression-free survival (PFS) rate was 73% in the TC group and 77.6% in the CPT-P group. There was no significant difference in efficacy between the 2 groups [13]. Although cytotoxic drugs have conventionally been used to treat recurrent CCC, there have been no reports of effective or well-established therapies for recurrent or persistent ovarian CCC. Crotzer et al. [7] reported that the median PFS and overall survival (OS) rates for recurrent CCC were 8 and 18.8 months, respectively [7]. Other studies have reported a median PFS of 13 months [12], and a median OS of 25.3 months [9,14]. A median post-recurrent survival (PRS) of 10.0 months has also been described [9]. PRS is used synonymously with post-progression survival (PPS). PPS was defined as the time interval from the date of recurrence to the date of death or censoring on the date of the last follow-up. There is currently significant interest in the development of molecular targeted therapies or immune checkpoint inhibitors for the treatment of recurrent CCC. It has recently been reported that the immune checkpoint inhibitor nivolumab has demonstrated efficacy against recurrent CCC [15].

Few studies thus far have compared the prognosis and PPS of patients with recurrent or persistent CCC. Therefore, the aim of the present study was to analyze cases of recurrent or persistent CCC from the JGOG3017/GCIG trial and investigate the clinical factors that affect PPS in CCC. This information will enable us to carry out future clinical trials on recurrent or persistent CCC.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of Mie University Hospital (UMIN000035764) and approval was obtained from the Institutional Review Boards at all participating hospitals. The JGOG3017/GCIG trial was a randomized phase III study designed to compare TC versus CPT-P in patients with stages I to IV CCC. Out of an initial 667 patients, 43 patients (6.4%) were ineligible due to non-CCC histology, 4 withdrew from the study, and 1 was a duplicate. A total of 619 patients with CCC were eligible for inclusion in the final cohort.

Out of 619 patients with CCC eligible for inclusion in the JGOG3017/GCIG trial, 166 had recurrent or persistent CCC, excluding those who died of the disease without recurrence. Thus, a total of 166 patients with recurrent or persistent CCC were analyzed in a post hoc analysis of the JGOG3017/GCIG trial. The primary endpoint was the PPS of patients with recurrent or persistent CCC. We compared PPS using the following criteria: platinum sensitivity, treatment arm, crossover chemotherapy, primary stage, residual tumor at primary surgery, performance status (PS), ethnicity and tumor reduction surgery at recurrence. We defined the residual tumor at primary surgery as follows: complete, optimal (<1 cm), and suboptimal (>1 cm). The secondary endpoints of this study were the site of recurrence and the crossover rate between the two treatment arms. PPS was defined as the time interval from the date of recurrence to the date of death or censoring on the date of the last follow-up. Relapse was diagnosed by imaging. Progression was defined by imaging according to the Response Evaluation Criteria in Solid Tumors version 1.0. The modes of tumor recurrence were defined as peritoneal, lymph node metastasis, and distant metastases. Sites of distant metastases included brain, lung, liver, spleen, bone, and subcutaneous tissues.

All patients with stages I to IV CCC who presented consecutively during the period from September 2006 to February 2011 were enrolled. Continuous variables were compared using the Mann–Whitney test and categorical variables were compared using Fisher's exact test. The Kaplan–Meier method, log-rank test and Cox regression were used for PPS analysis.

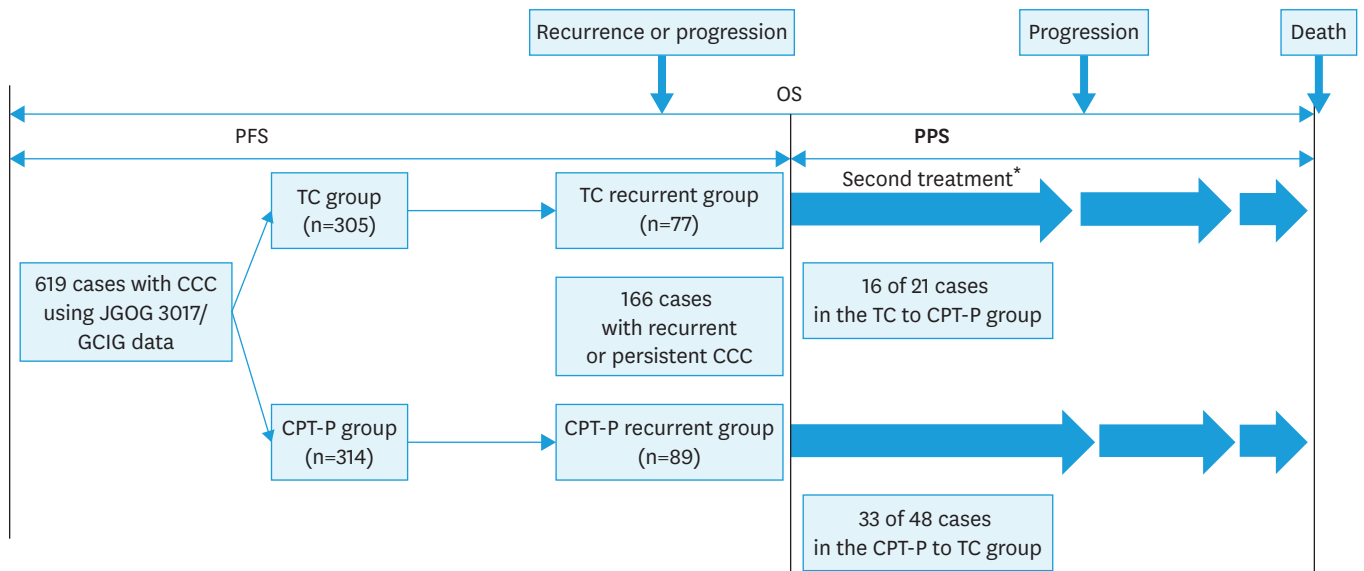
Cox-proportional hazards model was used to identify independent predictors of prognosis factors for PPS in recurrent or persistent CCC. Factors entered in the multivariable analysis include age, study arm, platinum sensitivity, primary stage, residual tumor at primary surgery and PS. Significance was set at $p < 0.05$. Statistical analysis was performed using R version 3.4.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The overall flow chart is shown in **Fig. 1** and the baseline characteristics of the cohort are shown in **Table 1**. Of the 619 patients, 166 had recurrent or persistent disease (3.6% stage IA/IB; 27.7% stage IC; 12% stage II; 48.2% stage III; and 8.4% stage IV). A total of 77 patients received TC, and 89 patients received CPT-P. The median age was 52 (45–59) years. There were 74 patients (44.6%) who were platinum-resistant (treatment-free period <182.6 days) and 88 patients (53%) who were platinum-sensitive (>182.6 days), with a median platinum-free interval (PFI) of 199.5 days.

The background characteristics of the TC and CPT-P groups are shown in **Table 2**. The baseline patient and disease characteristics were similar between the study groups. There

Recurrent or persistent ovarian clear cell carcinoma



*The patients who received second-line chemotherapy were considered subjects in crossover. Sixteen of 21 cases were eligible in the TC to CPT-P group, and 33 of 48 cases were eligible in the CPT-P to TC group.

Fig. 1. The overall flow chart.

CCC, clear cell carcinoma; JGOG, Japanese Gynecologic Oncology Group; GCIG, Gynecological Cancer InterGroup; PFS, progression-free survival; TC, paclitaxel plus carboplatin; CPT-P, irinotecan plus cisplatin; OS, overall survival.

Table 1. Baseline characteristics of the patients with recurrent or persistent CCC using JGOG3017/GCIG

Variable	Overall
No. of patients	166 (100.0)
Arm	
TC	77 (46.4)
CPT-P	89 (53.6)
Age	52.0 (45.0–59.0)
Race (%)	
Japanese	156 (94.0)
Non-Japanese	10 (6.0)
ECOG PS (%)	
0	133 (80.1)
1	30 (18.1)
Unknown	3 (1.8)
PFI	199.5 (27.0–364.0)
Platinum sensitivity	
Resistant	74 (44.6)
Sensitive	88 (53.0)
Unknown	4 (2.4)
Stage	
1A/1B	6 (3.6)
1C	46 (27.7)
2	20 (12.0)
3	80 (48.2)
4	14 (8.4)
Residual disease	
Complete	106 (63.9)
Optimal	27 (16.3)
Suboptimal	33 (19.9)

Values are presented as number of patients (%) or median (interquartile range).

CCC, clear cell carcinoma; JGOG, Japanese Gynecologic Oncology Group; GCIG, Gynecological Cancer InterGroup.

Table 2. Background characteristics of the TC and CPT-P groups

Variable	TC	CPT-P	p-value
No. of patients	77	89	
Age	51.0 (45.0–58.0)	53.0 (46.0–59.0)	0.390
Race			1.000
Japanese	72 (93.5)	84 (94.4)	
Non-Japanese	5 (6.5)	5 (5.6)	
ECOG PS			0.876
0	61 (79.2)	72 (80.9)	
1	15 (19.5)	15 (16.9)	
Unknown	1 (1.3)	2 (2.2)	
PFI	212.0 (60.5–410.5)	189.0 (25.5–354.5)	0.392
Platinum sensitivity			0.618
Resistant	31 (40.3)	43 (48.3)	
Sensitive	44 (57.1)	44 (49.4)	
Unknown	2 (2.6)	2 (2.2)	
Stage			0.629
1A/1B	2 (2.6)	4 (4.5)	
1C	25 (32.5)	21 (23.6)	
2	7 (9.1)	13 (14.6)	
3	37 (48.1)	43 (48.3)	
4	6 (7.8)	8 (9.0)	
Residual disease			0.769
Complete	49 (63.6)	57 (64.0)	
Optimal	14 (18.2)	13 (14.6)	
Suboptimal	14 (18.2)	19 (21.3)	

Values are presented as number of patients (%) or median (interquartile range).

TC, paclitaxel plus carboplatin; CPT-P, irinotecan plus cisplatin; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PFI, platinum-free interval.

were no significant differences in age, ethnicity, performance status (PS), PFI, platinum sensitivity, primary stage, or rate of residual disease between the two groups.

The characteristics of platinum-resistant and platinum-sensitive CCC are shown in **Table 3**. The majority of platinum-resistant patients (71.6%) initially presented as stage III (58.1%) or IV (13.5%) whereas the majority (54.6%) of platinum-sensitive patients had a primary stage of I (IA/IB 5.7%, IC 37.5%) or II (II 11.4%); the difference between these rates was significant ($p < 0.001$). Additionally, the rate of platinum-resistance/sensitivity differed significantly by ethnicity (0.92 [73/79] for Japanese vs. 0.11 [1/9] for non-Japanese; $p = 0.022$) and residual disease (0.42 [30/72] for complete vs. 1.70 [17/10] for suboptimal and 4.5 [27/6] for optimal; $p < 0.001$).

The primary endpoint in this study was PPS in patients with recurrent or persistent CCC ($n = 166$). The PPS rates were 79.4%, 58.2%, 40.8%, and 28.6% at 6, 12, 18, and 24 months, respectively, and the median PPS duration was 14.0 months. The Kaplan-Meier PPS curve is shown in **Fig. 2A**. A total of 166 patients with recurrent or persistent CCC in both the TC and CPT-P groups were analyzed (**Fig. 2B**). The median PPS was 13.5 months in the TC group, and 14.4 months in the CPT-P group, and there was no significant difference between the 2 groups (hazard ratio [HR]=1.02; 95% confidence interval [CI]=0.71–1.47; log-rank $p = 0.898$). The median PPS (10.9 months) of patients with platinum-resistant CCC ($n = 74$) was shorter than the median PPS (18.8 months) of patients with platinum-sensitive CCC ($n = 88$) (HR=1.88; 95% CI=1.30–2.72; $p < 0.001$), as shown in **Supplementary Fig. 1A**. There was no significant difference in median PPS between the PS 0 group (15.0 months) and the PS 1 group (8.4 months) (HR=1.25; 95% CI=0.79–1.99; $p = 0.340$). Finally, we estimated the median PPS of Japanese vs. non-Japanese patients with recurrent or persistent CCC. In the non-Japanese

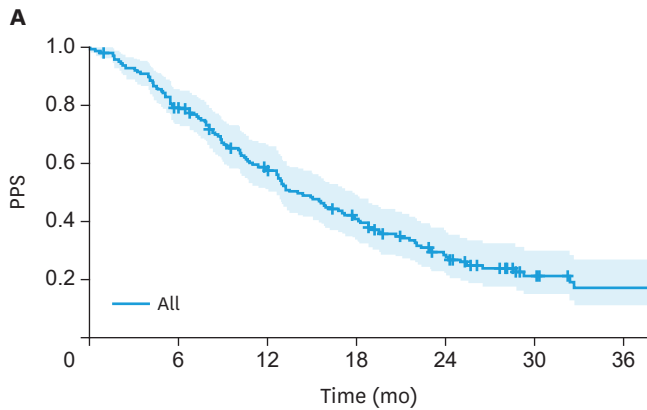
Recurrent or persistent ovarian clear cell carcinoma

Table 3. Background characteristics of the platinum-resistant and platinum-sensitive groups

Variable	Resistant	Sensitive	p-value
No. of patients	74	88	
Arm			0.344
TC	31 (41.9)	44 (50.0)	
CPT-P	43 (58.1)	44 (50.0)	
Age	50.0 (45.0–58.8)	53.0 (46.0–59.0)	0.471
Race (%)			0.022
Japanese	73 (98.6)	79 (89.8)	
Non-Japanese	1 (1.4)	9 (10.2)	
ECOG PS (%)			0.064
0	56 (75.7)	77 (87.5)	
1	18 (24.3)	11 (12.5)	
Stage (%)			0.001
1A/1B	1 (1.4)	5 (5.7)	
1C	10 (13.5)	33 (37.5)	
2	10 (13.5)	10 (11.4)	
3	43 (58.1)	36 (40.9)	
4	10 (13.5)	4 (4.5)	
Residual disease (%)			<0.001
Complete	30 (40.5)	72 (81.8)	
Optimal	17 (23.0)	10 (11.4)	
Suboptimal	27 (36.5)	6 (6.8)	

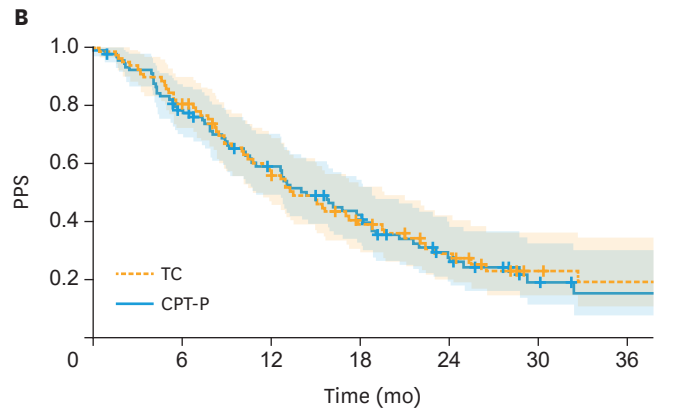
Values are presented as number of patients (%) or median (interquartile range).

TC, paclitaxel plus carboplatin; CPT-P, irinotecan plus cisplatin; ECOG, Eastern Cooperative Oncology Group; PS, performance status.



No. at risk	166	129	89	58	34	14	9
All	166	129	89	58	34	14	9

Month	PPS rate (95% CI)	Median PPS (95% CI)
6	79.4 (73.4–85.8)	14.0 (12.6–17.9)
12	58.2 (51.1–66.4)	
18	40.8 (33.7–49.3)	
24	28.6 (22.0–37.0)	



No. at risk	77	62	42	26	17	7	5
TC	77	62	42	26	17	7	5
CPT-P	89	67	47	32	17	7	4

Variable	CPT-P	TC	HR (95% CI)	Log-rank p
Median PPS (month, 95% CI)	14.4 (11.0–18.8)	13.5 (11.4–19.6)	1.02 (0.71–1.47)	0.898
6 months PPS rate (% , 95% CI)	78.4 (70.2–87.5)	80.5 (72.1–89.9)		
12 months	59.0 (49.4–70.5)	57.4 (47.2–69.8)		
18 months	42.4 (32.9–54.6)	39.0 (29.3–52.1)		
24 months	27.9 (19.4–40.2)	29.1 (20.1–42.3)		

Fig. 2. The Kaplan-Meier PPS curve of (A) all patients and (B) TC group and CPT-P group, separately.

PPS, post-progression survival; TC, paclitaxel plus carboplatin; CPT-P, irinotecan plus cisplatin; CI, confidence interval; HR, hazard ratio.

group, the median PPS was 18.2 months, compared to 13.3 months in the Japanese group; the difference between the 2 groups was not significant (HR=0.77; 95% CI=0.34–1.76; p=0.537).

The second chemotherapeutic regimens for the patients in this study were: TC (n=65; 39.2%), CPT-P (n=28; 16.9%), liposomal doxorubicin (n=12; 7.2%), other (n=36; 21.7%), and unknown (n=25; 15.1%). The treatment regimens with a total implementation rate of <5% were classified as other. The secondary endpoint of this study was a crossover comparison, whereby patients who received first-line TC/second-line CPT-P were compared with patients who received first-line CPT-P/second-line TC. The patients who subsequently received the second-line chemotherapies were the crossover subjects. Out of 21 patients, 16 were eligible for inclusion in the TC to CPT-P group, and 33 out of 48 patients were eligible to be in the CPT-P to TC group. The median PPS was 13.5 months in the TC to CPT-P group and 16.8 months in the CPT-P to TC group, with no significant difference between the 2 groups (HR=1.08; 95% CI=0.57–1.97; p=0.809). The PPS was slightly prolonged in platinum sensitive patients, with a median PPS of 22.9 months in the TC to CPT-P group and 17 months in the CPT-P to TC group.

Assessed by stage, the median PPS was 11.3 months for stage IA/IB (HR=2.05; 95% CI=0.77–5.47; p=0.139), 24 months for stage II (HR=0.85; 95% CI=0.42–1.74; p=0.665), 12.9 months for stage III (HR=2.00; 95% CI=1.25–3.22; p=0.003), and 7.1 months for stage IV (HR=3.22; 95% CI=1.64–6.31; p<0.001) (**Supplementary Fig. 1B**), compared with a median PPS of 18.8 months for stage IC. Furthermore, we compared PPS by residual tumor at primary surgery. The median PPS was 13.3 months for the optimal group (HR=1.18; 95% CI=0.72–1.93; p=0.509), and 8.8 months for the suboptimal group (HR=2.10; 95% CI=1.36–3.26; p<0.001), compared to 17.2 months in the complete group. The prognoses for the advanced stage or residual tumor (suboptimal >1 cm) groups were particularly poor relative to the early stage or initial complete groups.

We performed multivariate analysis, and have found that Cox-proportional hazards model identified independent predictors of prognosis factors for PPS in recurrent or persistent CCC. Factors entered in the multivariable analysis include age, treatment arm, platinum sensitivity, stage, residual tumor at primary surgery and PS (**Table 4**). The platinum sensitivity (resistant vs. sensitivity; HR=1.60; 95% CI=1.06–2.43; p=0.027) and primary stage (p=0.009) were identified as independent predictors of prognosis factors for PPS in recurrent or persistent CCC.

Table 4. Multivariate Cox regression analysis of prognosis factors for post-progression survival in recurrent or persistent CCC.

Variable	Level	HR (95% CI)	p-value	p-value by variable
No. of patients		162		
Age		1.01 (0.99–1.03)	0.410	
Arm	CPT-P/TC	1.03 (0.71–1.50)	0.882	
Platinum sensitivity	Resistant/Sensitive	1.60 (1.06–2.43)	0.027	
Stage (%)	1A and 1B/1C	2.13 (0.79–5.70)	0.133	0.009
	2/1C	0.70 (0.33–1.48)	0.352	
	3/1C	1.66 (0.97–2.84)	0.066	
	4/1C	2.60 (1.24–5.44)	0.012	
Residual disease	Optimal/Complete	0.79 (0.45–1.37)	0.394	0.197
	Suboptimal/Complete	1.37 (0.80–2.34)	0.247	
ECOG PS	1/0	1.01 (0.61–1.67)	0.979	

HR, hazard ratio; CI, confidence interval; CPT-P, irinotecan plus cisplatin; TC, paclitaxel plus carboplatin; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Finally, we analyzed whether there was a difference in the site of recurrence between the TC and CPT-P groups. This was also examined in the platinum-resistant and platinum-sensitive groups. The modes of tumor recurrence were classified as peritoneal, lymph node metastasis, and distant metastasis. The results for site of recurrence were as follows: 90 patients (54.2%) had peritoneal recurrence, 55 patients (33.1%) had pelvic and/or para-aortic metastatic lymph node recurrence, and 59 patients (35.5%) had distant metastases. Peritoneal metastasis occurred in 61% of the TC group, 48.3% of the CPT-P group, 56.8% of the platinum-resistant group, and 53.4% of the platinum-sensitive group. Lymph node metastasis occurred in 23.4% of the TC group, 41.6% of the CPT-P group, 31.1% of the platinum-resistant group, and 33.0% of the platinum-sensitive group, whereas distant metastasis occurred in 36.4% of the TC group, 34.8% of the CPT-P group, 39.2% of the platinum-resistant group, and 34.1% of the platinum-sensitive group. A total of 15 patients (9%) received tumor reduction surgery at recurrence. The PPS rates were 100.0%, 92.3%, 73.8%, and 73.8% at 6, 12, 18, and 24 months, respectively, the median PPS was not applicable (NA) (26.5 NA) in the tumor reduction surgery group. In the non-tumor reduction surgery group, the PPS rates were 77.3%, 54.8%, 37.7%, and 24.5% at 6, 12, 18, and 24 months, respectively. The median PPS was significantly different between the tumor reduction group (26.5 NA) and the non-tumor reduction surgery group (12.9 months) (HR=0.23; 95% CI=0.09–0.63; p=0.002).

DISCUSSION

Although most researchers agree that recurrent CCC is associated with resistance to standard treatment, the prognosis remains poorly understood. Kajiyama et al. [9] reported that the PRS (used synonymously with PPS) of patients with recurrent CCC was 10.0 months. In the study presented here, patients with recurrent CCC had a median PPS of 14.0 months. The median PPS of patients with platinum-resistant CCC was 10.9 months—shorter than the 18.8 months of patients with platinum-sensitive CCC. The rate of platinum-resistant cases to platinum-sensitive cases also differed significantly by residual disease for complete cases compared to suboptimal or optimal cases.

We also compared PPS by residual tumor at primary surgery. The median PPS for the suboptimal group were significantly reduced compared with the median PPS of the complete group at primary surgery. The prognoses for the advanced stage or residual tumor (suboptimal: >1 cm) groups were particularly poor relative to the early stages or initial complete groups.

Furthermore, in the multivariable analysis, the platinum sensitivity (resistant vs. sensitivity; HR=1.60; 95% CI=1.06–2.43; p=0.027) and primary stage (p=0.009) were identified as independent predictors of prognosis factors for PPS in recurrent or persistent CCC. However, residual tumor (optimal vs. complete, HR=0.79; 95% CI=0.45–1.37; p=0.394, suboptimal vs. complete, HR=1.37; 95% CI=0.80–2.34; p=0.247) were not identified.

To the best of our knowledge, CCC is markedly resistant to first- or second-line chemotherapy. Our findings indicate that platinum sensitivity and primary stage comprise the most significant clinical factors that influence PPS in patients with recurrent or persistent CCC.

Previous studies have reported that the PFS, PRS and OS were poor for recurrent CCC than for other EOCs [7,9,12,14,16,17]. A cohort consisting of 51 patients treated for recurrent CCC

reported that the median duration of PFS was 8 months, and the median OS was 18 months [7]. Kajiyama et al. [9] reported that the 5-year OS was 22.5 months in a Japanese population. Another study of 164 patients with recurrent CCC reported that the median PFS was 4 months and the median OS was 22.6 months [17]; however, this study did not involve a central pathology review.

The present study included 166 patients with recurrent or persistent CCC, which is the largest number of patients reported to date. Sensitivity and resistance to platinum-based chemotherapy for recurrent CCC has previously been reported to be 65% and 35%, respectively, in the MITO-9 study [16]. In the present study, 74 patients (44.6%) were platinum-resistant. This slight increase compared to the MITO-9 study is likely due to the fact that only 56% of patients were diagnosed with pure clear cell histology in the MITO-9 cohort. Furthermore, the relatively high number of platinum-resistant patients described here may have been related to study demographics, as >90% of the patients in our cohort were Japanese.

In the present study, there were no differences in PPS according to the type of chemotherapy received (TC or CPT-P). Consistent with a previous report, we found that stage and residual disease ≥ 1 cm (suboptimal surgery) as well as Japanese ethnicity may be prognostic factors. A subset analysis that sought to examine the ethnic differences in treatment and survival of Asian-American patients with EOC found that Vietnamese, Filipino, Chinese, Korean, Japanese, and Asian Indian/Pakistani ethnicities had 5-year disease-specific survival rates of 62.1%, 61.5%, 61.0%, 59%, 54.6%, and 48.2%, respectively ($p=0.001$) [18].

The prognoses for patients in the advanced stages are particularly poor relative to the early stages. However, in this study stages IA/IB and IC were associated with worse prognoses than stage II. This is likely due to the small number of stage IA/IB ($n=6$) and stage II ($n=20$) patients. Additionally, complete surgery was not performed on stage I patients; therefore, adhesions with the rectum, bladder, peritoneum, and endometriosis may have remained, which could include microscopic residual lesions. Matsuo et al. reported that among apparent stage I EOCs, the clear cell type possesses a disproportionately high risk of capsule rupture during adnexectomy and is associated with the worst prognosis [19]. However, these findings are limited due to the retrospective nature of the study and the small number of recurrent stage IA/IB ($n=6$) and stage II ($n=20$) patients.

Compared with other studies [20,21], the median PPS (10.8 months) for patients with recurrent platinum-resistant CCC was no different from other EOCs. However, the median PPS was significantly shorter for patients with recurrent platinum-sensitive CCC (18.8 months) than for patients with other EOCs. Generally, the median OS of recurrent platinum-sensitive high-grade serous carcinoma (HGSC) is >24 months with second-line platinum therapy [22], indicating that the use of a cytotoxic drug alone has limits in the treatment of recurrent platinum-sensitive or platinum-resistant CCC. The PFS of recurrent platinum-sensitive HGSC is clearly prolonged by the administration of a PARP inhibitor [23]. Unlike HGSC, which is chemotherapy-sensitive, complete resection at primary surgery is undoubtedly an important prognostic factor owing to the longer PFS, PPS and OS for CCC associated with complete resection. However, even in patients with early stage or complete surgery, the recurrence rate of CCC was high.

Although treatments with drugs, such as nivolumab may be beneficial in the future, further research is needed to assess the role of immunotherapy and the value of multidisciplinary treatment with surgery and standard chemotherapy in CCC. Several investigators have reported about the development of molecular targeted therapy for the treatment of CCC. Since the PI3K/AKT/mTOR signaling pathway is hyperactivated in CCC, strategies aimed at inhibiting this pathway may have therapeutic benefits [24]. The Gynecologic Oncology Group (GOG)-268 trial is an open-label, phase II trial for newly diagnosed stage III and stage IV ovarian CCC to examine the activity of temsirolimus, one of the mTOR inhibitors. The primary endpoint of this trial is the PFS rate at 12 months. The NRG-GY001 trial reported that the median PFS and OS of cabozantinib in recurrent ovarian CCC were 3.6 and 8.1 months, respectively [25]. Sunitinib is a highly potent, selective inhibitor of protein tyrosine kinases, including vascular endothelial growth factor-receptor and platelet-derived growth factor-receptor, that has demonstrated minimal activity in second- and third-line treatment of persistent or recurrent clear cell ovarian carcinoma in the GOG-254 trial [11]. The median PFS was 2.7 months, and the median OS was 12.8 months [11]. However, only a few small clinical studies have reported on the efficacies of temsirolimus, sunitinib, and cabozantinib for ovarian CCC [11,25,26].

The patterns of relapse with CCC were also analyzed. We identified 90 patients (54.2%; 90/166) with peritoneal recurrence, 55 patients (33.1%; 55/166) with pelvic and/or para-aortic metastatic lymph node recurrence, and 59 patients (35.5%; 59/166) with distant metastases. The primary sites of recurrence that have previously been reported in patients with CCC have been the pelvis (11.4%) and distant metastatic lymph nodes (11.4%), however lymphadenectomy was performed in 41.8% of women with CCC [27]. The reported pelvic and para-aortic lymph node recurrence rate was 25% in patients with CCC, and 77.8% of such patients were not treated with lymphadenectomy [28]. Additionally, there was a high rate of lymph node metastases (33.1%), even in patients treated with pelvic and para-aortic lymphadenectomy. Lymphadenectomy is usually performed for CCC, but the survival benefits associated with lymphadenectomy for CCC are controversial [28-30]. However, Harter et al. reported that the frequency of lymph node metastases was 55% in EOC and HGSC, equivalent to that in CCC [31]. No CCC-specific recurrence site was identified in the present study.

In this study, we identified platinum sensitivity and primary stage as one of the clinical factors that affects post-progression survival in patients with recurrent or persistent CCC, as well as other histologic subtypes of ovarian cancer. Estimates of PPS in patients with recurrent CCC should serve as the basis for future clinical trials involving this patient population.

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SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

The median PPS curve. (A) The median PPS rates for patients with platinum-resistant (n=74) and platinum-sensitive (n=88) CCC. (B) The Kaplan–Meier PPS curve for patients with stages I A/ IB, IC, II, III, and IV separately.

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