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Role of diagnostic laparoscopy in deciding primary treatment in advanced-stage ovarian cancer

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ABSTRACT

Objective: We evaluated the usefulness of preoperative diagnostic laparoscopy for treatment planning in patients with advanced-stage ovarian cancer.
Methods: We retrospectively analyzed 614 patients diagnosed with advanced-stage ovarian cancer between January 2010 and May 2018. Primary debulking surgery (PDS) or neoadjuvant chemotherapy (NAC) followed by interval debulking surgery were selected based on preoperative laparoscopic (Group 1, n=192) and computed tomography findings (Group 2, n=422). The primary outcomes in the PDS and NAC groups were suboptimal cytoreduction (residual disease >1 cm) rate and non-high-grade serous carcinoma (non-HGSC) rate, respectively.
Results: The patients who underwent PDS in group 1 and group 2 were 49 (25.5%) and 279 (66.1%), respectively. The suboptimal cytoreduction rate after PDS was lower in Group 1 than in Group 2 (2.0% vs 11.1%, p=0.023). Moreover, Group 1 showed a tendency toward a lower proportion of non-HGSC patients who underwent NAC than that in Group 2 (9.1% vs. 15.4%, p=0.069). Further, Group 1 showed lower rates of postoperative morbidity than Group 2 (5.2% vs. 10.4%, p=0.033). However, Kaplan–Meier analysis showed no significant differences in survival outcomes between the 2 groups.
Conclusion: Diagnostic laparoscopy reduced the suboptimal cytoreduction rate in the PDS group and the implementation rate of NAC in non-HGSC patients. Moreover, it reduced postoperative morbidity without affecting survival in both groups. Thus, diagnostic laparoscopy is a valuable diagnostic tool for determining the primary treatment.

Keywords: Ovarian Cancer; Surgical Diagnostic Technique; Cytoreductive Surgery; Neoadjuvant Chemotherapy

Synopsis

Diagnostic laparoscopy is a valuable tool for treatment planning in patients with advanced-stage ovarian cancer. Decision-making using diagnostic laparoscopy reduced the futile laparotomy and complication rates. Diagnostic laparoscopy reduced the implementation rate of neoadjuvant chemotherapy in non-high-grade serous carcinoma patients.

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

Author Contributions
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INTRODUCTION

Epithelial ovarian cancer is the main cause of death from gynecologic malignancies, and its incidence and mortality rates are constantly increasing in Korea [1,2]. Primary debulking surgery (PDS) followed by chemotherapy comprising carboplatin and paclitaxel is the standard treatment. However, there is a trend for preferring interval debulking surgery (IDS) over PDS as the primary treatment in patients with advanced-stage ovarian cancer. Four randomized clinical trials demonstrated that neoadjuvant chemotherapy (NAC) followed by IDS was not inferior to PDS with respect to survival and resulted in fewer complications and lower postoperative mortality [3-6].

The goal of debulking surgery is to achieve no residual disease or at least a maximum diameter of less than 1 cm, because the size of the residual tumor is an important prognostic factor for survival [7,8]. However, optimal debulking is difficult to achieve, especially in cases of widespread disease in the abdominal cavity, liver, or pleural fluid. Leaving residual tumor larger than 1 cm is defined as a futile laparotomy. And it is important to identify patients who are at high risk for futile laparotomy [9,10]. In cases where futile laparotomy is likely, NAC should be used to avoid complications [11]. The extent of the tumor burden can be predicted by a standard diagnostic work-up in patients with suspected advanced ovarian cancer. However, despite using advanced imaging modalities, there is no proven model to predict the likelihood of achieving cytoreduction to <1 cm and preventing futile laparotomy [12]. More recently, diagnostic laparoscopy has been performed as a standard procedure in some institutes, without solid evidence. It has been suggested as a diagnostic procedure to accurately predict tumor extensiveness and determine its resectability [13-15].

Ovarian cancer is a heterogeneous group including high-grade serous carcinoma (HGSC), endometrioid carcinoma, clear-cell carcinoma, mucinous carcinoma, and low-grade serous carcinoma. Previous studies have reported that histologic subtypes other than high-grade serous carcinoma (non-HGSC) have poorer prognoses than HGSC due to resistance and reduced sensitivity to conventional platinum-based combination chemotherapy [16-19]. However, it is difficult to determine the histological subtype of ovarian cancer prior to NAC. Diagnostic laparoscopy could make it easier to identify the histological subtype by obtaining tissue for pathological examination.

The aim of this study was to evaluate whether adding laparoscopy to the diagnostic work-up could prevent futile laparotomy and reduce the proportion of patients with non-HGSC subtypes who received NAC for advanced-stage ovarian cancer.

MATERIALS AND METHODS

1. Study design and population

We retrospectively analyzed the medical records of patients with pathologically confirmed International Federation of Gynecology and Obstetrics (FIGO) stage III or IV epithelial ovarian cancer who underwent PDS or NAC at the Yonsei University College of Medicine between 2010 and 2018. This study was approved by the Institutional Review Board of Severance Hospital at Yonsei University College of Medicine (No. 4-2018-0518).

All patients with suspected ovarian cancer received a standard diagnostic work-up consisting of magnetic resonance imaging of the pelvis; computed tomography (CT) of the pelvis and thorax with intravenous contrast agents; and assessment of levels of serum tumor markers, including cancer antigen (CA)-125, to assess the patient's performance status to undergo PDS. A positron emission tomography/CT was performed if extra-abdominal metastasis was suspected. After the diagnostic workup, patients underwent either PDS or NAC. The presence of epithelial ovarian cancer was histologically confirmed using diagnostic laparoscopic/laparotomy biopsy, image-guided aspiration biopsy, or cytology of ascites/pleural effusion before the administration of NAC.

Based on the method of deciding the primary treatment, we divided patients into 2 groups. The primary treatment was decided based on the diagnostic laparoscopy findings in Group 1 and on preoperative CT findings in Group 2. In Group 1, diagnostic laparoscopy was performed before primary treatment to systematically evaluate the intra-abdominal extent of the disease. In all patients, the decision to perform cytoreductive surgery, which would result in <1 cm of residual disease, was made based on the Fagotti scores [14,20] obtained during the diagnostic laparoscopy. The Fagotti score was calculated based on 7 parameters: 1) liver superficial metastasis, 2) omental cake, 3) peritoneal carcinomatosis, 4) diaphragmatic carcinomatosis, 5) mesenteric retraction, 6) bowel infiltration, and 7) stomach infiltration [14]. If PDS that would leave <1 cm of residual tumor was thought to be possible (Fagotti score <8) during laparoscopy, patients were considered for conversion to laparotomy or laparoscopy for PDS. However, if PDS with <1 cm of residual disease did not seem feasible without increasing the risk for complications (Fagotti score ≥8), patients were assigned to receive NAC followed by IDS. The operation time was less than 30 minutes in most cases, and the estimated blood loss was also minimal in most cases of diagnostic laparoscopy. In Group 2, the extent of the tumor burden was evaluated using preoperative CT. CT findings such as metastatic retroperitoneal lymph nodes >1 cm above the renal hilum (including supradiaphragmatic), diffuse small-bowel adhesions or thickening, perisplenic lesions >1 cm, small-bowel mesentery lesions >1 cm, root of the superior mesenteric artery lesions >1 cm, lesser sac lesion >1 cm, liver parenchymal metastasis >1 cm, and diffuse peritoneal carcinomatosis at the diaphragm, suggested a risk of suboptimal debulking surgery with increased postoperative complications [21,22]. If CT findings showed the possibility of optimal cytoreduction, laparotomy or laparoscopy was performed for PDS. However, patients with too extensive a disease to achieve residual disease <1 cm after PDS or with a risk of major complications were assigned to receive NAC followed by IDS.

At our institution, protocol-based triage was proposed to select appropriate patients to avoid unnecessary PDS [23,24]. Tumor burden evaluation and determination of the primary treatment were based on combinations of preoperative CT, diagnostic laparoscopy findings, and the patient's performance status. Diagnostic laparoscopy for determining the Fagotti score was considered in specific situations such as age ≤75 years, American Society of Anesthesiologists (ASA) status < 3, and absence of distant metastases. However, it has not yet been activated and is not performed perfectly according to the protocol. In our institution, there are differences in the primary treatment choice among gynecologic oncology surgeons depending on the situation. All patients in whom laparoscopic evaluation was feasible underwent diagnostic laparoscopy. Therefore, some patients with poor performance status (ASA 3), age >75 years, and/or preoperative CT findings predicting suboptimal debulking surgery were included in Group 1.

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Standard surgical procedures included total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic/para-aortic lymphadenectomy. Radical surgery included at least one of the following procedures: bowel resection, diaphragm/peritoneal surface stripping, splenectomy, liver resection, partial gastrectomy, partial cystectomy/ureteroneocystostomy, cholecystectomy, or distal pancreatectomy. One of 5 gynecologic oncology surgeons performed all surgical procedures to achieve optimal debulking surgery with residual disease <1 cm. The extent and complexity of the surgery were graded using the surgical complexity scoring system [21]. Postoperative complications were graded on a scale of 1–5 according to the Memorial Sloan Kettering Cancer Center surgical secondary events grading system [25].

2. Statistical analysis

Statistical analyses were conducted using IBM SPSS version 23 for Windows (IBM Corp., Armonk, NY, USA). Descriptive statistics, including frequency, percentage, median, and range, were used for demographic and clinical data. Patients were classified according to the method of deciding the primary treatment. Differences in the categorical variables between the groups were assessed using the χ^2 test and Fisher's exact test. Student's t-test or Mann–Whitney U test was used for continuous variables. Progression-free survival (PFS) and overall survival (OS) were compared between the groups using Kaplan–Meier curves and tested using the log-rank test. Statistical significance was set at $p<0.05$.

RESULTS

A total of 614 patients treated between January 2010 and May 2018 were included in the study. The primary treatment was determined based on diagnostic laparoscopy findings (Group 1) and preoperative CT (Group 2) findings in 192 and 422 patients, respectively. In Group 1, 49 (25.5%) of 192 patients underwent PDS after diagnostic laparoscopy, 125 (65.1%) of 192 patients received NAC followed by IDS, and 18 (9.4%) of 192 patients underwent only NAC, without IDS. In Group 2, 279 (66.1%) of 422 patients underwent PDS and 143 (33.9%) of 422 patients received NAC followed by IDS (**Fig. 1**).

The baseline characteristics of the 2 treatment groups are presented in **Table 1**. There were no significant differences in age, body mass index, serum CA-125 level, FIGO stage, total number of chemotherapy cycles, or chemotherapy regimen between the 2 groups. Patients in Group 1 were more likely to have poor performance status, defined as ASA score ≥3 (37.0% vs. 25.4%, $p<0.001$) and use of NAC (74.5% vs. 33.9%, $p<0.001$) than those in Group 2. In Group 1, 13 (9.1%) of 143 patients who underwent NAC were diagnosed with the non-HGSC histologic subtype versus 22 (15.4%) of 143 patients in Group 2 ($p=0.069$).

A comparison of the surgical outcomes between the 2 treatment groups is shown in **Table 2**. **Table 2** shows the data of patients who underwent cytoreductive surgery. The proportion of patients who underwent preoperative laparoscopy was higher in Group 1 than in Group 2 (10.9% vs. 5.7%, $p=0.025$). Futile laparotomy with residual disease >1 cm after surgery was observed in 1 of 174 patients in Group 1 and 31 of 422 patients in Group 2 (2.0% vs. 11.1%, $p=0.023$). Cytoreduction with no residual disease was observed in 30 (61.2%) of the 49 patients who underwent PDS in Group 1 and 96 (34.4%) of the 279 patients in Group 2 ($p=0.013$). Group 2 had a significantly higher rate of radical surgery than Group 1 (64.7% vs. 53.4%, $p=0.010$). Analysis of patients who underwent PDS showed similar results (68.8% vs. 51.0%, $p=0.015$). However, there were no significant differences in the proportion of patients

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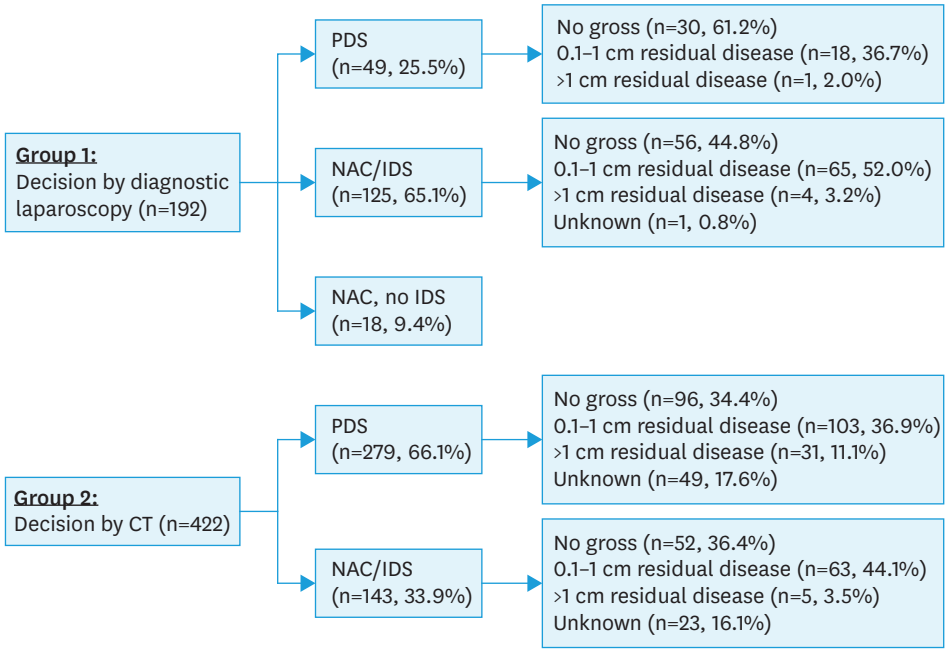

Fig. 1. Residual disease after debulking surgery in patients who made decision by diagnostic laparoscopy versus by computed tomography.
IDS, interval debulking surgery; NAC, neoadjuvant chemotherapy; PDS, primary debulking surgery.

undergoing NAC between the 2 groups. Surgical procedures with a high surgical complexity score (score=3) were required in 31.0% and 19.2% of patients in Groups 1 and 2, respectively (p=0.005). Analysis of patients who underwent PDS or NAC with IDS showed similar results (38.8% vs. 21.5%, p=0.024; 28.0% vs. 14.7%, p=0.003). Furthermore, there was a higher prevalence of patients with major complications (Grades 3–5) in Group 2 than in Group 1 (10.4% vs. 5.2%, p=0.033). Three (0.7%) Grade 5 complications (postoperative death within 30 days after surgery) were observed in Group 2. However, there were no serious laparoscopy-related complications in any patient.

The median follow-up duration was 53.4 months in Group 1 and 64.5 months in Group 2. During this period, there were 88 recurrences in Group 1 and 285 in Group 2 (p<0.001). Furthermore, 36 and 156 patients died in Groups 1 and 2, respectively (p<0.001). The Kaplan–Meier curves and log-rank test results are shown in **Fig. 2**. The median PFS and OS were 17.3 months and 18.3 months and 53.4 months and 64.5 months in Groups 1 and 2, respectively. There were no significant differences in PFS or OS between the 2 groups (p=0.847 and p=0.491, respectively). In addition, subgroup analyses of survival according to treatment strategy (PDS or NAC) were performed. No differences were observed in PFS or OS between the 2 subgroups of patients who underwent PDS (p=0.227 and p=0.801, respectively) and NAC (p=0.454 and p=0.983, respectively) (**Figs. 3** and **4**).

DISCUSSION

In this study, we investigated the role of diagnostic laparoscopy in deciding the primary treatment for patients with advanced-stage ovarian cancer. Decision-making using diagnostic laparoscopy significantly reduced the futile laparotomy and complication rates. Furthermore,

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Table 1. Patients characteristics (n=614)

Characteristics	Group 1 (n=192)	Group 2 (n=422)	p-value
Median age (yr)	57.0 (27.0–84.0)	55.5 (26.0–83.0)	0.340
Median BMI (kg/m²)	23.2 (16.6–40.2)	22.8 (15.8–38.7)	0.256
Median CA-125 level (U/mL)	1,162.7 (15.0–23,919.0)	1,022.5 (8.0–30,000.0)	0.782
ASA score			<0.001
1	15 (7.8)	94 (22.3)	
2	106 (55.2)	210 (49.8)	
3	71 (37.0)	104 (24.6)	
4	0 (0)	3 (0.7)	
Unknown	0 (0)	11 (2.6)	
FIGO stage			0.578
III	107 (55.7)	225 (53.3)	
IIIA	2 (1.0)	24 (5.7)	
IIIB	16 (8.3)	33 (7.8)	
IIIC	89 (46.4)	168 (39.8)	
IV	85 (44.3)	197 (46.7)	
Histology			<0.001
HGSC	164 (85.4)	285 (67.5)	
Non-HGSC	25 (13.0)	116 (27.5)	
Unknown	3 (1.6)	21 (5.0)	
NAC*			0.069
HGSC	127 (88.8)	110 (76.9)	
Non-HGSC	13 (9.1)	22 (15.4)	
Unknown	3 (2.1)	11 (7.7)	
NAC			<0.001
Yes	143 (74.5)	143 (33.9)	
No	49 (25.6)	279 (66.1)	
Chemotherapy regimen			0.671
Taxane/platinum	187 (97.4)	409 (96.9)	
Others	1 (0.5)	5 (1.2)	
Cycles of total chemotherapy			0.159
<6	23 (12.0)	36 (8.5)	
≥6	165 (85.9)	384 (91.0)	
Unknown	4 (2.1)	2 (0.5)	

Values are presented as number (range) or number (%).
ASA, American Society of Anesthesiologists; BMI, body mass index; CA 125, cancer antigen 125; FIGO, Federation of Gynecology and Obstetrics; HGSC, high-grade serous carcinoma; NAC, neoadjuvant chemotherapy.
*This group included only patients who underwent NAC.

the incorporation rate of NAC in the non-HGSC subtype tended to decrease. There was no significant difference in survival outcomes between patients who underwent primary treatment based on diagnostic laparoscopy findings and patients whose primary treatment was decided based on preoperative CT findings.

In some institutions, diagnostic laparoscopy is the standard diagnostic work-up to determine operability. Several studies have proposed diagnostic laparoscopy as a minimally invasive and reliable surgical option for identifying patients who are fit for PDS. In 2006, Fagotti et al. [20] reported a laparoscopy-based scoring system that predicted suboptimal surgery with a positive predictive value of 100% and a negative predictive value of 70% [13]. In 2008, Brun et al. [26] validated their prediction model, and in 2015, Petrillo et al. [27] updated the scoring system for improved discrimination. However, they suggested that if diagnostic laparoscopy is a reliable additional diagnostic tool for predicting PDS outcomes, it should prevent futile laparotomy. Therefore, they defined futile laparotomy as any residual disease after PDS and reported a 33% risk of futile laparotomy.

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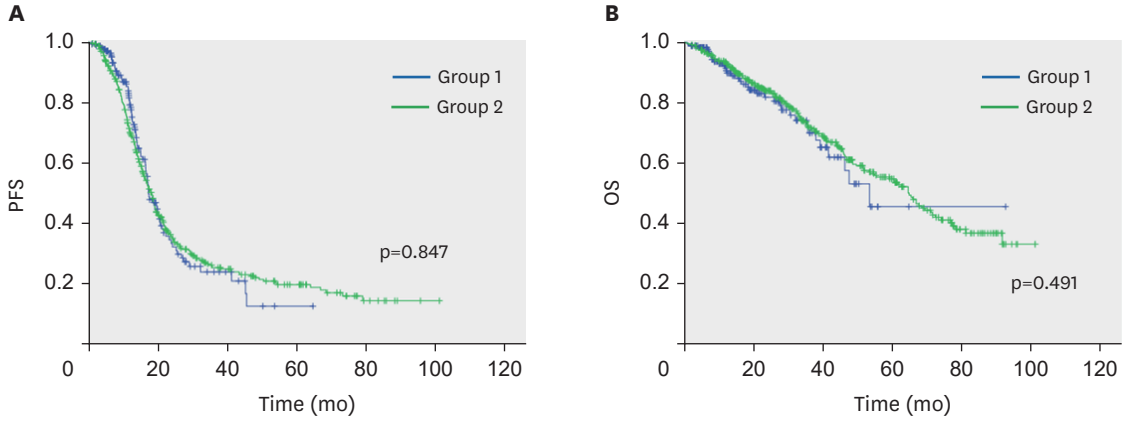
Table 2. Surgery-related details (n=596)

Characteristics	Group 1 (n=174)	Group 2 (n=422)	p value
Method of surgery			0.025
Laparotomy	155 (89.1)	398 (94.3)	
Laparoscopy	19 (10.9)	24 (5.7)	
Residual disease			0.003
≤1 cm	168 (96.6)	314 (74.4)	
>1 cm	5 (2.9)	36 (8.5)	
Unknown	1 (0.6)	72 (17.1)	
PDS*			0.023
≤1 cm	48 (98.0)	199 (71.3)	
>1 cm	1 (2.0)	31 (11.1)	
Unknown	0 (0)	49 (17.6)	
Radical surgery†			0.010
None	81 (46.6)	149 (35.3)	
Any Radical surgery	93 (53.4)	273 (64.7)	
Surgical complexity‡			0.005
1	4 (2.3)	7 (1.7)	
2	116 (66.7)	334 (79.1)	
3	54 (31.0)	81 (19.2)	
Postoperative complication grade§			0.004
0	67 (38.5)	183 (43.4)	
1	2 (1.1)	20 (4.7)	
2	96 (55.2)	164 (38.9)	
3	9 (5.2)	38 (9.0)	
4	0 (0)	3 (0.7)	
5	0 (0)	3 (0.7)	
Unknown	0 (0)	11 (2.6)	
Major complications			0.033
0–2	165 (94.8)	367 (87.0)	
3–5	9 (5.2)	44 (10.4)	
Unknown	0 (0)	11 (2.6)	

PDS, primary debulking surgery.
*This group included only patients who underwent PDS; †Radical surgery included at least one of the following procedure: bowel resection, diaphragm/peritoneal surface stripping, splenectomy, liver resection, partial gastrectomy, partial cystectomy/ureteroneocystostomy, cholecystectomy, or distal pancreatectomy; ‡According to Aletti et al. [21]; §According to Memorial Sloan Kettering Cancer Center surgical secondary events grading system.



Median PFS
17.3 months (Group 1) vs. 18.3 months (Group 2)

Median OS
53.4 months (Group 1) vs. 64.5 months (Group 2)

Fig. 2. Kaplan–Meier curves of progression-free (A) and overall survival (B).
OS, overall survival; PFS, progression-free survival.

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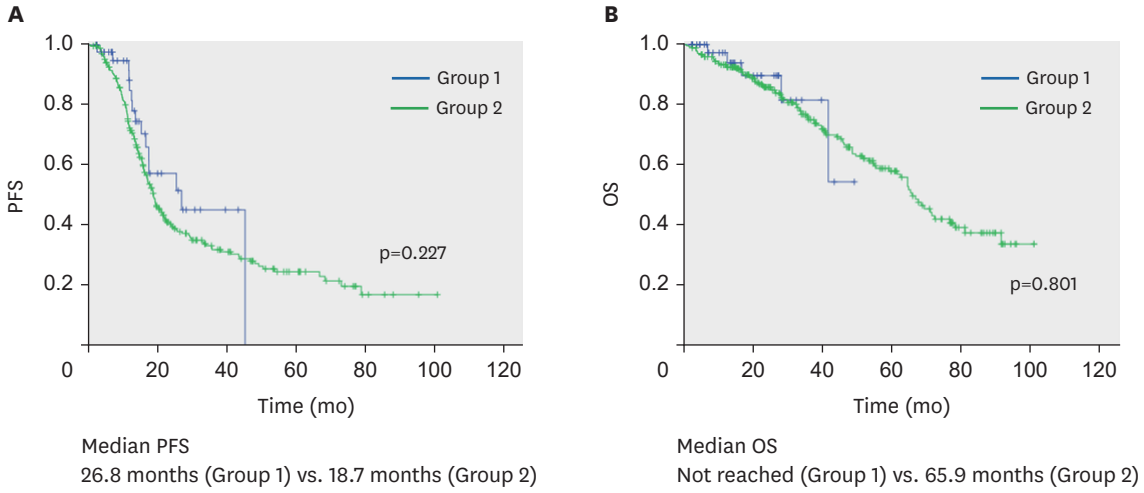
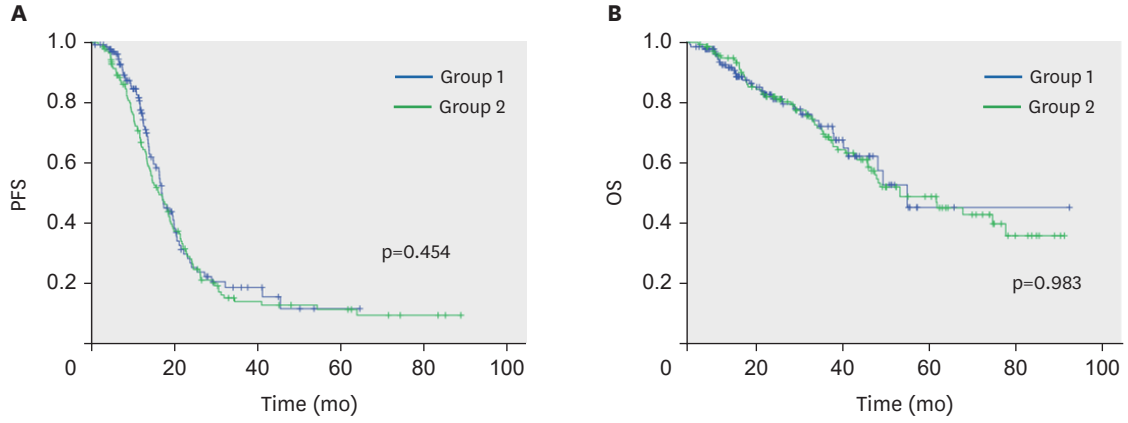


Median PFS
26.8 months (Group 1) vs. 18.7 months (Group 2)

Median OS
Not reached (Group 1) vs. 65.9 months (Group 2)

Fig. 3. Kaplan–Meier curves of progression-free (A) and overall survival (B) in the primary debulking surgery subgroup.
OS, overall survival; PFS, progression-free survival.



Median PFS
17.2 months (Group 1) vs. 16.4 months (Group 2)

Median OS
53.4 months (Group 1) vs. 51.6 months (Group 2)

Fig. 4. Kaplan–Meier curves of progression-free (A) and overall survival (B) in the NAC subgroup.
OS, overall survival; PFS, progression-free survival.

Our results showed a significant decrease in the incidence of futile laparotomy (2.0% vs. 11.1%, p=0.023), and the rate of cytoreduction with no residual disease was 61.2% in patients undergoing PDS in the laparoscopy group. The results of the present study correspond with those of previous studies that reported that diagnostic laparoscopy could predict PDS outcomes. Recently, Rutten et al. [28] demonstrated that incorporating diagnostic laparoscopic assessment into the standard of care resulted in a significant decrease in the incidence of futile laparotomy (10% vs. 39%, p<0.001), and complete cytoreduction was achieved in 57% of the patients undergoing PDS in the laparoscopy group.

During diagnostic laparoscopy, we used the laparoscopic scoring assessment previously described by Fagotti et al. [14,20] to categorize the patients into 2 groups (PDS and NAC). These methods contrast with those reported by Rutten et al. [28] who performed diagnostic laparoscopy to predict operability based on specific laparoscopic findings determined by their own institution, and not on a previously validated scoring assessment. Furthermore, in our analysis, diagnostic laparoscopy reduced the radical surgery and postoperative

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complication rates, whereas Rutten et al. [28] reported no difference between the study groups. In this study, the rate of radical surgery was 53.4% in Group 1 and 64.7% in Group 2. Rutten et al. [28] reported that the rate of extensive surgery was 36% in the diagnostic laparoscopy group and 27% in the primary surgery group, which was not superior to the rate of radical surgery at our institution. Surgery with a high tumor burden requires extensive procedures to achieve optimal resection, with a subsequent high risk of morbidity [4-6]. By avoiding PDS using diagnostic laparoscopy, the rates of radical surgery and postoperative complications could be decreased in patients with extensive disease at our institution.

In the present study, the survival rates were not significantly different between the 2 groups, which is similar to the results of Rutten et al. [28]. The median PFS and OS in Group 1 were 19.7 and 53.4 months, respectively, in our study, compared with 13.7 and 44.4 months, respectively, in the study by Rutten et al. [28] Despite the differences observed between the 2 groups, the improvement in optimal resection rates did not significantly affect the survival outcomes. Furthermore, previous studies that compared PDS with NAC+IDS reported no survival benefit for either treatment strategy [3,4]. Therefore, survival may not be a valid endpoint for cross comparisons in this study.

The strength of our study is that it is the first to investigate the role of diagnostic laparoscopy in preventing non-HGSC patients from receiving NAC, because NAC does not seem to be useful for patients with chemoresistant histology (i.e., the non-HGSC subtype). There are few studies on the outcomes of NAC in the non-HGSC subtype. Consensus reviews by the Gynecologic Cancer InterGroup have emphasized that the use of NAC should be avoided in the non-HGSC subtype [29-31]. Furthermore, a previous study reported that patients with non-HGSC have a poor prognosis when receiving NAC [32]. Using diagnostic laparoscopy, we could confirm the histologic diagnosis from the excised tissue and could identify patients with the non-HGSC subtype who would not benefit from NAC. However, with regard to NAC, there was a tendency toward a lower proportion of patients with non-HGSC in Group 1 compared to that in Group 2, but the difference was not statistically significant. This is due to the small number of non-HGSC patients and surgeons' discretion in selecting NAC for non-HGSC patients. Owing to the low incidence of the non-HGSC subtype, further clinical studies and data collection are required to determine whether NAC should be avoided in patients with this subtype.

The rate of high surgical complexity in Group 1 was significantly higher than that in Group 2, in both the PDS and NAC subgroups. The apparently increased rate of high surgical complexity in Group 1 was due to the trend for maximal surgical effort to improve the optimal debulking surgery rates at our institution during this time period. At our institution, diagnostic laparoscopy was introduced in 2010, and its use has increased rapidly since 2014. Therefore, there was a significant difference in patient distribution according to time between the 2 groups. However, our data showed that high surgical complexity did not result in increased surgical complication rates due to surgical quality improvement. It is becoming more common to identify histopathologic types through less invasive preoperative pathology tests such as CT-guided needle biopsy. The advantages of diagnostic laparoscopy compared to less invasive pathological test is that it provides histopatholgic results, and help to determine whether optimal surgery is possible by exploring disease distribution to avoid unnecessarily morbid, suboptimal laparotomies.

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The limitation of our study is its retrospective nature, and selection bias due to the lack of an activated protocol-based triage is another potential limitation. Establishing clear estimations for patient selection could reduce selection bias. Furthermore, the increased rate of high surgical complexity in Group 1 may have affected the residual disease in patients who underwent PDS. However, this does not need to be considered because there is no significant difference in residual disease between the 2 subgroups that underwent NAC.

In conclusion, diagnostic laparoscopy reduced the rates of futile laparotomy and implementation of NAC in patients with non-HGSC without affecting the postoperative complications and survival outcomes. Diagnostic laparoscopy is an effective and safe tool for patient selection for primary treatment. Therefore, the addition of laparoscopy to the conventional initial diagnostic work-up is essential for optimal management of patients with advanced-stage ovarian cancer.

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