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Survival Effects of Cytoreductive Surgery for Refractory Patients after Neoadjuvant Chemotherapy in Advanced Epithelial Ovarian Cancer

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Purpose: Salvage second-line chemotherapy is usually recommended for patients with advanced epithelial ovarian cancer (AEOC) who develop progressive disease (PD) after neoadjuvant chemotherapy (NAC). Herein, we investigated the role of cytoreductive surgery (CRS) for such patients.

Materials and Methods: We retrospectively reviewed the medical records of 36 patients with AEOC who developed PD after receiving NAC at two tertiary academic centers with different treatment strategies between 2001 and 2016. Patients who developed PD after NAC were consistently treated with CRS at one hospital (group A; n=13) and second-line chemotherapy at another (group B; n=23). The clinical characteristics and treatment outcomes were compared between the groups.

Results: Overall survival (OS) was longer in group A than in group B (19.4 months vs. 7.9 months; p=0.011). High-grade serous histology was associated with longer OS than non-high-grade serous types. In group A, optimal surgery resection (<1 cm) was achieved after CRS in 6 patients (46%). Multivariate analysis showed that the treatment option was the only independent predictive factor for OS (hazard ratio, 2.30; 95% confidence interval, 1.02–5.17; p=0.044).

Conclusion: CRS may result in a survival benefit even in patients with AEOC who develop PD after NAC.

Key Words: Neoadjuvant therapy, epithelial ovarian cancer, follow-up studies, treatment outcome, cytoreductive surgery

INTRODUCTION

Epithelial ovarian cancer (EOC) is the second most common type of gynecologic malignancy and the leading cause of death due to gynecologic cancer in Western nations.[1] In South Korea, the rate of ovarian cancer is continuously increasing and is associated with the highest mortality among gynecologic cancers.[2,3] Primary cytoreductive surgery (CRS) followed by platinum-based adjuvant chemotherapy is the standard treatment for patients with EOC.[4]

Recently, neoadjuvant chemotherapy (NAC) followed by CRS has shown outcomes similar to those obtained with primary CRS followed by adjuvant chemotherapy,[5,6] thus resulting in the use of NAC for patients with advanced ovarian cancer.[7] However, there is no definitive evidence of an optimal treatment strategy for patients who experience progressive disease (PD) after NAC, although second-line chemotherapy

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is recommended per the 2019 National Comprehensive Cancer Network (NCCN) guidelines.[8] The results of previous studies on breast and colorectal cancers have indicated that selective salvage surgical treatment can result in improved clinical outcomes, and some studies have investigated the use of a predictive marker with which to evaluate responses to neoadjuvant treatment:[9-12] surgery can improve the prognosis of patients with locally advanced breast cancer developing PD after NAC.[9] Similarly, surgery can be a salvage treatment option for patients with locally advanced colorectal cancer developing PD after neoadjuvant concurrent chemoradiotherapy.[12] Accordingly, the present study was designed to compare the treatment outcomes of CRS versus second-line chemotherapy for patients with advanced EOC (AEOC) who develop PD after NAC.

MATERIALS AND METHODS

The medical records of patients with EOC who were treated with platinum-based NAC at two urban tertiary academic hospitals in South Korea between January 2001 and December 2016 were retrospectively reviewed. According to the NCCN guidelines for EOC, NAC may be considered for patients with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV disease who are unlikely to undergo cytoreduction without any macroscopic residual tumor or for patients who are poor candidates for surgical treatment. Although both institutions have their own indications for NAC in patients with ovarian cancer (Table 1), these indications do not greatly differ. According to the criteria for NAC, patients with FIGO stage III or IV disease who were not candidates for primary CRS were included. Most patients were of poor performance status or had unresectable extraperitoneal disease (observed on computed tomography). Patients with other concurrent malignancies, Eastern Cooperative Oncology Group performance status score of >3, or abnormal end-organ function were excluded. Treatment responses to NAC were determined on the basis of radiologic evaluation after three cycles of chemotherapy. All patients underwent CRS at Samsung Medical Center (SMC) in Seoul, Korea (group A) or received second-line chemotherapy at the National Cancer Center (NCC) in Goyang, Korea (group B) (Fig. 1).

The correlations between variables were assessed using the Fisher exact or Student's t-test. Overall survival (OS) rates were estimated via Kaplan-Meier analysis. The log-rank test was used to compare survival curves. Cox regression analysis was performed to determine predictive factors for prognosis, along with hazard ratios (HRs). *P* values <0.1 were considered to be significant. This retrospective study was approved by the Institutional Review Boards of each institution who waived the need for informed consent (IRB No. National Cancer Center NCC 2018-0080, Samsung Medical Center 2019-03-084).

RESULTS

Between January 2001 and December 2016, a total of 36 patients developed PD after platinum-based NAC. The baseline patient characteristics are summarized in Table 1. The median patient age was 55 years. The presence of PD after NAC was determined on the basis of RECIST criteria 1.1.[13] More patients in group B had a relatively low performance status (p=0.01), and the histology was different between the groups. Group A had more cases of high-grade serous histology than group B (p=0.015). All malignancies were confirmed via biopsy specimens, fine-needle aspirate, or ascites cytology, and the serum levels of tumor markers were evaluated before administering any chemotherapeutic agent (Table 1). Nine patients (24.3%) were diagnosed with high-grade serous carcinoma (HGSC), eight with adenocarcinoma, and 19 (52.78%) with other histologies, such as clear cell or mucinous carcinoma. Eight patients (22.2%) were diagnosed via laparotomy, 5 (13.89%) via laparoscopic biopsy, 9 (25%) via fine-needle aspiration, and 13 (36.11%) via ascites cytology. Among the 13 patients who were diagnosed via ascites cytology, eight were finally diagnosed with adenocarcinoma; they did not undergo surgery, and hence, their tumor specimen was not collected. Accordingly, detailed histology information was not collected for these 13 (36.11%) patients. Moreover, in order to exclude non-ovarian malignancies, esophagogastroduodenoscopy and colonoscopy were performed for all patients in addition to using the exclusion criteria of the CA125/CA19-9 ratio or CEA level >20. All patients received three cycles of platinum-based NAC: 34 patients received paclitaxel and carboplatin, one received docetaxel and carboplatin, and one received carboplatin only.

Among all 36 patients, 13 (group A) underwent CRS followed by adjuvant chemotherapy when they were diagnosed with PD, whereas 23 (group B) received second-line chemotherapy when they were diagnosed with PD. In group A, 11 patients (84.6%) underwent total hysterectomy and bilateral salpingo-oophorectomy, 6 (46%) underwent bowel surgery, and 8 (61.5%) underwent metastatic tumorectomy. Interestingly, 6 patients (46.2%) achieved optimal surgery, with a residual tumor of <1 cm (Table 2). After CRS, 9 patients received platinum-based chemotherapy as an adjuvant treatment and 1 patient received docetaxel only. Among these 10 patients, 3 (33.3%) showed a partial response (PR) and seven developed PD. Moreover, 3 patients (33.3%) showed a PR to platinum-based chemotherapy after CRS in contrast to PD after previous platinum-based NAC (Table 2). Three patients could not receive postoperative chemotherapy, as their general condition was very poor.

In group B, 15 patients received topotecan single agent chemotherapy, six received pegylated liposomal doxorubicin, one received ifosfamide and cisplatin, and one continued with paclitaxel and carboplatin as the second-line treatment. Twelve patients developed PD, six of whom stopped chemotherapy owing to worsening general conditions. Four patients were lost

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to follow-up. Among the remaining 13 patients who were evaluated for their response to second-line chemotherapy, only 1 (7.7%) showed stable disease, whereas 12 developed PD (92.3%) (Table 2).

OS was longer in group A than in group B (19.4 months vs. 7.9 months; p=0.011). When patients were classified on the basis of clinical variables, high-grade serous histology was associated with a longer OS than non-high-grade serous types

Table 1. Patient Characteristics According to Treatment Strategies for Patients showing PD after NAC

	Total (n=36)	Group A; cytoreductive surgery (n=13)	Group B; second-line chemotherapy (n=23)	*p* value
Age (yr)	55.00±10.35	59.46±10.26	52.48±9.72	0.050
Pretreatment CA-125 level, median (range)	518.15 (23–31000)	501.3 (28–4580)	535 (23–31000)	0.949
FIGO stage				0.281
≤IIIb	1	1 (7.69)	0 (0.00)	
IIIc	17	7 (53.85)	10 (43.48)	
IV	18	5 (38.46)	13 (56.52)	
ECOG score				0.016
0	8	0 (0.00)	8 (34.78)	
1	23	10 (76.92)	13 (56.52)	
>2	3	1 (7.69)	2 (8.7)	
Unknown	2	2 (15.38)	0 (0.00)	
Histology				0.015
HGSC	9	6 (46.15)	3 (13.04)	
Adenocarcinoma, unspecified	8	0 (0.00)	8 (34.78)	
Others*	19	7 (53.85)	12 (52.17)	
Type of biopsy				0.799
Laparotomy	8	4 (30.77)	4 (17.39)	
Laparoscopy	5	2 (15.38)	3 (13.04)	
Fine-needle aspiration	9	2 (15.38)	7 (30.43)	
Ascites cytology	13	5 (38.46)	8 (34.78)	
Curettage	1	0 (0.00)	1 (4.35)	
Indications of NAC				
1. Inability to undergo complete resection				
- Involvement of the porta hepatis				
- Suprarenal lymph node metastasis				
- Dense infiltrative diaphragm mass >2 cm	13	5 (38.46)	8 (34.78)	0.398
- Multiple small bowel serosal involvement				
- Mesenteric root involvement				
2. Extraperitoneal disease				
- Liver parenchymal metastases				
- Extraperitoneal lymph node metastasis				
• Except malignant pleural effusion only	18	5 (38.46)	13 (56.52)	
3. Others				
- Poor performance status (ECOG score ≥2)	5	3 (23.08)	2 (8.70)	
- Older patients (>75 years)				
- Poor medical conditions (heart, lung, and kidney issues)				
Disease progression confirmation according to RECIST Criteria 1.1				0.901
Target lesion PD	24	11 (68.75)	13 (59.09)	
Non-target lesion PD	8	3 (18.75)	5 (22.73)	
Any new lesion	6	2 (12.5)	4 (18.18)	

PD, progressive disease; NAC, neoadjuvant chemotherapy; FIGO, International Federation of Gynecology and Obstetrics; ECOG, Eastern Cooperative Oncology Group; HGSC, high-grade serous carcinoma.
Data are presented as mean±standard deviation or n (%).
*Mucinous 4, clear cell 6, endometrioid 3, low grade serous 1, and poorly differentiated 5.

(Fig. 2).

In univariate logistic regression analysis, OS was significantly influenced by the treatment option [second-line chemotherapy vs. CRS: hazard ratio (HR), 2.67; 95% confidence interval (CI), 1.22–5.86; p=0.014] and patient age (HR, 0.96; 95% CI, 0.93–1.00; p=0.057).The parameter of histology has unknown histology subtype, and we removed this parameter for univariate logistic regression analysis. In subsequent multivariate analysis, the treatment option was the only independent predictive factor for OS (HR, 2.30; 95% CI, 1.02–5.17; p=0.044) (Table 3).

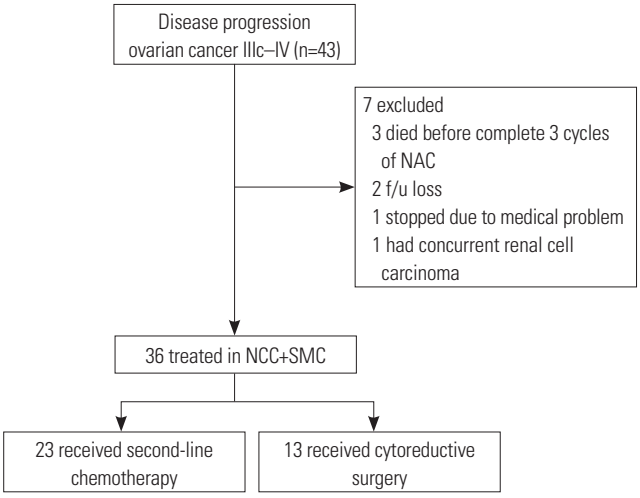

Fig. 1. Study design. NAC, neoadjuvant chemotherapy; NCC, National Cancer Center; SMC, Samsung Medical Center.

DISCUSSION

Among patients with AEOC, those who develop PD after NAC usually have the poorest prognosis. According to a large randomized NAC trial, 5% to 10% of all patients who receive NAC show a refractory response.[5,6] Thus, it was anticipated that responses to second-line chemotherapy in these patients would not be good, because they were already resistant to platinum-based chemotherapy.[14] Furthermore, satisfactory CRS also seemed difficult because such patients are known to be poor candidates for CRS before NAC. Nonetheless, in the current study of patients with PD after NAC, group A (CRS) showed better OS than group B did (second-line chemotherapy; 19 months vs. 8 months; p=0.012). Until now, no studies have evaluated

Table 2. Treatment Records for Each Group

	n (%)	Response to chemotherapy			Treatment discontinued	Follow-up loss
		PD	SD	PR		
Group A (n=13)						
Surgical procedure						
TAH BSO	11 (84.6)					
PLND PALND	5 (38.5)					
Omentectomy	11 (84.6)					
Bowel surgery	6 (46.2)					
Other surgical procedure	8 (61.5)					
Splenectomy	2 (15.4)					
Metastatic mass removal	8 (61.5)					
Distal pancreatectomy	1 (7.8)					
Macroscopic residual tumor						
No	6 (46.2)					
Yes	7 (53.8)					
Adjuvant chemotherapy regimens						
Paclitaxel-carboplatin	6 (46.2)	4	0	2		
Topotecan-carboplatin	2 (15.4)	2	0	0		
Gemcitabine-carboplatin	1 (7.8)	0	0	1		
Docetaxel	1 (7.8)	1	0	0		
No chemotherapy	3 (23.8)					
Group B (n=23)						
Second-line regimens						
Topotecan	15 (65.2)	9	1	0	3	2
PLD	6 (26.1)	3	0	0	1	2
Others	2 (8.7)	1	0	0	1	0
Ifosfamide-cisplatin						
Paclitaxel-carboplatin						

PD, progressive disease; SD, stable disease, PR, partial response; TAH, total abdominal hysterectomy; BSO, bilateral salpingooophorectomy; PLND, pelvic lymphadenectomy; PALND, para-aortic lymphadenectomy; PLD, pegylated liposomal doxorubicin.

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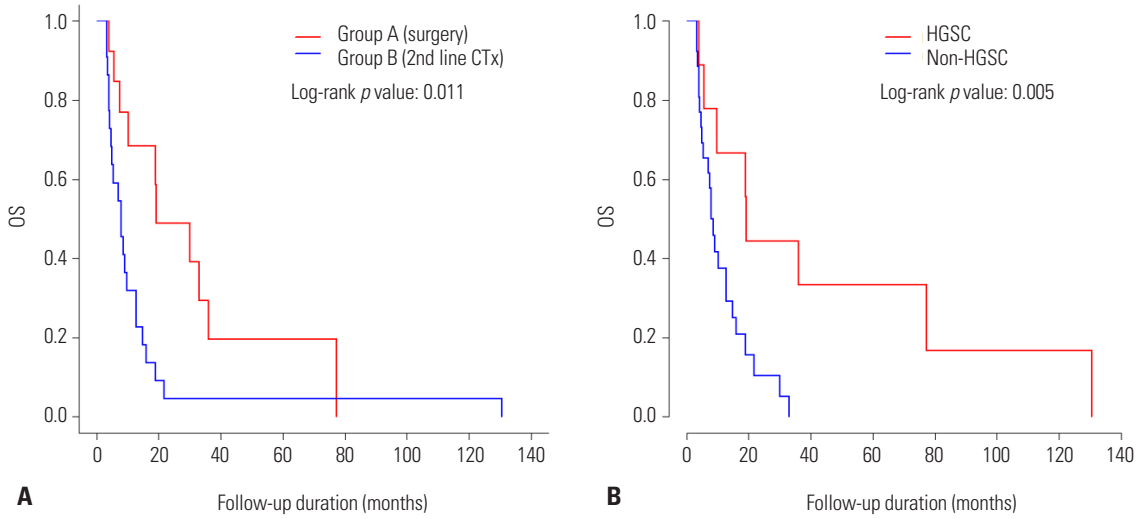

Fig. 2. Kaplan-Meier survival curves according to (A) treatment type and (B) histology. OS, overall survival; HGSC, high-grade serous carcinoma.

Table 3. Univariate and Multivariate Cox Proportional Hazard Analyses

	Number	Event (%)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*p* value	HR (95% CI)	*p* value
Treatment option						
Surgery	13	10 (76.92)	1 (ref)		1 (ref)	
Second-line chemotherapy	23	22 (95.65)	2.67 (1.22–5.86)	0.014	2.30 (1.02–5.17)	0.044
Age	36	32 (88.89)	0.96 (0.93–1.00)	0.057	0.97 (0.93–1.02)	0.202
ECOG score (missing data: 2)						
1 or less	31	28 (90.32)	1 (ref)			
2 or more	3	3 (100.00)	1.90 (0.54–6.70)	0.351		
FIGO stage						
IIIC or less	18	15 (83.33)	1 (ref)			
IVA or more	18	17 (94.44)	0.64 (0.31–1.32)	0.229		

HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

which strategy (CRS or second-line chemotherapy) is superior for patients who develop PD after NAC. The results of the current study suggest that surgical treatment might provide a survival benefit in such patients. Nevertheless, further studies are warranted regarding the role of surgery in this subset of patients, contradictory to the present recommendations, such as the NCCN guidelines, on administering conventional salvage second-line chemotherapy.

The survival benefit in group A (CRS) can be explained by several reasons. First, because the tumor was removed via CRS (46% of patients who underwent CRS after developing PD following NAC achieved optimal surgical resection in the current study), the chemotherapy-resistant tumor burden was reduced,[15] thereby improving sensitivity to chemotherapy. In EOC, surgical resection increases OS.[16-18] Second, HGSC shows greater sensitivity to platinum-based chemotherapy than nonserous histologic types,[19-22] even if the tumor is resistant to initial platinum-based chemotherapy.[23] The proportion of HGSC cases was higher in group A than in group B (46% vs. 13%; p=0.015) (Table 1). Although multivariate analysis showed that the treatment option was the only independent prognostic factor for OS, patients with HGSC histology showed better OS than those with nonserous types in univariate analysis (p=0.023) (Table 3). Therefore, this issue needs to be clarified in a future study. Third, CRS can provide symptom relief, such as bowel obstruction, creating a more favorable condition for chemotherapy. Interestingly, 3 of 9 patients (33.3%) who underwent platinum-based chemotherapy after CRS showed a PR in contrast to PD following previous platinum-based NAC (Table 2).

Currently, there are limited treatment options for patients who develop PD after initial chemotherapy. The recent 2019 NCCN guidelines suggest that second-line chemotherapy should be administered to these patients. However, there is no conclusive evidence to support this guideline, although several studies have evaluated this in breast and colorectal cancers refractory to NAC.[9-12] In patients with locally advanced breast cancer developing PD after NAC, surgery or concurrent chemoradiotherapy can improve prognoses.[9] In fact, 80% of patients developing PD after first NAC could receive surgery after undergoing nonsurgical salvage treatment. Similarly, in patients

with locally advanced colorectal cancer developing PD after neoadjuvant concurrent chemoradiotherapy, surgery can be a salvage treatment option.[12] After PD, the no surgery group showed a poorer outcome than the salvage surgery group did.

To the best of our knowledge, the current study is the first to have evaluated patients with AEOC who showed PD after NAC. However, some issues require further evaluation. For example, HGSC is more sensitive to chemotherapy than other histologic subtypes are, such as clear cell, mucinous, and endometrioid tumors.[21,22] In the current cohort, there were only nine cases of HGSC. This ratio is different from the general ratio of the HGSC subtype among EOC cases,[24] which may be owing to selection bias based on NAC and limited histologic evaluation via ascites cytology. Even in large randomized clinical trials on NAC, such as the CHemotherapy OR Upfront Surgery (CHORUS) for newly diagnosed advanced ovarian cancer and European Organisation for Research and Treatment of Cacncer (EORTC) 55971 trials, some malignancies were confirmed via only ascites cytology and not histology.[5,6] However, it is important to evaluate a patient's histology before starting NAC. Laparoscopic biopsy is necessary not only for biopsy but also for making a decision about resectability and for calculating either Fagotti score or the peritoneal carcinomatosis index. Accordingly, knowing the exact histology before NAC is important. If the result is non-HGSC, it may be advantageous to choose primary debulking surgery rather than NAC. On the other hand, if the result is HGSC, surgery may be helpful for patients developing PD after NAC.

According to a large randomized NAC trial, 5% to 10% of all patients who receive NAC show a refractory response.[5,6] However, there are no guidelines or suggestions about which category of patients develops PD after NAC. Therefore, the findings of the current study might be helpful, although future well-designed prospective studies are needed to determine the treatment strategies.

The current study has some limitations. First, this was a retrospective analysis, which might have several biases, including patient selection and incompleteness of medical records.[4] Second, the number of patients in the present study was relatively small to evaluate the exact impact of each treatment option. Third, we only compared OS between the two groups. However, in this palliative treatment setting, quality of life is also very important.[25,26] Therefore, further studies are needed to evaluate the quality of life in addition to tolerability, satisfaction, and performance during and after treatment. Fourth, treatment differences would exist between the two tertiary centers. For example, chemotherapeutic agents were administered to patients at the inpatient clinic at SMC, but at the outpatient center at the NCC. Moreover, chemotherapy was initiated after 7–10 days at SMC, while it was initiated after 14 days at the NCC. These differences might have influenced the patients' prognoses.

In conclusion, the results of the current study suggest that CRS can be a treatment option for patients who develop PD after NAC, although further studies are warranted to confirm the findings of the current study.

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AUTHOR CONTRIBUTIONS

Conceptualization: Wonkyo Shin, Joseph J. Noh, Myong Cheol Lim, and Byoung-Gie Kim. Data curation: Wonkyo Shin and Joseph J. Noh. Formal analysis: Wonkyo Shin and Joseph J. Noh. Investigation: Myong Cheol Lim and Byoung-Gie Kim. Methodology: Wonkyo Shin and Joseph J. Noh. Project administration: Myong Cheol Lim and Byoung-Gie Kim. Resources: Wonkyo Shin, Joseph J. Noh, Sang-Soo Seo, Sokbom Kang, Chel-Hun Choi, Sang-Yoon Park, and Myong Cheol Lim. Software: Joseph J. Noh. Supervision: Myong Cheol Lim and Byoung-Gie Kim. Validation: Sang-Soo Seo, Sokbom Kang, Chel-Hun Choi, and Sang-Yoon Park. Visualization: Wonkyo Shin. Writing—original draft: Wonkyo Shin and Joseph J. Noh. Writing—review & editing: Sang-Soo Seo, Sokbom Kang, Chel-Hun Choi, Sang-Yoon Park, and Myong Cheol Lim. Approval of final manuscript: all authors.

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