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Original Article

The efficacy of secondary cytoreductive surgery for recurrent ovarian, tubal, or peritoneal cancer in Tian-model low-risk patients

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ABSTRACT

Objective: In patients with recurrent ovarian cancer (ROC) in whom surgery is likely to render them disease-free, it is unclear whether secondary cytoreductive surgery (SCS) combined with chemotherapy is superior to chemotherapy alone. The aim of this study was to evaluate the 2 treatment options in Tian-model low-risk patients.
Methods: We retrospectively reviewed 118 ROC cases treated in our hospital between 2004 and 2016. Of these, 52 platinum-sensitive cases were classified as low-risk (complete resection anticipated) using the Tian model. Prognostic factors were assessed with univariate and multivariate analysis using Cox's regression model. Progression-free survival (PFS) and overall survival (OS) were compared in patients treated with SCS plus chemotherapy (SCS group) and those treated with chemotherapy alone (chemotherapy group), using a propensity-score-based matching method.
Results: By multivariate analysis, the only factor associated with better OS was SCS. PFS and OS were significantly longer in the SCS group compared to the chemotherapy group in the matched cohort (median PFS: 21.7 vs. 15.1 months, p=0.027 and median OS: 91.4 vs. 33.4 months, p=0.008, respectively). In cases with multiple-site recurrence, the SCS group also showed significantly longer OS than the chemotherapy group (median 91.4 vs. 34.8 months, p=0.022). In almost all SCS cases, cooperation was required from other departments, and operation time was lengthy (median 323 minutes); however, no serious complications occurred.
Conclusion: SCS combined with chemotherapy results in better PFS and OS than chemotherapy alone in first platinum-sensitive ROC patients categorized as low-risk by Tian's model.

Keywords: Carcinoma, Ovarian Epithelial; Recurrence; Cytoreduction Surgical Procedures; Chemotherapy; Tian Model

INTRODUCTION

Ovarian, tubal, or peritoneal cancer (ovarian cancer) is increasing, with approximately 5,000 people dying annually from the disease in Japan [1]. According to global estimates, 295,414 new cases and 184,799 deaths occur each year [2]. Approximately two thirds of patients with ovarian cancer present with advanced stage disease due to lack of early symptoms. This

Presentation
This study was presented in 'SGO 50th annual meeting on women's cancer in 2019' on March 2019.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: S.M., M.T., B.T.; Data curation: A.K., H.J., B.T.; Formal analysis: S.M., M.T., M.R.; Investigation: S.M., M.T.; Methodology: S.M., M.T., B.T.; Project administration: B.T.; Resources: M.R.; Software: S.M., M.T., M.R.; Supervision: M.M.; Validation: M.R., A.K., H.J., B.T., M.M.; Visualization: S.M., M.T.; Writing - original draft: S.M.; Writing - review & editing: M.T., M.R., A.K., H.J., B.T., M.M.

results in a high recurrence rate within 12 to 18 months [3]. Thus, it is important to explore effective treatment for recurrent ovarian cancer (ROC).

Secondary cytoreductive surgery (SCS) is a treatment option for ROC when complete resection is anticipated, as prognosis is better with SCS if resection is complete than if it is incomplete [4,5]. In 2012, Tian et al. [6] established a model for preoperative prediction of complete resection in SCS. The model categorized platinum-sensitive ROC patients into low-risk and high-risk groups by scoring 6 variables: International Federation of Gynecology and Obstetrics (FIGO) stage, macroscopic residual disease after primary cytoreduction, disease-free interval (DFI), performance status (PS) at recurrence, cancer antigen 125 (CA125) at recurrence, and ascites at recurrence. The low-risk group is regarded as suitable for SCS. The Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) model is another commonly used means of establishing selection criteria for SCS [7]. Although these models evaluate predictors for complete resection, it remains unclear whether SCS combined with chemotherapy is superior to chemotherapy alone, this being the main therapy for ROC in patients who meet the criteria [8].

In this study, we compared the efficacy of SCS combined with chemotherapy to chemotherapy alone for the treatment of first recurrence in ROC patients in whom evaluation by the Tian model predicted that surgery would likely render them disease-free.

MATERIALS AND METHODS

This is a retrospective study and ethics approval was granted by the Kyoto University Graduate School and Faculty of Medicine, Ethics Committee (reference number G531). Informed consent was waived because of the retrospective nature of the study.

A total of 435 patients with ovarian cancer were treated in our hospital between 2004 and 2016. Of these, 118 with first recurrence were analyzed. Patients were excluded if treatment was initiated due to increasing tumor markers without detectable lesions (n=4). The diagnosis of first recurrence was based on physical examination and diagnostic imaging such as computed tomography (CT), magnetic resonance imaging or positron emission tomography-CT. We scored the 118 cases using the Tian model (**Supplementary Table 1**). Of 70 cases who were classified as low-risk, we excluded 18 platinum-resistant cases, defined as less than 6 months of DFI. These patients were also excluded in Tian's study [6]. In 52 platinum-sensitive and Tian-model low-risk cases, 22 were treated with SCS plus chemotherapy (SCS group) and 30 were treated with chemotherapy alone (chemotherapy group). Suitability for SCS was comprehensively assessed in each case according to the patient's age and PS, histologic type, DFI, sites of recurrence, and ascites volume. We discussed treatment options in a multidisciplinary cancer team, including radiologists, oncologists and, if necessary, urologists or surgeons. Clinicians informed the patients of the options proposed at this meeting, and the patients made the final treatment selection. Prognostic factors were assessed with univariate and multivariate analysis using Cox proportional hazards regression model. We also applied the propensity-score matching method. Finally, 44 cases (22 cases each in the SCS and chemotherapy groups) were compared (**Fig. 1**).

For subgroup analysis, we divided the 52 cases into those with multiple-site recurrence (n=41) and those with solitary site recurrence (n=11). The diagnosis of multiple or solitary sites was

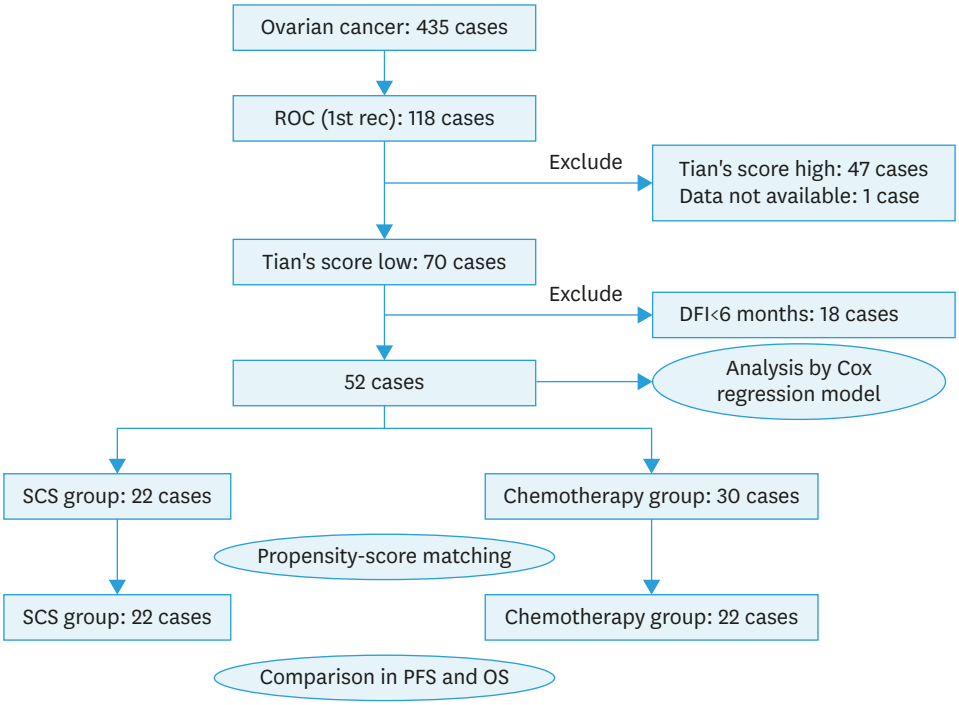

Fig. 1. Flow chart for this study.
DFI, disease-free interval; OS, overall survival; PFS, progression-free survival; ROC, recurrent ovarian cancer; SCS, secondary cytoreductive surgery.

based on the imaging performed initially, not on intraoperative tumor count at SCS. The propensity-score matching method was also used, after which the SCS group was compared to the chemotherapy group (16 cases in each group).

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics [9]. Propensity scores were estimated using package "matching" [10], and calculated using a logistic regression model based on clinical variables considering distribution of the data. Optimal one-to-one matching without replacement was performed. Fisher's exact probability test, Mann-Whitney U test and Student's t-test were used to compare the groups. Survival curves were constructed using the Kaplan-Meier method. All tests were 2-sided and p-values <.05 were considered significant. A Bonferroni adjustment was applied to correct the effect of multiple analyses and the threshold for the significance was set at 0.017 (0.05/3).

RESULTS

1. Patient characteristics

The patient characteristics are shown in **Table 1**. The cases with poor PS were removed from the chemotherapy group after propensity-score matching. The year of treatment, age at recurrence, histologic type, FIGO stage, neoadjuvant chemotherapy at primary treatment, residual disease at primary debulking surgery, the number of recurrence sites, DFI, PS at recurrence, CA125 level at recurrence, ascites at recurrence, chemotherapy regimen for

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recurrence, and Tian score were not significantly different in the matched cohort. Recurrence patterns of the SCS group were as follows: multiple peritoneal implants 5, peritoneal implant(s) and lymph node(s) 5, peritoneal implant(s) and a distinct organ 4, multiple lymph nodes 2, single peritoneal implant 2, single lymph node 2, single distinct organ 2. Recurrence patterns of the chemotherapy group were as follows: peritoneal implant(s) and lymph node(s) 10, multiple peritoneal implants 6, peritoneal implant(s) and a distinct organ 4, single peritoneal implant 3, multiple lymph nodes 2, distinct organ(s) 2, lymph node(s) and a distinct organ 2, single lymph node 1. Platinum-doublet chemotherapy without bevacizumab was used in the majority of cases of adjuvant treatment in the SCS group and

Table 1. Patient characteristics of entire and matched cohort

Characteristics	Before matching			After matching		
	SCS	Chemotherapy	p-value	SCS	Chemotherapy	p-value
No. of patients	22	30		22	22	
Age at recurrence (yr)	63.5 (36–73)	65 (46–82)	0.227	63.5 (36–73)	60 (46–82)	0.769
FIGO stage			0.226			0.137
I	7	3		7	2	
II	2	2		2	2	
III	10	20		10	17	
IV	3	5		3	1	
Histologic type			0.061			0.226
High grade serous	10	22		10	15	
Clear cell	6	1		6	1	
Endometrioid	2	3		2	2	
Mucinous	1	0		1	0	
Others	3	4		3	4	
NAC at primary surgery			0.573			1.000
Yes	8	14		8	8	
No	14	16		14	14	
Debulking at primary surgery			0.775			1.000
Complete	15	19		15	14	
Not complete	7	11		7	8	
DFI (mo)			1.000			1.000
≥16	14	20		14	14	
<16	8	10		8	8	
PS at recurrence			0.502			1.000
0	22	28		22	22	
Others	0	2		0	0	
No. of recurrence sites			0.495			0.457
Multiple	16	25		16	19	
Solitary	6	5		6	3	
CA125 at recurrence (U/mL)			1.000			0.721
≤105	18	24		18	16	
>105	4	6		4	6	
Ascites at recurrence			1.000			1.000
Yes	0	0		0	0	
No	22	30		22	22	
Year of treatment for recurrence			1.000			1.000
2004–2008	4	6		4	3	
2009–2013	7	10		7	7	
2014–2016	11	14		11	12	
Chemotherapy for recurrence (or adjuvant therapy after SCS)			0.578			0.612
Platinum-doublet without BEV	15	24		15	18	
Combination with BEV	3	3		3	2	
Other	4	3		4	2	
Tian score	2.3 (0.8–3.3)	2.3 (0.9–4.1)	0.525	2.3 (0.8–3.3)	2.3 (0.8–4.1)	0.561

Values are presented as median (interquartile range) or number (%).
BEV, bevacizumab; CA125, cancer antigen 125; DFI, disease-free interval; FIGO, International Federation of Gynecology and Obstetrics; NAC, neoadjuvant chemotherapy; PS, performance status; SCS, secondary cytoreductive surgery.

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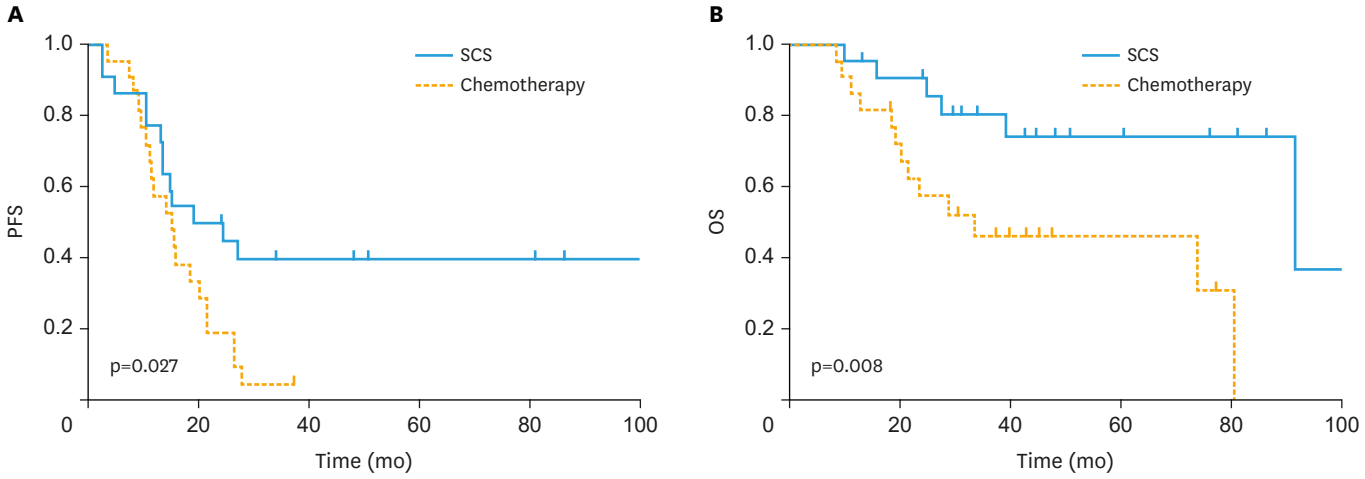

Fig. 2. Kaplan-Meier survival curves for the probability of PFS (A) and OS (B) in the SCS and chemotherapy groups for the entire cohort.
OS, overall survival; PFS, progression-free survival; SCS, secondary cytoreductive surgery.

as the chemotherapy regimen in the chemotherapy group. A few instances of bevacizumab usage were observed in both groups. We did not examine BRCA status in this study and no patients were treated with poly (ADP-ribose) polymerase (PARP) inhibitors.

2. Survival analysis

Solitary recurrence and SCS were potential better prognostic factors for overall survival (OS) after first recurrence in univariate analysis. Multivariate analysis revealed that only SCS was associated with better OS (**Table 2**). In the matched cohort, the median progression-free survival (PFS) and OS after first recurrence were 21.7 and 91.4 months in the SCS group and 15.1 and 33.4 months in the chemotherapy group, respectively. The SCS group had

Table 2. Univariate and multivariate analysis for overall survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at recurrence (yr)				
≥60 vs. <60	1.483 (0.650–3.382)	0.349	1.258 (0.518–3.054)	0.613
FIGO stage				
I, II vs. III, IV	0.860 (0.356–2.078)	0.738	-	-
Histologic type				
High grade serous vs. others	0.639 (0.286–1.430)	0.276	-	-
NAC at primary surgery				
Yes vs. no	0.702 (0.299–1.648)	0.416	-	-
Debulking at primary surgery				
Complete vs. incomplete	0.604 (0.272–1.340)	0.215	0.896 (0.382–2.102)	0.801
DFI (mo)				
<16 vs. ≥16	1.193 (0.521–2.731)	0.676	-	-
PS at recurrence				
0 vs. others	0.283 (0.036–2.220)	0.230	0.199 (0.020–2.018)	0.172
No. of recurrence sites				
Multiple vs. solitary	4.454 (1.044–19.00)	0.044*	4.242 (0.865–20.82)	0.075
CA125 at recurrence (U/mL)				
>105 vs. ≤105	1.738 (0.687–4.393)	0.243	-	-
SCS				
Yes vs. no	0.241 (0.088–0.658)	0.005*	0.286 (0.104–0.788)	0.016*

CA125, cancer antigen 125; CI, confidence interval; DFI, disease-free interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NAC, neoadjuvant chemotherapy; PS, performance status; SCS, secondary cytoreductive surgery.
*Statistically significant.

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significantly longer PFS and OS than the chemotherapy group (PFS: hazard ratio [HR]=0.45; 95% confidence interval (CI)=0.22–0.91; p=0.027 and OS: HR=0.28; 95% CI=0.11–0.72; p=0.008) (**Fig. 2**). The rate of complete resection of SCS was 73% (16/22). The complete resection group had significantly longer OS (median, 91.4 months) than the chemotherapy group (HR=0.25; 95% CI=0.10–0.66; p=0.007), while no difference was observed between the incomplete resection group (median, 39.1 months) and the chemotherapy group (HR=0.63; 95% CI=0.18–2.24; p=0.477).

3. Subgroup analysis in multiple and solitary site recurrence

Of the 41 patients with multiple-site recurrence, 16 had SCS and chemotherapy and 25 had chemotherapy alone. After matching by propensity score, 16 cases in each group were compared. There was no significant difference in patient characteristics (**Supplementary Table 2**). Although no significant difference was observed in PFS, the median OS was significantly longer in the SCS group than in the chemotherapy group (91.4 vs. 34.8 months; HR=0.32; 95% CI=0.12–0.85; p=0.022) (**Fig. 3**). Despite 44% (7/16) of patients having preoperatively detected recurrence in more than 4 sites, the complete resection rate was acceptable at 69% (11/16).

Six of 11 patients with solitary site recurrence underwent SCS. All patients were alive for a median 60.2 months of follow-up, including 5 patients who were disease-free (**Supplementary Table 3**).

4. Surgical findings at SCS

Surgical findings at SCS are shown in **Table 3**. 95% (21/22) of the surgery required assistance from a general surgeon, and the operation time tended to be long with a median of 323 minutes (interquartile range, 221–630). The median blood loss was 593 mL (interquartile range, 128–2,055). Transfusion was performed in 8 cases (36%). Perioperative complications included intraoperative inferior vena cava injury (n=1), intestinal obstruction (n=4), portal vein thrombosis (n=1), and surgical site infection (n=1) after surgery. No perioperative deaths were observed.

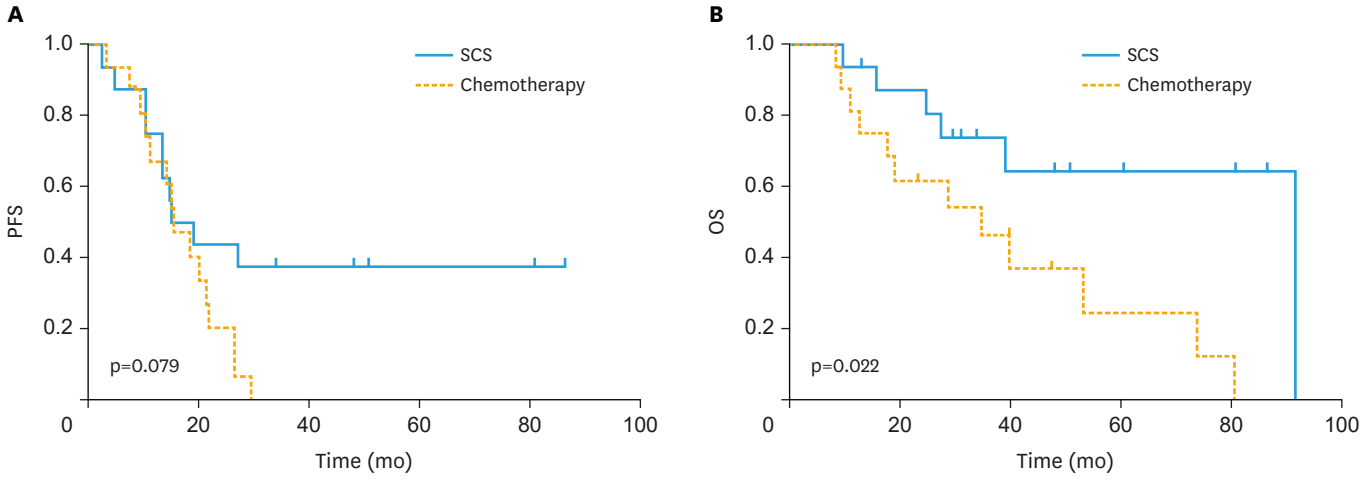

Fig. 3. Kaplan-Meier survival curves for the probability of PFS (A) and OS (B) in the SCS and chemotherapy groups in patients with multiple-site recurrence.
OS, overall survival; PFS, progression-free survival; SCS, secondary cytoreductive surgery.

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Table 3. Surgical findings of secondary cytoreductive surgery

Variables	Values
Resected lesion	Peritoneal implants 18 (82)
	Extrapelvic peritoneum 11 (50)
	Diaphragm 4 (18)
	Gastrointestinal 10 (45)
	Intestine/colon 8 (36), stomach 2 (9)
	Hepatobiliary 10 (45)
	Liver 4 (18), spleen 5 (23), gallbladder 2 (9)
	Lymph nodes 9 (41)
	Pelvic/para-aortic 4 (18)
	Other distant lymph nodes 5 (23)
	Genitourinary 6 (27)
	Brain 1 (5)
Cooperation with other departments	None 1 (5)
	1 department 12 (54)
	≥2 departments 9 (41)
Operation time (min)	323 (221–630)
Bleeding (mL)	593 (128–2,055)
Transfusion	8 (36)
Perioperative complications	Intraoperative
	Inferior vena cava injury 1 (5)
	Postoperative
	Intestinal obstruction 4 (18)
	Portal vein thrombosis 1 (5)
	Surgical site infection 1 (5)
Hospitalization after operation (days)	16 (12–23)

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

DISCUSSION

It is commonly stated that complete resection at SCS correlates with better prognosis, but superiority of SCS combined with chemotherapy compared to chemotherapy alone in ROC patients has not been proven. This is the first study to show that SCS results in longer OS after recurrence than chemotherapy alone in a background-matched cohort. In this study, the OS after recurrence in the SCS group was 91.4 months, which was not inferior to previous reports of 54 or 82 months [11,12].

There is 1 retrospective study which compared SCS combined with chemotherapy to chemotherapy alone, considering the bias of patient background. It showed longer PFS but no improvement in OS in the SCS group [13]. Recently, Gynecologic Oncology Group (GOG) 213, the first randomized controlled trial (RCT) that compared SCS to chemotherapy, was reported. The result of this study showed no significant difference in PFS or OS between the 2 groups [14]. On the other hand, DESKTOP III, a similar RCT conducted in Europe, showed longer PFS in the SCS group; the OS analysis is still awaited [15]. The differing results of GOG 213 and DESKTOP III may be caused by the difference in patient selection criteria and bevacizumab use. No specific predefined criteria were detailed in GOG 213, while patients were selected based on the AGO model in DESKTOP III. This suggests the necessity for appropriate selection criteria for SCS. In addition, frequent use of bevacizumab in GOG 213 might have resulted in a decrease in surgical efficacy because of the high efficacy of bevacizumab. In this study, bevacizumab was used in only 3 cases in the SCS group and 2 in the chemotherapy group. This less frequent use of bevacizumab was due to late application to insurance in Japan. No patients in this study were treated with PARP inhibitors, another promising drug for ROC patients. Although these highly effective drugs may change

the priority of SCS in the future, SCS remains a valuable option in situations in which molecular target drug use is discouraged due to concerns about specific side effects, e.g. gastrointestinal perforation and chronic myelosuppression, as well as high drug cost.

The Tian model and AGO model are both commonly used to select appropriate patients for SCS. The AGO model decides on operability based on 3 variables: no macroscopic residual disease after primary cytoreduction, 0 or 1 PS at recurrence, and no ascites at recurrence. Patients who satisfy these criteria are regarded as AGO-positive (positive for SCS). Because the 3 factors are all included in the Tian model, most AGO-positive patients are categorized as low-risk with the Tian model. As cases with residual disease at the primary surgery are not eligible for SCS, the AGO model has stricter criteria than the Tian model. In fact, 18 of 52 cases categorized as low-risk by the Tian model were not classified as AGO-positive. In contrast, there were no Tian-model high-risk patients classified as AGO-positive in this study. The complete resection rate for Tian-model low-risk patients is not inferior to AGO-positive patient in previous reports; 80% vs. 82% by van de Laar et al. [11], and 88% vs. 87% by Cowan et al. [12]. Therefore, a wider range of patients qualify for SCS using the Tian model than the AGO model, without compromising the rate of complete resection.

It is noteworthy that SCS combined with chemotherapy was superior to chemotherapy alone in cases with multiple-site recurrence in this study. There is no study to compare SCS to chemotherapy in cases with multiple tumors. Because multiple organ involvement correlates with low complete resection rate [16] and poor prognosis [17], surgery for multiple-site recurrence is often discouraged. In this study, better prognosis was achieved by SCS with an acceptable rate of complete resection. This result implies that SCS is also effective for multiple-site recurrence if the patients are selected by appropriate preoperative criteria.

Although surgical time was lengthy, SCS was completed with no serious complications or deaths. However, almost all SCS could not be completed by the gynecologic oncologist alone. Preoperative discussion and intraoperative cooperation with other departments is necessary for safer and more effective surgery. Because SCS is technically challenging, it should be performed only at institutions with a high volume of cases and surgical experience and expertise.

Minimally invasive surgery (MIS) SCS should be considered to decrease the operative burden on patients. Feasibility of MIS for ROC has recently been reported [18,19], but the selection criteria and the oncologic outcome remain unclear. We are confident in using MIS for localized recurrence in lymph nodes or distant organs. There were 2 cases in this study treated by MIS using a thoracoscope for single mediastinal lymph node recurrence. However, for peritoneal implants, we should be cautious in the use of MIS, even if only one lesion is detected prior to surgery. We frequently encounter preoperatively-missed implants during surgery, and open surgery is more desirable than laparoscopic surgery to detect and remove them completely.

There are several limitations to this study. First, due to its retrospective nature, as well as being a single institution study, the reproducibility may be questioned. Second, we did not analyze second or later recurrences, or patients with Tian-model high-risk; therefore, the efficacy of SCS in these cases remains unclear. Finally, we cannot ignore the fact that there are some inoperable cases in the Tian-model low-risk group. One case which satisfied the Tian-model low-risk criteria was treated by chemotherapy alone for bilateral lung metastases, and SCS was not applicable. Thus, the Tian model does not provide absolute criteria to make a decision regarding SCS.

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In conclusion, SCS combined with chemotherapy correlated with longer OS after recurrence than chemotherapy alone for the treatment of first recurrence in platinum-sensitive ROC patients categorized as Tian-model low-risk. SCS should be considered even in cases with multiple-site recurrence, if the patients satisfy the criteria.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Tian's risk model for secondary cytoreductive surgery

Click here to view

Supplementary Table 2

Patient characteristics with multiple-site recurrence

Click here to view

Supplementary Table 3

Patient characteristics with SCS for solitary recurrence

Click here to view

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