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Impact of surgical optimality on the survival for patients diagnosed with clear cell carcinoma of ovary: a propensity score analysis with long-term follow-up

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Summary

Purpose of Investigation: The authors aimed to investigate the impact of surgical optimality on clear cell carcinoma (CCC) versus serous adenocarcinoma of ovary (SAC). *Materials and Methods:* A retrospective analysis of a prospectively collected healthcare database in a single institution, recruiting consecutive patients diagnosed with Stage III epithelial ovarian cancer between January 2001 and December 2010, was conducted. *Results:* For optimal disease, median overall survival (95% confidence interval) was 57.1 (42.5−78.6) months for SAC and 52.6 (35.3−61.1) months for CCC, respectively (hazard ratio = 1.28, $p = 0.222$). For suboptimal disease, the corresponding value was 43.3 (36.5−58.2) months for SAC and 24.6 (21.9−37.1) months for CCC, respectively (hazard ratio = 2.33, $p < 0.001$). *Conclusion:* For optimal residual disease, CCC shows equal survival to SAC, while for suboptimal residual disease, CCC still shows very dismal outcome compared to SAC, suggesting the urgent need to test novel drugs to treat this subset of patients.

Key words: Ovarian cancer; Clear cell carcinoma; Serous carcinoma; Optimal disease.

Introduction

Clear cell carcinoma (CCC) of ovary represents distinctly clinical behavior and molecular expression profile from that of other subtypes of epithelial ovarian cancer [1]. CCC harbors the characteristics of having a high incidence of Stage I disease, rarely occur bilaterally, and is often associated with endometriosis, thromboembolic complications, and metabolic disturbances [2-4].

Compared with other subtypes, CCC has been recognized to show a chemoresistant phenotype to platinum-based chemotherapy, leading to poorer prognosis [5]. Several mechanisms involved in drug resistance have been proposed for CCC, including decreased drug efflux, increased DNA repair activity, and increased drug detoxification [6-8].

Although the incidence of CCC is low in Europe (4%) [9], and the United States (5%) [10]; however, some countries in Asia, for example Japan and Taiwan, show an incidence of up to 20% [11, 12]. Up to now, seminal reports of survival analysis regarding CCC were mainly published from the western countries [13-16], compared to less reports from high incidence countries [11, 17], and all these reports were essentially observational studies or pooling analysis of clinical trial studies. With the advent of more options of second-line chemotherapy (e.g., liposomal doxorubicin approved in 2005, and gemcitabine approved in 2006) and targeted therapy, especially anti-angiogenesis agents in the treatment of ovarian cancer, it is time to update the survival analysis of CCC.

Database analyses belong to one kind of observational studies, which can generate credible evidence despite of some inherent drawbacks. They are more clinically relevant than randomized trials, with better generalizability and applicability in routine clinical practice. However, the major drawback of an observational study is that its validity is threatened by confounding by indication [18], which occurs when treatments are preferentially prescribed to some group of patients based on their underlying characteristics [19]. Conventional statistical methods used to adjust for confounding (e.g., multivariable regression, a conventional methods used in the analysis of CCC), may lead to biased results [20]. Recently, there has been increasing interest in applying propensity score technique to reduce or to eliminate the effects of confounding when analyzing observational data [21].

The pivotal role of surgical optimality, defined by the amount of residual disease, in the treatment of advanced ovarian cancer has been well established [22]. In published

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Table 1. — *Clinical characteristics of eligible patients before and after propensity score matching stratified by residual tumor status*[a]

	Suboptimal						Optimal					
	before matching			after matching			before matching			after matching		
	SAC (n = 189)	CCC (n = 82)	p value	SAC (n = 71)	CCC (n = 71)	p value	SAC (n = 146)	CCC (n = 87)	p value	SAC (n = 83)	CCC (n= 83)	p value
Age (mean ± SD)	50.5 (± 4.6)	53.8 (± 6.8)		52.1 (± 4.8)	52.7 (± 4.9)		50.8 (± 4.6)	54.2 (± 6.1)		51.6 (± 5.9)	52.9 (± 5.8)	
BMI												
< = 18.5	14 (7.2%)	6 (7.2%)		3 (4.1%)	4 (6.2%)		9 (5.9%)	6 (6.8%)		5 (5.6%)	6 (7.2%)	
18.6 - 24.9	126 (66.5%)	53 (64.8%)		51 (72.3%)	53 (74.6%)		101 (69.3%)	67 (77.1%)		63 (76.3%)	63 (75.9%)	
25.0 - 29.9	43 (22.5%)	15 (18.9%)		15 (21.1%)	12 (16.3%)		31 (21.2%)	11 (12.7%)		13 (15.4%)	11 (13.2%)	
> = 30.0	6 (3.8%)	7 (9.1%)		2 (2.5%)	2 (2.8%)		5 (3.6%)	3 (3.4%)		2 (2.7%)	3 (3.6%)	
			0,261			0,963			0,433			0,971
GOG Performance												
0 or 1	168 (88.9%)	59 (72.4%)		60 (84.2%)	59 (83.1%)		102 (69.7%)	73 (83.9%)		70 (84.6%)	72 (86.6%)	
> = 2	21 (11.1%)	23 (27.6%)		11 (15.8%)	12 (16.9%)		44 (30.1%)	14 (16.1%)		13 (15.4%)	11 (13.4%)	
			< 0.001			0,813			0,015			0,658
Front-line regimen												
Non Paclitaxel-based	64 (33.9%)	13 (15.8%)		3 (4.2%)	3 (4.2%)		33 (22.8%)	11 (12.6%)		8 (9.4%)	7 (8.6%)	
Paclitaxel-based	125 (66.1%)	69 (84.1%)		68 (89.4%)	68 (95.8%)		113 (77.2%)	76 (87.3%)		75 (90.6%)	76 (91.4%)	
			< 0.001			0,999			0,019			0,786
Route of front-line regimen												
intravenous	155 (82.1%)	60 (72.9%)		65 (91.5%)	59 (82.8%)		105 (71.9%)	77 (88.5%)		73 (87.8%)	75 (90.8%)	
intraperitoneal	34 (17.9%)	22 (27.1%)		6 (8.5%)	12 (17.2%)		31 (21.2%)	10 (11.5%)		10 (12.2%)	8 (9.2%)	
						0,131			< 0.001			0,617
Maintenance chemotherapy[b]												
no	156 (82.3%)	51 (62.5%)		51 (71.8%)	50 (70.4%)		123 (84.3%)	65 (74.7%)		64 (77.1%)	63 (75.9%)	
9 6	33 (17.7%)	31 (37.5%)		20 (28.2%)	21 (29.6%)		23 (15.7%)	22 (25.3%)		19 (22.9%)	20 (20.1%)	
			0,028			0,673			0,036			0,515
Bowel obstruction[c]												
no	160 (84.6%)	65 (79.2%)		65 (92.1%)	64 (90.5%)		134 (91.8%)	72 (82.7%)		72 (86.7%)	72 (86.7%)	
9 6	29 (15.3%)	17 (20.7%)		6 (8.5%)	7 (9.5%)		14 (9.5%)	15 (17.2%)		11 (13.3%)	11 (13.3%)	
			0,002			0,771			< 0.001			0,999
Charlson co-morbidity index												
0	152 (80.5%)	61 (74.3%)		58 (81.2%)	60 (84.6%)		129 (88.4%)	66 (75.9%)		67 (80.7%)	65 (78.3%)	
> = 1	37 (19.5%)	22 (26.8%)		13 (18.3%)	11 (15.4%)		17 (11.6%)	21 (24.1%)		16 (19.3%)	18 (21.7%)	
			0,021			0,653			0,008			0.416
Use of bevacizumab[d]												
no	174 (92.1%)	72 (87.8%)		62 (87.3%)	63 (88.7%)		127 (86.9%)	70 (80.4%)		66 (79.5%)	68 (81.9%)	
9 6	15 (7.9%)	10 (12.2%)		9 (12.7%)	8 (11.3%)		19 (13.1%)	17 (19.5%)		17 (20.5%)	15 (18.1%)	
			0,038			0,828			0,044			0,693

Abbreviation: CCC, clear cell carcinoma; SAC, serous ovarian carcinoma

[a] Use nearest 1:1 matching with caliper = 0.25σ as a matching algorithm (s = standard deviation of logit of propensity score); [b] Mainly intravenous paclitaxel on a monthly administration; [c] Diagnosed either in front-line or second-line treatment

[7] Used in either front-line or second-line setting

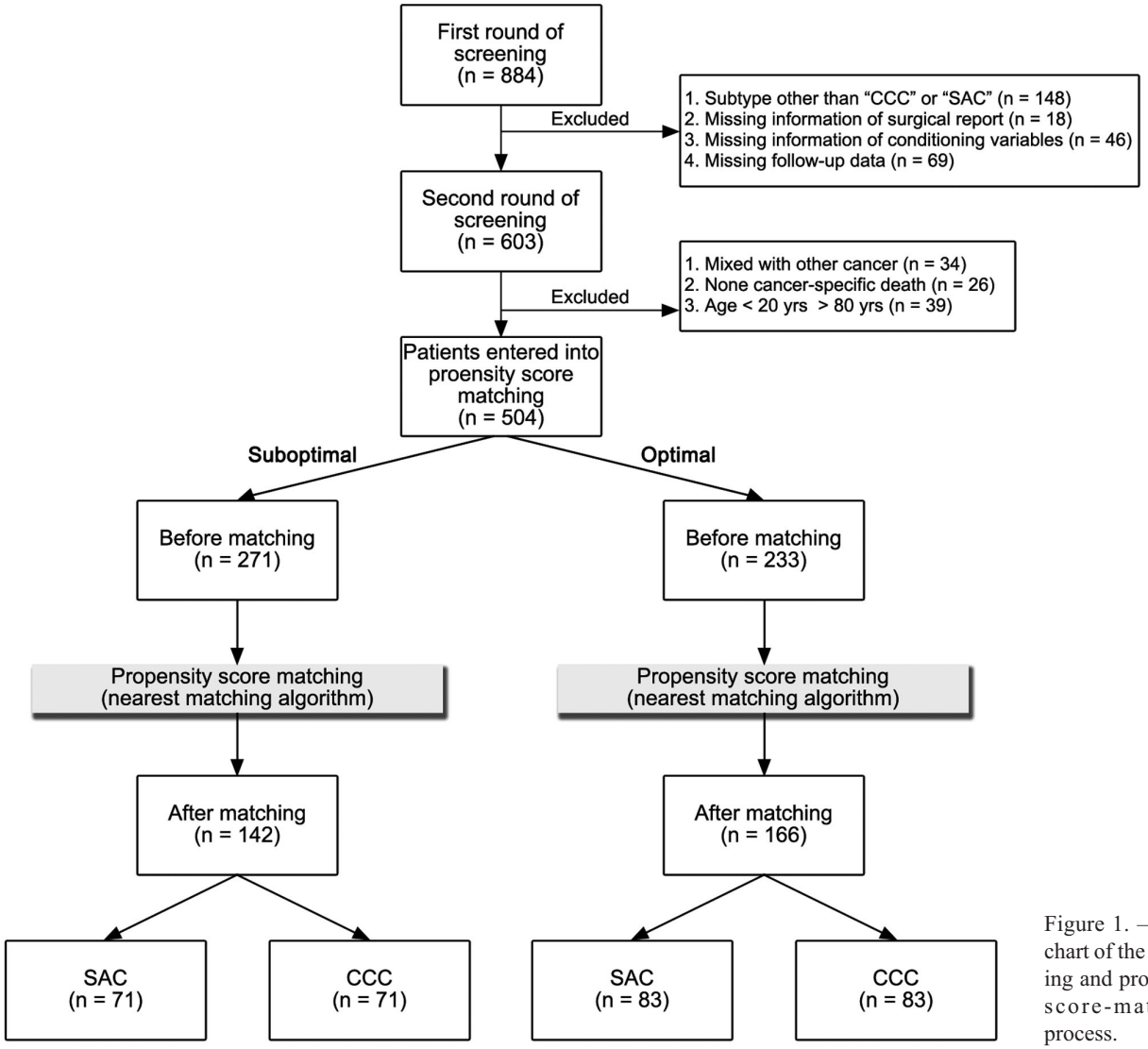

Figure 1. — Flow chart of the screening and propensity score-matching process.

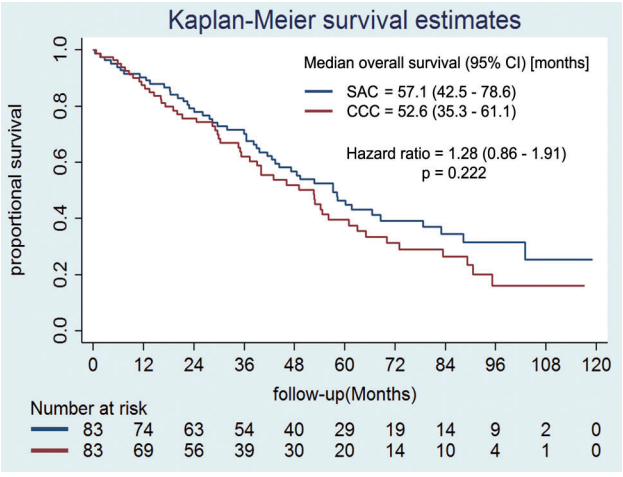

Figure 2. — Kaplan-Meier overall survival for optimal residual disease.

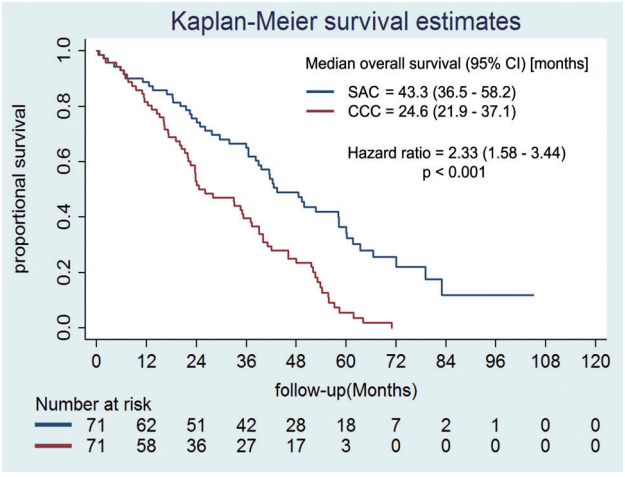

Figure 3. — Kaplan-Meier overall survival for suboptimal residual disease.

Table 2. — *Comparison of distribution pattern of platinum sensitivity in recurrent patients stratified by optimal and suboptimal residual disease*

Recurrent patients	Type of platinum sensitivity			
	Platinum-refractory	Platinum-resistant	Platinum-sensitive	p value
		Optimal residual		
SAC (n = 49)	6 (12.2%)	12 (24.5%)	31 (63.3%)	
CCC (n = 50)	8 (16.0%)	13 (26.0%)	29 (58.0%)	
				0.826
		Suboptimal residual		
SAC (n = 48)	31 (64.6%)	11 (22.9%)	6 (12.5%)	
CCC (n = 66)	59 (89.4%)	7 (10.6%)	0 (0%)	
				< 0.001

Abbreviations: CCC, clear cell carcinoma; SAC, serous ovarian carcinoma

[a] Data are presented as number (%)

literature, the impact of surgical optimality on the survival outcome of CCC has rarely been investigated. In this work, the authors adopted a propensity score matching technique to evaluate the impact of surgical optimality on CCC outcome, using a prospectively collected administrative healthcare database constructed in a tertiary-care center based in Taiwan, a country with high incidence of CCC.

Materials and Methods

The current study entailed a retrospective analysis of a prospectively collected healthcare database in a single institution (Taipei Veterans General Hospital), recruiting consecutive patients diagnosed with Stage III epithelial ovarian cancer between January 2001 and December 2010. Diagnosis of histological subtypes of epithelial ovarian cancer, including serous, endometrioid, mucinous, clear cell, undifferentiated, or mixed type were carefully reviewed by a senior pathology expert (C.R. Lai).

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital. The procedures used in this study were performed according to the guidelines of the Helsinki Declaration on human experimentation.

Standard primary cytoreductive surgery included total hysterectomy, bilateral salpingo-oophorectomy, retroperitoneal lymph nodes sampling, infracolicomentectomy, and cytoreduction of all tumor nodules in the peritoneal cavity. The gynecologic oncologist took responsibility for the initial step of surgery, with the aim of removing all resectable tumors. An ad-hoc general surgeon or colorectal surgical specialist team was consulted once bowel, liver, spleen, or pancreas surgery was deemed necessary. If the patient had undergone any stomy procedure, then a specific stomy care team provided nursing and educational support.Optimal debulking surgery was defined as residual tumor implant with diameter less than one cm according to Gynecologic Oncology Group (GOG) [23].

Patients with recurrent disease are categorized as platinum-resistant disease and included patients who progressed while receiving initial chemotherapy (defined as platinum-refractory) or within six months (defined as platinum-resistant), or greater than six or more (defined as platinum-sensitive) of completing initial platinum-based chemotherapy [24].

Continuous variables are presented as the mean (± standard deviations) and compared using Student's unpaired *t*-test. Categorical variables are presented as counts and percentages and are compared using the c^2 test when appropriate (expected frequency > 5). Overall survival was defined as the duration from the date of initial diagnosis to death or last follow-up. The date of the last follow-up was arbitrarily set on October 31, 2014. Survival was estimated using the Kaplan-Meier method and compared using the log-rank test.

For propensity score analysis, which is a summary confounder score that is modeled using exposure or treatment (e.g., IP chemotherapy in the current work), was used as the dependent variable for score calculation and matching [25, 26].

For the matching procedure, the authors performed a two-step analysis. At step 1, they used nine conditioning variables to develop propensity scores. At step 2, they used an algorithm of the nearest neighbor matching within a specified caliper distance (0.25s in the current study; s, standard deviation of logit of propensity score) without replacement to create matched samples [27, 28]. Thus, for a given experimental subject (i.e., case with diagnosis of CCC), one would identify all of the control subjects (i.e., case with diagnosis of SAC) whose propensity score lay within a specified distance of that of the experimental subjects. From this restricted set of control subjects, the control subject whose propensity score that was closest to that of the experimental subject would be selected for matching to this experimental subject. Eventually, two samples with an equal sample size (i.e., CCC *vs*. SAC with 1:1 matching) would be created. All analyses were performed using STATA SE version 12; $p < .05$ was considered statistically significant.

Results

Eight hundred and eighty-four patients were initially identified from the database. After the first round of screening, patients who fulfill the following defined criteria, including histological subtype other than SAC or CCC, missing information of surgical report, missing conditioning variables, and missing follow-up data, were excluded. Next, more scrutinized screening was performed in the remaining patients (n = 603). Patients who had no cancer-

specific death, coexistent with other cancer, and age less than 20 or greater 80 years, were further excluded. Remained patients (n = 504) were dichotomized into optimal or suboptimal residual disease and were entered into propensity score matching process.

Calculation of propensity score was conducted for each patient based on the following nine conditioning variables, including age, body mass index, GOG performance score, histological grade, regimen for front-line chemotherapy, delivery route of front-line regimen, maintenance chemotherapy, bowel obstruction, Charlson co-morbidity index, and use of bevacizumab. The reason why these conditioning variables were chosen was that they were associated with survival outcome but were not balanced between SAC and CCC before matching, except for body mass index distribution. After propensity score matching, all conditioning variables were well balanced (Table 1). A flow chart describing the steps of screening and matching process is presented in Figure 1.

Next, Kaplan-Meier overall survival curves for both optimal and suboptimal residual disease are presented (Figure 2 for optimal disease and Figure 3 for suboptimal disease, respectively). For optimal disease, median overall survival (95% confidence interval) was 57.1 (42.5−78.6) months for SAC and 52.6 (35.3−61.1) months for CCC, respectively (hazard ratio = 1.28, $p = 0.222$, log-rank test). For suboptimal disease, the corresponding value was 43.3 (36.5−58.2) months for SAC and 24.6 (21.9−37.1) months for CCC, respectively (hazard ratio = 2.33, $p < 0.001$, log-rank test). Collectively, for optimal disease, SAC and CCC shows no survival difference, while for suboptimal disease, CCC showed worse survival than SAC.

During the long-term follow-up of matched patients, for optimal disease, 59.0% (49/83) in SOC and 60.2% (50/83) in CCC were eventually found to have disease recurrence. The distribution pattern stratified by platinum sensitivity showed no different distribution pattern ($p = 0.826$, Chi-square test). In contrast, for suboptimal disease, 67.6% (48/71) in SAC and 92.9% (66/71) in CCC were eventually found to have disease recurrence. The distribution pattern stratified by platinum sensitivity showed significantly different distribution pattern, with higher proportion belongs to platinum-refractory category in CCC patients ($p < 0.001$, Chi-square test) (Table 2).

Discussion

Overall, CCC has been recognized as a chemoresistant subtype; the present data show that, for optimal residual disease, CCC and SAC show equal survival for Stage III disease. In contrast, for suboptimal residual disease, CCC shows very dismal prognosis compared with SAC, displaying less than 5% chance of five-year survival (Figure 3). As such, the present authors propose here that, for optimal residual disease of Stage III disease, CCC can be treated with current standard therapy. However for suboptimal disease, there is an urgent need to develop novel therapy for this subset of patients.

The results of the current work are partially in line with those reported by Sugiyama *et al.* [17]. In that report, the estimated survival rates in patients with no gross tumor were not significantly different between CCC and SAC, both survival rates in the patients with < two cm macroscopic residual disease and those with ≥ two cm residual disease were significantly lower in CCC than in SAC. The only difference between the present and their report is that, for < one cm macroscopic residual tumor, CCC showed equal survival to SAC in this report, while CCC shows worse survival than SAC in Sugiyama *et al.*'s report. It is speculated that this difference may be due to more options of second-line chemotherapy and the advent of targeted therapy, especially bevacizumab, in the treatment of ovarian cancer [29-32].

Molecular pathway studies have recently provided a dualistic model for ovarian carcinogenesis, which are designated as type I, where precursor lesions have clearly been described, and type II, where such lesions have not been described clearly and tumors may develop de novo from the tubal and/or ovarian surface epithelium [33]. In the context of this dual model, CCC belongs to type I, while SAC belongs to type II ovarian cancer. It has been shown that the molecular signature of CCC is characterized by the activation of stress-related genes and metabolism-related genes [34]. Among these genes, HNF-1b plays a critical driving force in the biology of CCC [35]. Further, gene expression microarray data combined with bioinformatic tools have demonstrated that sorafenib, a multi-kinase inhibitor, shows a promising candidate drug in the treatment of CCC [36]. Collectively, for patient diagnosed with CCC who have suboptimal residual tumor, it is advised to test the efficacy of sorafenib in a clinical trial setting.

Although the current work demonstrated that surgical optimality plays a critical role in the treatment of CCC; however, the present study still encompasses several limitations. First, the composition of the study subjects may be affected by referral bias due to its monocentric design. Second, there is missing patient-level information. For example, socioeconomic factors have been found to be associated with cancer mortality [37], and the lack of this important conditioning variable may affect the reliability of the estimated propensity score. Third, the propensity score-matched samples may not be representative of the original study population of interest, and thus, the external validity may be compromised [38, 39].

Conclusion

In conclusion, although it is well established that CCC shows a chemoresistant phenotype, the present data demon-

strated that, for optimal residual disease, CCC shows equal survival to SAC. This finding represents a little improvement of survival as compared to previous report of CCC [17] which may be a reflection of more options of second-line chemotherapy and the advent of targeted therapy in the past ten years. However, for suboptimal residual disease, CCC still shows very dismal outcome compared to SAC, suggesting the urgent need to test novel drugs to treat this subset of patients. Microarray profiling data combined with bioinformatic tools have demonstrated that sorafenib, a multi-kinase inhibitor, shows a promising role in the treatment of CCC. As such, it may be pertinent to test this drug for CCC patients who have suboptimal residual disease in a clinical trial setting. Furthermore, a world-wide prospective clinical study to compare irinotecan plus cisplatin (CPT-P) *vs*. paclitaxel plus carboplatin (TP) as the first-line chemotherapy for CCC, GCIG/JCOG (Gynecologic Cancer Intergroup/Japanese Gynecologic Oncology Group) 3017, is now ongoing [40]. All this information indicates that novel therapy may eventually replace the current paclitaxel-based standard therapy for the treatment of CCC in the future.

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