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Survival of advanced epithelial ovarian/fallopian tube/primary peritoneum carcinoma after high-complexity upper abdominal surgery

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Summary

Objective: To analyze the survival effects of upper abdominal procedures (UAPs) in patients with the International Federation of Gynecology and Obstetrics (FIGO) Stage IIIb to IV ovarian cancer stratified by initial presence of upper abdominal disease (UAD) and UAP performance. *Materials and Methods:* The authors retrospectively reviewed records of patients with FIGO Stage IIIb to IV epithelial ovarian cancer confirmed by pathology between January 2007 and December 2016 from the gynecologic cancer registry of Kangbuk Samsung Hospital. *Results:* During the study period, 74 patients with FIGO Stage IIIb to IV epithelial ovarian cancer underwent primary cytoreductive surgery. Among them, 28 patients had no UAD and no UAPs (group 1), 30 had UAD but did not undergo complete UAPs, especially without diaphragmatic resection (group 2), and 16 had UAD and underwent complete UAP including diaphragmatic resection (group 3). Except for age, most baseline characteristics did not vary among the three groups. In group 3, diaphragm peritonectomy was the most commonly performed UAP (93.8%), followed by liver resection (6.8%) with significant differences between groups 2 and 3 ($p < 0.01$). Five-year OS was 77.9% in group 1, 9.5% in group 2, and 76.7% in group 3 ($p < 0.01$). Median PFS was 37 months in group 1, 10 months in group 2, and 25 months in group 3 ($p < 0.01$). *Conclusions:* UAPs including complete removal of diaphragmatic lesions led to better survival outcomes for advanced-stage ovarian cancer.

Key words: Advanced-stage ovarian cancer; Upper abdominal surgery; Survival.

Introduction

Most patients with epithelial ovarian cancer are diagnosed with advanced-stage disease [1]. For these patients, standard initial therapy is primary debulking surgery followed by platinum-based chemotherapy [2]. Several studies have shown that patients who have undergone optimal cytoreduction (< 1 cm residual disease) had survival advantages compared to patients who had suboptimal cytoreduction [3-6]. Bristow *et al.* reported in a meta-analysis that during the platinum era, primary cytoreduction improved survival outcomes [3]. Chi *et al.* showed that removal of all macroscopic disease is associated with improved survival. The study concluded that minimizing residual tumor is important, even if complete gross resection is not possible [4].

As surgical techniques, instruments and perioperative care develop, surgeons are able to perform maximal cytoreduction in patients with advanced stage ovarian cancer. These advances enable improvement in the rate of optimal cytoreduction and removal of metastatic sites previously thought unresectable.

Optimal cytoreduction rates can vary widely among institutions and studies with a reported range of 15–85%. Achieving the highest rates of optimal cytoreduction often requires surgeons skilled in upper abdominal procedures (UAPs), such as diaphragm stripping or resection, splenectomy, distal pancreatectomy, liver resection, cholecystectomy, and resection of tumors from the porta hepatis [3, 7-9].

Aletti *et al.* in 2006 found an association of aggressive surgical resection, including by UAPs, with lowest residual disease and longest survival [7]. Zivanovic *et al.* showed that the presence of large-volume upper abdominal disease found during surgery does not preclude survival after optimal cytoreduction [10]. The present center started extensive UAPs in 2012 to improve optimal debulking rates and thereby survival rates for patients with advanced ovarian cancer. Diaphragmatic stripping and/or resection, in particular, was the most commonly performed among these upper abdominal procedures. Without these procedures, patients would have suboptimal cytoreduction for metastatic ovarian cancer in the diaphragm area. Therefore, the present authors analyzed the effects of upper abdominal procedures on progression-free survival (PFS) and overall survival (OS) in patients with FIGO Stage IIIb to IV ovarian cancer in this hospital. The authors stratified patients by initial

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Table 1. — *Baseline patients' demographics.*

	All patients (n=74)	Group 1 (n=28, 37.9%)	Group 2 (n=30, 40.5%)	Group 3 (n=16, 21.6%)	*p*
Date of surgery					
2007-2012	31	14 (50.0)	15 (50.0)	0	
2012-2016	43 14 (50.0)	15 (50.0)	16 (100)		
Age (years)	57 ± 10	57 ± 9	61 ± 10	48 ± 9	< 0.01
BMI (kg/m^2)	24.3 ± 3.5	24.6 ± 3.8	24.3 ± 3.2	24.3 ± 3.5	0.76
Stage of disease, n (%)					0.46
IIIb	13 (17.6)	8 (28.6)	3 (10.0)	2 (12.5)	
IIIc	49 (66.2)	16 (57.1)	22 (73.3)	11 (68.8)	
IV	12 (16.2)	4 (14.3)	5 (16.7)	3 (18.8)	
Tumor grade, n (%)					0.80
Low	1 (1.4)	0	1 (3.3)	0	
Moderate	10 (13.5)	4 (14.3)	3 (10.0)	3 (18.8)	
High	63 (85.1)	24 (85.7)	26 (86.7)	13 (81.2)	
Histologic type, n (%)					0.24
Serous	62 (83.8)	25 (89.3)	26 (86.7)	11 (68.8)	
Mucinous	2 (2.7)	0	2 (6.7)	0	
Endometrioid	1 (1.4)	0	0	1 (6.3)	
Clear	4 (5.4)	1 (3.6)	1 (3.3)	2 (12.5)	
Mixed	1 (1.4)	1 (3.6)	0	0	
Small cell	1 (1.4)	0	0	1 (6.3)	
Transitional cell	3 (4.1)	1 (3.6)	1 (3.3)	1 (6.3)	
Pre-op CA-125 (IQR)	477 (152-2120)	445.6 (113-1788)	475.3 (194-3219)	732.4 (203-2187)	0.58

Data are expressed as mean ± standard deviation, median (IQR) or number (%).

presence of upper abdominal disease (UAD) and performance of upper abdominal procedures, especially diaphragm stripping and/or resection.

Materials and Methods

The authors retrospectively identified 103 patients who had FIGO Stage IIIb, IIIc or IV epithelial ovarian cancer confirmed by pathology between January 2007 and December 2016 from the gynecologic cancer registry of Kangbuk Samsung Hospital. Among the 103 patients, 74 underwent primary cytoreductive surgery at the institutions. Records were reviewed and patients were divided into three groups based on the presence of upper abdominal disease and performance of upper abdominal procedure. UAD was defined as metastatic implants involving the diaphragm, liver, porta hepatis, spleen, pancreas, stomach, celiac axis, or lesser sac.

All patients had routine laboratory tests and imaging studies, such as computed tomography or magnetic resonance imaging before surgery. All received basic, standard surgery procedures such as peritoneal washing, total abdominal hysterectomy, bilateral salpingo-oophorectomy, multiple random biopsy of peritoneal surfaces, appendectomy, omentectomy, and pelvic and para-aortic lymphadenectomy.

Group 1 was defined as patients with no gross upper abdominal involvement so UAPs, such as diaphragmatic stripping or resection were not necessary. Group 2 was defined as patients with gross upper abdominal disease including diaphragmatic involvement, but who underwent partial upper abdominal procedures without diaphragmatic lesion stripping and/or resection. In group 3, patients had gross upper abdominal disease including diaphragmatic involvement. Complete upper abdominal procedures were performed including diaphragmatic stripping and/or resection.

UAPs were defined as diaphragm stripping and/or resection, splenectomy, distal pancreatectomy, liver resection, cholecystectomy, and resection of tumors from the porta hepatis [3, 7-9].

Suboptimal surgical outcome was defined as residual lesion measuring larger than 1 cm in the single largest dimension at surgery completion. Optimal cytoreduction was defined as no residual disease or residual disease smaller than 1 cm. Transfusion was performed when symptomatic anemia occurred with hemoglobin lower than 8 g/dL. Postoperative complications were defined as adverse events occurring within 30 days of surgery as a result of the procedure.

Progression was determined on the basis of either the objective Response Evaluation Criteria in Solid Tumors (RECIST) or serum CA-125 criteria. When both criteria were met, the earlier date was used for progression date.[11]

Complete response (CR) was defined as complete disappearance of all lesions or normalization of the serum CA-125 level. Partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameter of all target lesions, persistence of one or more non-target lesions, or maintenance of serum CA-125 levels above 35 U/mL after an initial ≥ 50% decrease. Progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameter of target lesions, appearance of one or more new lesions, or unequivocal progression of existing nontarget lesions. CT scan results, if applicable, superseded serum CA-125 levels in determining response.

Patients were also classified according to whether they had platinum-sensitive, platinum-resistant, or platinum-refractory disease at the time of relapse or disease progression. Platinum-resistant disease was defined as progression within six months of last platinum treatment. Platinum-refractory disease was defined as progression while on platinum treatment.

Patients were evaluated in groups, and statistical tests were performed as appropriate for data distributions. Categorical variables were evaluated by χ^2 analysis or Fisher's exact test, as appropriate for category size. Continuous variables were evaluated by ANOVA for normally distributed or Kruskal-Wallis test for non-normally distributed variables. All statistical tests were two-sided,

Table 2. — *Cytoreductive procedures.*

	Group 1 (n=28, 37.9%)	Group 2 (n=30, 40.5%)	Group 3 (n=16, 21.6%)	*p*
Standard				
Hysterectomy	27 (96.4)	25 (89.3)	15 (93.8)	0.83
BSO	28 (100)	30 (100)	16 (100)	1.00
Omentectomy	23 (82.1)	24 (85.7)	16 (100)	0.22
PLND	27 (96.4)	21 (75.0)	15 (93.8)	0.53
PALND	25 (89.3)	20 (71.4)	15 (93.8)	0.14
Small-bowel resection	0	1 (3.3)	0	1.00
Large-bowel resection	11 (39.3)	10 (35.7)	11 (68.8)	0.10
Extensive upper abdomen procedure				
Diaphragm peritonectomy	0	0	15 (93.8)	<0.01
Splenectomy	1 (3.6)	1 (3.3)	2 (12.5)	0.56
Liver resection	0	0	3 (18.8)	<0.01
Cholecystectomy	0	1 (3.3)	1 (6.3)	0.69

Data are expressed as number (%). BSO = bilateral salpingo-ophorectomy; PLND = pelvic lymph node dissection; PALND = para-aortic lymph node dissection.

Table 3. — *Surgical outcome.*

	Group 1 (n= 28)	Group 2 (n=30)	Group 3 (n=16)	*p*
Largest tumor size (cm)	6.5 ± 4.1	6.8 ± 2.8	9.0 ± 4.6	0.10
Residual disease				< 0.01
No gross	23 (82.1)	3 (10.0)	13 (80.4)	
< 1.0 cm	4 (14.3)	10 (33.3)	2 (12.5)	
> 1.0 cm	1 (3.6)	17 (56.7)	1 (7.1)	
Transfusion	20 (71.4)	24 (80.0)	14 (87.5)	
Intra/post-operative complications				0.65
Ileus	1 (3.6)	3 (11.5)	2 (14.3)	
Lymphocele	2 (7.1)	1 (3.8)	2 (14.3)	
Post-operative bleeding	1 (3.6)	0	0	
Ureter injury	1 (3.6)	0	0	
Colon perforation	0	1 (3.8)	1 (7.1)	
Wound dehiscence	2 (7.1)	2 (7.7)	2 (14.3)	
Bladder injury	0	1 (3.8)	1 (7.1)	
Pleural effusion	0	2 (7.7)	4 (25.0)	
Persistent disease	1 (3.6)	18 (60.0)	1 (7.1)	<0.01

Data are expressed as number (%) or mean ± standard deviation.

Table 4. — *Postoperative chemotherapy response.*

	Group 1 (n= 28)	Group 2 (n=30)	Group 3 (n=16)	*p*
Post-op chemotherapy start day	9 (8-15)	9 (8-14)	11 (9-17)	0.54
Number of CTx cycles	6 (5-9)	6 (2-12)	6 (5-9)	1.00
Response to CTx				< 0.01
CR	24 (85.7)	10 (33.3)	14 (87.5)	
PR	4 (14.3)	16 (53.4)	2 (12.5)	
PD	0	4 (13.3)	0	
Platinum response after 6mo CTx				< 0.01
Sensitive	25 (89.3)	15 (50.0)	14 (87.5)	
Resistant	3 (10.7)	10 (33.3)	2 (12.5)	
Refractory	0	5 (16.7)	0	

Data are expressed as median (IQR) or number (%). CR = complete response; PR = partial response; PD = progressive disease; CTx = chemotherapy.

and differences were considered statistically significant at $p < 0.05$. PFS and OS were calculated from date of initial cytoreductive surgery. The Kaplan-Meier method was used to estimate PFS and OS curves for patient groups. Log-rank test was used to detect differences between survival curves for stratified variables. Continuous variables that were not normally distributed such as CA-125 were analyzed as categorical variables greater or less than the median value for the cohort. Kaplan-Meier curves were plotted using SPSS statistical software (version 21.0). All other data analyses were performed with Stata statistical software (version 8.2).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and the 1964 Helsinki Declaration, with its later amendments or comparable ethical standards. The need for informed consent was waived under approval of the hospital institutional review board (IRB no. 2017-03-

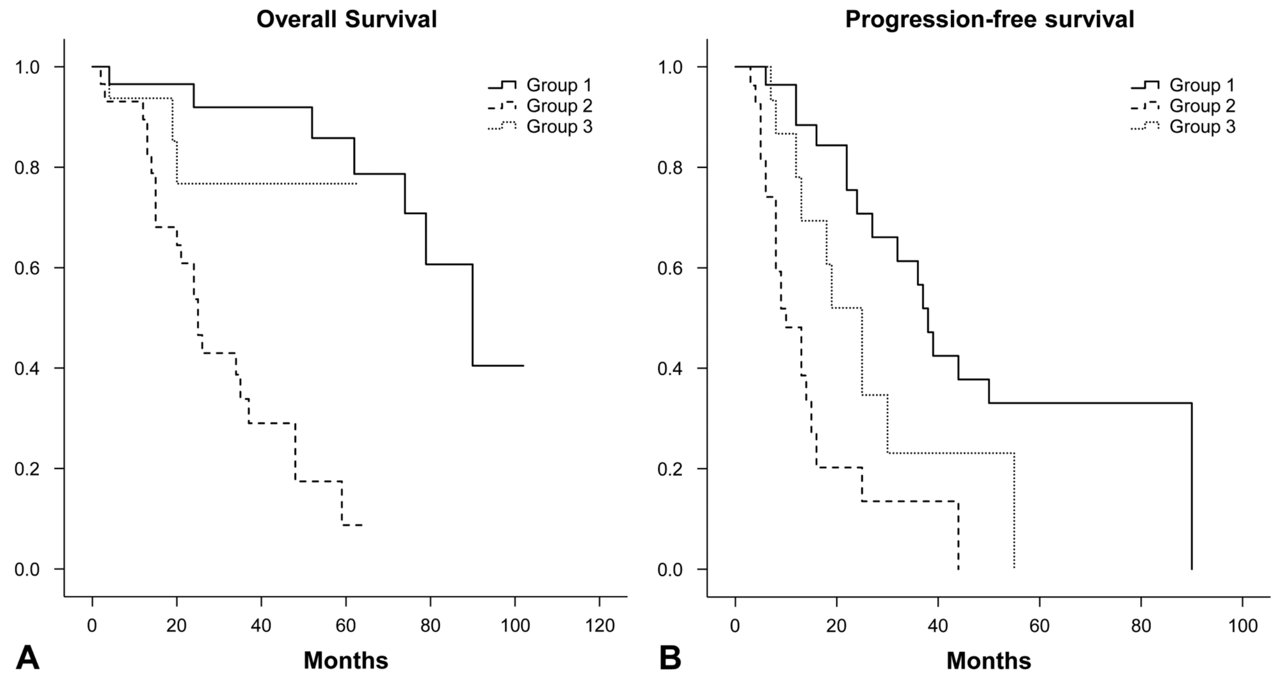

Figure 1. — Comparison of OS and DFS between three groups. (A) Five-year OS rate: group 1 77.9% *vs*. group 2 9.5% *vs*. group 3 76.7% ($p < 0.01$). (B) Median PFS: 37 months in group 1 *vs*. 10 months in group 2 *vs*. 25 months in group 3 337 ($p < 0.01$).

011) because of the retrospective and observational design of this study.

Results

Records were analyzed for 74 patients with FIGO Stage IIIb, IIIc or IV epithelial ovarian cancer. Among these, 28 patients had no UAD and no UAP (group 1), 30 had UAD but did not undergo complete UAP (group 2), and 16 had UAD and complete UAP (group 3). Group 1 patients were evenly distributed before and after 2012. In Group 2, 15 patients (50.0%) had surgery after 2012 with 15 (50.0%) undergoing surgery before 2012. All 16 patients in group 3 underwent surgery after 2012. Baseline characteristics of patients are shown in Table 1. Mean age was 57 ± 9 years for group 1, 61 ± 10 years for group 2, and 48 ± 9 years for group 3, with significant differences between groups ($p < 0.01$).

In Group 1, eight patients had FIGO Stage IIIb, 16 had Stage IIIc, and four had Stage IV disease. In group 2, three patients had Stage IIIb, 22 had Stage IIIc, and five had Stage IV disease. In group 3, two patients had FIGO Stage IIIb, 11 had Stage IIIc, and three had Stage IV disease. Stage of disease and other baseline characteristics of body mass index, histologic cell type, tumor grade and preoperative CA 125 level were not significantly different among the three groups (Table 1). Serous carcinoma was most common and high-grade carcinoma was also most prevalent in the three groups.

The distribution of cytoreductive surgical procedures performed during the study period is shown in Table 2. For the standard procedure, groups 1, 2, and 3 had no significant differences. In group 2, one patient underwent splenectomy and one underwent cholecystectomy. In group 3, diaphragm peritonectomy was the most common upper abdominal procedure performed, in 15 (93.8%) patients. The second most common procedure was liver resection, performed in three (18.8%) patients. Numbers for these two procedures were significantly different between groups 2 and 3 ($p < 0.01$).

Surgical outcomes are shown in Table 3. Mean tumor size was larger in group 3 than in groups 1 and 2, but the groups were not significantly different ($p = 0.10$). Residual disease greater than 1 cm was more common in group 2 compared to groups 1 and 3 ($p < 0.01$) and persistent disease after chemotherapy completion was more common in group 2 than in groups 1 and 3 ($p < 0.01$). Optimal debulking rate was 96.4% (27/28) in group 1, 43.3% (13/30) in group 2, and 92.9% (15/16) in group 3, resulting in 75.6% (55/74) for all patients. No differences were observed between the three groups in perioperative complications.

Postoperative treatment courses were similar, with all patients receiving equivalent primary chemotherapy regimens and numbers of cycles (Table 4). In all three groups, patients began chemotherapy after similar interval periods after surgery.Groups 1 and 3 had similar rates of clinical CR (85.7% *vs*. 87.5%, respectively). However, pa-

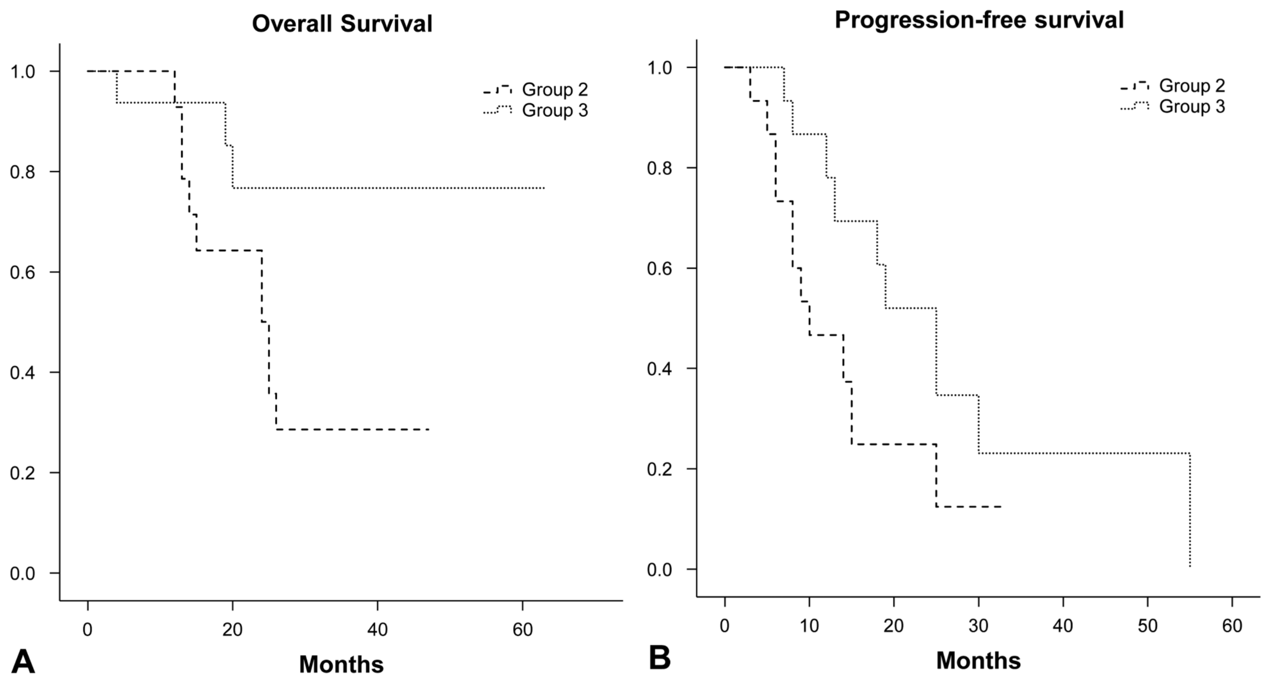

Figure 2. — Comparison of OS and PFS between groups 2 and 3 during 2012–2016. (A) OS ($p = 0.039$). (B) PFS ($p = 0.070$).

tients in group 2 were less likely to achieve clinical CR (33.3%; $p < 0.01$). In addition, significant differences were seen in platinum status at six months from last chemotherapy between group 2 and groups 1 and 3 ($p < 0.01$).

Median follow-up for surviving patients was 30 months for the entire cohort, 55 months for group 1, 25 months for group 2, and 26 months for group 3. During the follow-up period, seven patients in group 1, 22 in group 2, and three in group 3 died. The five-year OS rate was 77.9% in group 1, 9.5% in group 2, and 6.7% in group 3 ($p < 0.01$). The number of patients with recurrence or disease progression was 16 in group 1, 22 in group 2, and ten in group 3. Median PFS was 37 months in group 1, ten months in group 2, and 25 months in group 3 ($p < 0.01$).

When we compared UAPs (group 3) *vs*. incomplete UAPs (group 2), the authors found that UAPs were significantly associated with improved median PFS and the five-year OS rate (Figure 1). In contrast, the five-year survival rate (Figure 2A, $p = 0.323$) and median PFS (Figure 2B, $p = 0.056$) were not significantly different between groups 1 and 3. Median OS was 90 months for group 1 and the median OS not yet reached in group 3.

The authors also compared PFS and OS for group 2 and 3 patients who underwent surgery during 2012–2016 (n=15 and n=16, respectively). Significant differences were detected in PFS ($p = 0.070$) and OS ($p = 0.039$) (Figure 2).

Discussion

Many studies have reported on the efficacy of optimal cytoreductive surgery for advanced stage ovarian cancer. Eisenhauer *et al.* showed that resection of bulky disease before chemotherapy improved the survival rate from cytoreduction in patients with advanced ovarian cancer [12]. This result was confirmed by several subsequent studies and is the treatment paradigm for patients with advanced ovarian cancer [3, 5, 13].

In 2012, the present department began extended upper abdominal procedures to patients with widespread upper abdominal disease. Commencing this extensive cytoreductive surgery was somewhat late in this department because until 2012, this hospital did not have a gynecologic oncologist with experience performing extended UAPs. Therefore, operations for all patients in group 3 were by a single surgeon with experience in extended UAPs and operations for all patients in group 2 were by other gynecologic surgeons. Bowel resection, liver resection, and cholecystectomy procedures were performed by general surgeons because a multidisciplinary approach was relatively simple to schedule at this center.

Several studies reported on the morbidity of UAPs for advanced ovarian cancer. Magtibay *et al.* reported a 23.2% complication rate and a 5% perioperative mortality rate for 112 patients who underwent splenectomy during primary or secondary cytoreductive surgery [14]. For distal pancreatectomies during cytoreductive surgery for advanced ovarian cancer, perioperative complications rates are 13–66% [15-17]. However, diaphragm stripping and/or resection can be performed with acceptable morbidity. Kuhn *et al.* did not find increased morbidity associated with diaphragm surgery for 41 patients with advance epithelial ovarian cancer who had upper abdominal surgery [9]. In the present study, morbidity was not higher in a group who underwent UAP and no difference was seen in perioperative or postoperative complications compared with Group 2. Postoperative pleural effusion was more common in group 3 as expected; however, these events were well controlled using chest tube insertion without sequelae.

The previous reports and the present results show that optimal debulking can be achieved without significant morbidity, even if UAPs are performed in the presence of UAD.

The median number of combination chemotherapy cycles was six in all three groups. However, significant differences were seen in clinical response and platinum sensitivity. The rate of complete remission was nearly same between groups 1 (85.7%) and 3 (87.5%), compared with a low complete remission rate (33.3%) in group 2 ($p < 0.01$). In previous reports, optimal debulking and better clinical response were directly associated [12].

The present authors confirmed in this study that patients with UAD who underwent addition of extensive UAP for optimal cytoreduction had similar PFS and OS to patients for whom cytoreduction was optimal without UAP. The authors found that patients with optimal cytoreduction had better survival rates than patients whose residual disease was greater than 1 cm. They also found a significant difference in platinum sensitivity between group 3, in which patients received complete UAP and group 2, with incomplete UAP. Only 50% (15/30) of patients in group 2 had platinum sensitivity compared to 89.3% (25/28) in group 1 and 87.5% (14/16) in group 3.

Median PFS was 37 months for group 1 and 25 months in group 3 ($p = 0.056$). This result was similar to the 21- to 22-month PFS reported for platinum-paclitaxel after optimal cytoreduction in the GOG 114 and GOG 152 studies [18, 19].

Median PFS in group 2 was only ten months compared to group 1 (37 months) or 3 (25 months) ($p = 0.011$). Differences in five-year survival rate were significant between Groups 2 and 3 ($p = 0.022$). The present results suggested that aggressive diaphragm surgery might be useful for improving PFS and OS in selected patients for whom the diaphragm was the only site of residual disease.

No surgical attempt for complete UAP was made for any of the 30 patients in group 2. Most had diaphragmatic metastatic lesions as the only gross residual disease. Many, but not all of these patients might have benefitted from surgeons performing aggressive diaphragm surgery for complete disease resection, possibly improving survival. The reason for not performing aggressive diaphragm surgery could be the extent of disease in some patients or lack of surgeon experience. Considering that most group 2 patients had diaphragmatic disease as the only gross residual disease, aggressive surgical efforts to resect diaphragmatic disease may have been warranted to improve survival of patients with advanced stage epithelial ovarian cancer.

Bristow *et al.* developed a theoretical model in which optimal cytoreduction rates and survival outcomes are proportional. The model showed that a 10% increase in optimal cytoreduction rate prolonged median survival by 5.5% [3]. The present study had a nearly 50% difference in the optimal cytoreduction rate between groups 2 and 3; their survival difference was similar to Bristow's theoretical model.

One potential criticism of these findings is that increased survival from extensive upper abdominal surgery may be merely a function of tumor biology rather than surgical technique [20, 21]. Tumor biology does affect patient outcomes. Whether tumor biology or surgical skill leads to optimal cytoreduction remains controversial. Nonetheless, there is little debate that suboptimal cytoreduction does not provide survival benefit to patients [3, 5, 22, 23].

The limitations of this study were its retrospective design and small number of patients, although the authors analyzed patients over ten years from a single hospital. In addition, the present study included patients with Stage IIIb ovarian cancer patients (eight in group 1 and 2 each in groups 2 and 3) Inclusion of Stage IIIb patients would probably have a favorable effect on survival. However, groups 2 and 3 had only two patients each. Therefore, inclusion of these patients would not have affected survival comparison between these two groups. Although the number of patients analyzed during this period was small, the present authors postulate from the results that surgical efforts may increase survival outcomes.

In conclusion, UAPs, especially when completely removing diaphragmatic lesions, may result in improved survival for selected patients, especially when gross residual disease is on the diaphragm only. Therefore, if complete resection is possible by removing diaphragmatic lesions, the authors recommend performing upper abdomen procedures to leave no gross residual disease and improve survival.

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