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Impact of the time interval from completion of neoadjuvant chemotherapy to initiation of postoperative adjuvant chemotherapy on the survival of patients with advanced ovarian cancer

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HIGHLIGHTS

- We examined the relationship between the NAC-POAC interval and survival.
- Patients with intervals >42 days showed poorer progression-free and overall survival.
- Longer time intervals were thus associated with higher risks of recurrence and death.

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ABSTRACT

Objective. To investigate the relationship of the time interval from the completion of neoadjuvant chemotherapy (NAC) to the initiation of postoperative adjuvant chemotherapy (POAC) with the survival outcomes in patients with ovarian cancer.

Methods. We retrospectively investigated 220 patients with pathologically confirmed epithelial ovarian cancer who received NAC at Yonsei Cancer Hospital between 2006 and 2016. The time interval was defined as the period from the completion of NAC, spanning interval debulking surgery (IDS), to the initiation of POAC.

Results. The median time interval was 42 (range 16–178) days; 103 patients (53.1%) received POAC within 42 days after NAC while 91 patients (46.9%) received it after 42 days. There were no significant differences in patient characteristics between these 2 groups. Kaplan-Meier analysis showed that patients with longer time intervals (>42 days) had poorer progression-free survival and overall survival ($P = 0.039$ and 0.005, respectively). In the multivariate analysis, patients with longer time intervals had significantly poorer progression-free (hazard ratio, 1.41; 95% confidence interval, 0.98–2.03; not significant) and overall survivals (hazard ratio, 2.03; 95% confidence interval, 1.16–3.54). When the patients were categorized according to time interval quartiles (≤37, 38–42, 43–50, and >50 days), longer time intervals were associated with higher risks of recurrence and death (P for trend: 0.006 and <0.001, respectively).

Conclusion. The time interval from the completion of NAC to the initiation of POAC appears to influence survival. Efforts to reduce the time interval might improve the outcomes in ovarian cancer patients undergoing NAC.

1. Introduction

Ovarian cancer is a highly lethal gynecologic cancer, and its incidence and mortality rates in Korea are increasing [1,2]. Primary cytoreductive surgery (PDS) followed by platinum-based chemotherapy is the current standard of care for advanced ovarian cancer [3]. Recently, several phase 3 clinical trials have demonstrated that survival and the postoperative morbidity and mortality rates after receiving neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) are not inferior to those following PDS in women with stage III–IV ovarian cancer [4–7]. Therefore, NAC followed by IDS is an alternative approach for treating advanced-stage ovarian cancer [8]. Moreover, the tumor response to NAC predicts survival and can be considered a surrogate prognostic marker [9].

IDS and postoperative adjuvant chemotherapy (POAC) are mandatory following NAC. However, the appropriate time interval between the completion of NAC and the initiation of POAC has not been thoroughly addressed in large randomised clinical trials; in fact, most previous trials did not specify a recommended interval. Surgery after NAC is

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usually performed when the neutropenic window is overcome; however, a delay in surgery frequently occurs in clinical practice. For various solid tumors, some studies have suggested that surgery should be performed within 4–6 weeks after NAC [10,11], while another study showed that the time to surgery after NAC did not impact the survival of patients with breast cancer [12]. Regarding adjuvant chemotherapy after surgery, several retrospective studies tried to identify the ideal interval between surgery and NAC in patients with advanced-stage ovarian cancer. As several studies showed that delaying chemotherapy after PDS worsened prognosis [13–17], there is a general consensus that unnecessary delays should be avoided. However, the optimal time interval between IDS completion and POAC initiation has not been determined.

With this in mind, in the present study, we evaluated the relationship of the time interval between the end of NAC and the initiation of POAC with the survival outcomes among patients with advanced-stage ovarian cancer. We hypothesized that delayed IDS after NAC may jeopardize the clinical benefit of NAC, and that a delay in the initiation of POAC after IDS may impair the clinical benefit of the latter in ovarian cancer patients.

2. Materials and methods

2.1. Study population

We performed a retrospective review of the medical records of 220 patients with pathologically confirmed epithelial ovarian cancer who received at least 1 cycle of NAC at Yonsei Cancer Hospital between 2006 and 2016. All patients were histologically or cytologically confirmed to have International Federation of Gynecology and Obstetrics (FIGO) stage III or IV epithelial ovarian cancer before starting chemotherapy. The diagnosis was performed either via laparoscopic or image-biopsy samples, or by using fine-needle aspiration of a tumor site or ascites/effusion. All surgical procedures were performed by 1 of 5 gynecologic oncology surgeons at our institute. The histological diagnoses were based on World Health Organization criteria, and all microscopic slides were reviewed by 2 experienced gynecologic pathologists. NAC was performed if at least 1 of the following 3 criteria was met: 1) pulmonary and/or hepatic parenchymal metastases were observed on imaging studies before surgery, 2) the patient was medically inoperable, and/or 3) optimal cytoreduction was not achievable due to a high tumor burden (Fagotti score ≧8) observed by diagnostic laparoscopy [18,19]. According to our institutional policy, IDS was performed after 3 cycles of NAC. The timing of IDS was delayed when optimal cytoreduction was not achievable, determined at the clinician's discretion. We excluded women who were still receiving POAC at the time of data collection (n = 9); those who did not undergo IDS after NAC (n = 6); those who underwent NAC, IDS, and POAC elsewhere and for whom medical records were not available (n = 2); and those who were lost to follow-up (n = 9). Ultimately, the final study population comprised 194 women (Fig. 1). All patients received taxane and platinum combination chemotherapy. Conventional surgical procedures included the sampling of free fluid or peritoneal washings for cytology; a thorough inspection of the abdomen and pelvis, including the upper abdominal viscera, diaphragm, and retroperitoneal spaces; and hysterectomy, bilateral oophorectomy and omentectomy, pelvic/para-aortic lymph node dissection, and appendectomy. Radical surgery included bowel resection; diaphragm or other peritoneal surface stripping; splenectomy; partial hepatectomy; partial gastrectomy; or partial cystectomy and/or ureteroneocystostomy, cholecystectomy, and/or distal pancreatectomy [20–22]. Perioperative complications were graded according to the Memorial Sloan-Kettering Cancer Center surgical secondary events grading system [23,24]; a score ≥3 points indicated a major complication. Operative mortality was defined as death occurring within 30 days after surgery (grade 5).

The following data were extracted from the patients' medical records: age, body mass index, American Society of Anesthesiologists (ASA) score, pretreatment serum cancer antigen-125 (CA-125) levels, FIGO stage, histology, performance of radical surgery, residual disease after IDS, chemotherapy regimens, total chemotherapy cycles, date of surgery, date of NAC and POAC initiation, date of progression or recurrence, and date of last follow-up.

The time interval was defined as the period between the completion of NAC and the initiation of POAC. The time to surgery was defined as the time (in days) from the end of NAC to IDS, while the time to chemotherapy was defined as the time from IDS to the initiation of POAC (Fig. 2). The present study was reviewed and approved by our Institutional Review Board (Registration number: 4-2015-1158).

2.2. Statistical analysis

SPSS statistical software (version 21.0; IBM Corp., Armonk, NY) was used for the statistical analyses. Descriptive statistics were used for demographic data and are summarized as the median (range) or frequency (percentage). Differences in the patient characteristics were compared in relation to the time intervals using the chi-square or Mann-Whitney *U* test. The endpoints included the progression-free survival (PFS) and overall survival (OS). PFS was defined as the interval between the date of diagnosis and the date of first recurrence. OS was defined as the interval between the date of diagnosis and the date of death. We routinely performed CA-125 and imaging studies for surveillance. Our institutional follow-up strategy was to follow-up with the patients every 3 months for the first 2 years after treatment and every 6 months thereafter. Recurrence was defined as the date of appearance of radiologically-detected disease during a follow-up examination. A rise of CA-125 without clinical signs of relapse was not counted as progression but generally triggered further radiological examinations. PFS and OS were analyzed with the Kaplan-Meier method and log-rank test. Factors identified as significant in the univariate analyses were

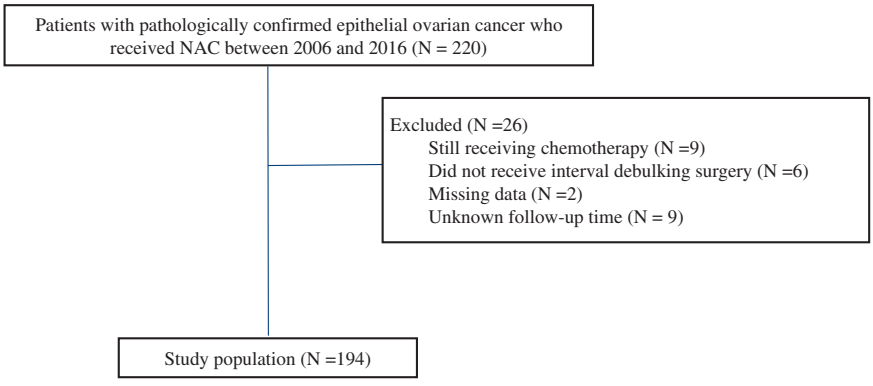

Fig. 1. Flow diagram of the study population. NAC, neoadjuvant chemotherapy.

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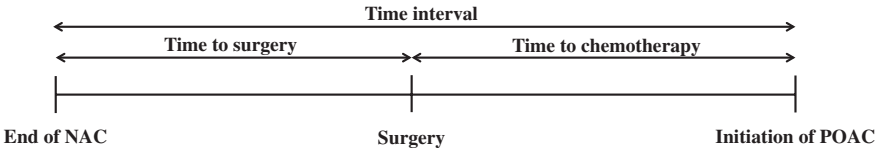

Fig. 2. Definitions of the time intervals between neoadjuvant chemotherapy and adjuvant chemotherapy. NAC, neoadjuvant chemotherapy; POAC, postoperative adjuvant chemotherapy.

subjected to multivariate analysis. Cox regression analysis was used to evaluate the effects of the prognostic factors, expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). For all analyses, $P < 0.05$ was considered statistically significant.

3. Results

The patient and clinical characteristics are shown in Table 1. A total of 194 patients were included in the study; the median age was 57 (range, 31–78) years, 91 patients (47.1%) had an ASA score of 2, and the median CA-125 was 1887.6 (range, 44.3–30,000) U/mL. The median value of CA-125 before IDS was 46.1 U/mL, and 86 (44.3%) patients were normalized prior to IDS. Of all patients, 178 (91.8%) had serous histology. Eighty-two patients (42.3%) underwent radical surgery, including 30 (15.5%) who underwent bowel surgery. In 86 patients (44.3%), no gross residual tumor was present after IDS. All patients received platinum-based combination chemotherapy. A total of 155 patients (79.6%) received paclitaxel plus carboplatin, and the median number of cycles of total chemotherapy was 8 (range, 4–12).

For the analyses, the patients were divided into 2 time interval groups according to the median interval time: the short (≤42 days) and long (>42 days) interval groups. As a result, 103 (53.1%) and 91 (46.9%) patients underwent POAC within and after 42 days of their last dose of NAC. There were no significant differences in the patient characteristics, such as age, body mass index, ASA score, baseline CA-125, FIGO stage, histologic types, CA-125 before IDS, surgery extent, residual disease, complication rate, chemotherapy regimens, and cycles of total chemotherapy between the 2 groups. The median numbers of NAC cycles were 3 (range, 1–5) and 3 (range, 2–9) in the short (≤42 days) and long (>42 days) time interval groups, respectively.

Table 1
Patient and clinical characteristics (N = 194).

Characteristics	All patients (N = 194)	Time interval[a] ≤42 days (n = 103)	Time interval >42 days (n = 91)	P-value
Median age, years (range)	57 (31–78)	56 (32–77)	59 (31–78)	0.117
Median BMI, kg/m^2 (range)	22.9 (16.4–40.4)	22.7 (16.4–40.4)	23.4 (17.8–35.8)	0.704
ASA score, n (%)				
1	50 (25.7%)	31 (30.4%)	19 (7.8%)	0.190
2	91 (47.1%)	42 (41.2%)	49 (53.8%)	
3	51 (26.2%)	29 (28.3%)	22 (24.2%)	
4	1 (0.5%)	0 (0%)	1 (1.1%)	
Not available	1 (0.5%)	1 (0.1%)	0 (0%)	
Median CA-125 level, U/mL (range)	1887.6 (44.3–30,000)	2335.9 (44.3–30,000)	1589.7 (75–30,000)	0.059
Median CA-125 level before IDS, U/mL (range)	46.1 (5.1–7913.1)	39.8 (5.1–7913.1)	50.3 (5.1–815.6)	0.986
FIGO stage, n (%)				
IIIB	5 (2.6%)	5 (4.8%)	0 (0%)	0.120
IIIC	44 (22.7%)	21 (20.4%)	23 (25.2%)	
IVA	87 (44.8%)	49 (47.6%)	38 (41.8%)	
IVB	58 (29.9%)	28 (27.2%)	30 (33.0%)	
Histologic type, n (%)				
HGSC	178 (91.8%)	97 (94.1%)	81 (89.0%)	0.703
Endometrioid	3 (2.1%)	1 (1.0%)	2 (2.2%)	
Mucinous	4 (1.5%)	1 (1.0%)	3 (3.3%)	
Others	9 (4.6%)	4 (3.9%)	5 (5.5%)	
Radical surgery[b], n (%)				
None	112 (57.7%)	58 (56.3%)	54 (59.3%)	0.670
Any radical surgery	82 (42.3%)	45 (43.7%)	37 (40.7%)	
Residual disease, n (%)				
No	86 (44.3%)	50 (48.5%)	36 (39.6%)	0.209
Any residual	108 (55.7%)	53 (51.5%)	55 (60.4%)	
Complication grade[c]				
0–2	185 (95.3%)	99 (96.1%)	86 (94.5%)	0.737
3–5	9 (4.7%)	4 (3.9%)	5 (5.5%)	
Chemotherapy regimen, n (%)				
Paclitaxel + carboplatin	155 (79.6%)	80 (77.7%)	75 (82.4%)	0.495
Docetaxel + carboplatin	34 (17.9%)	21 (20.4%)	34 (14.3%)	
Paclitaxel + carboplatin + bevacizumab	4 (2.0%)	2 (1.9%)	2 (2.2%)	
Paclitaxel + cisplatin	1 (0.5%)	0 (0%)	1 (1.1%)	
Cycles of total chemotherapy, median (range)	8 (4–12)	8 (4–12)	8 (5–12)	0.635

BMI, body mass index; ASA, American Society of Anesthesiologists; CA-125, cancer antigen 125; IDS, Interval debulking surgery; FIGO, International Federation of Gynecology and Obstetrics; HGSC, high-grade serous carcinoma.

[a] The time interval was defined as the time between the end of neoadjuvant chemotherapy to the initiation of postoperative adjuvant chemotherapy.

[b] Radical surgery includes any of following: bowel surgery, video-assisted thoracoscopic surgery, splenectomy, liver resection, supraclavicular fossa resection, ureter resection, and others.

[c] According to Aletti et al. [23,24].

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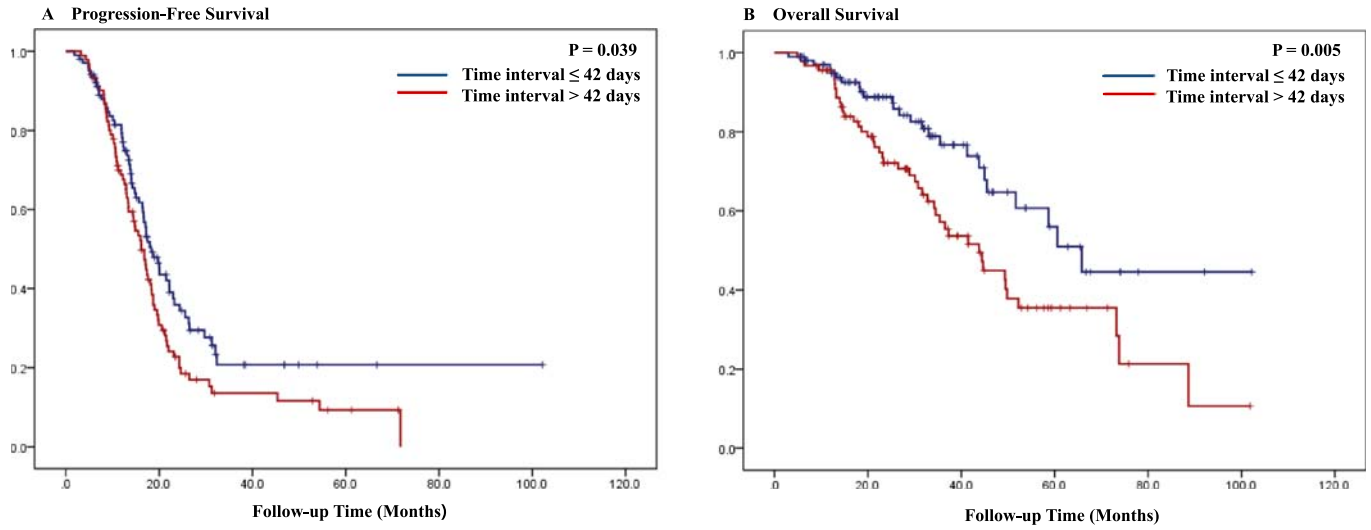

Fig. 3. Kaplan-Meier curves of progression-free survival (A) and overall survival (B) according to the time interval from the end of NAC to POAC initiation. NAC, neoadjuvant chemotherapy; POAC, postoperative adjuvant chemotherapy.

At the time of analysis, 70 patients (36.1%) had died and 136 (70.1%) had experienced recurrence. The median time to surgery after NAC was 25 (range, 8–82) days; 100 patients (51.5%) had IDS within 25 days of their last dose of NAC while 94 (48.5%) underwent IDS after 25 days. The median time to POAC after IDS was 16 (range 6–154) days; 104 patients (53.6%) had POAC within 16 days of their last dose of NAC while 94 (46.4%) initiated POAC after 16 days.

Among the 91 patients in the long interval (>42 days) group, 56 (62.2%) had a delayed time to surgery (>25 days) and 65 patients (71.4%) had a delayed time to chemotherapy (>16 days); the cutoffs represent each group's median value. In 30 patients (32.9%), both the time to surgery and the time to chemotherapy were delayed. The reasons for delaying the time to surgery (n = 56) were chemotherapy-related toxicity (n = 19), medical consultation and evaluation for operability (n = 10), and organizational shortcomings (n = 27). The reasons for delaying the time to chemotherapy (n = 65) included complications after surgery (such as ileus, infection, and wound complications) (n = 43), poor general conditions after surgery (n = 15), and patients' requests (n = 7).

Kaplan–Meier curves for OS and PFS are shown in Fig. 3. Patients in the long interval group (>42 days) had poorer PFS (P = 0.039) and OS (P = 0.005) than those in the short interval group (≤42 days). In the subgroup analysis, patients with a long time interval (>42 days) due to organizational shortcomings had poorer PFS and OS than those with a short interval (≤42 days) (Fig. S1). Kaplan-Meier curves for OS and PFS according to the time to surgery and time to chemotherapy are shown in Figs. S2 and S3, respectively. Notably, patients with longer times to surgery (>25 days) had significantly poorer OS (P = 0.026) than those with a shorter time to surgery (≤25 days); however, the difference in PFS was not significant (P = 0.552). Furthermore, there were no differences in the PFS and OS between patients who initiated POAC after IDS before vs. after 16 days (P = 0.353 and 0.563, respectively).

The results of the univariate and multivariate Cox regression analyses of PFS and OS in all patients are shown in Table 2. In terms of recurrence, multivariate analysis showed that a longer time interval was not a statistically significant prognostic factor, although there was a trend (HR, 1.41; 95% CI, 0.98–2.03). Moreover, FIGO stage (HR, 1.66; 95% CI, 1.03–2.67), non-high-grade serous carcinoma histology (HR, 2.13; 95% CI, 1.11–4.08), and any residual disease (HR, 1.71; 95% CI, 1.17–2.49) were independent prognostic factors associated with a higher risk of progression. For OS, multivariate analysis showed that a longer time interval was an independent prognostic factor in all patients (HR, 2.03; 95% CI, 1.16–3.54). Furthermore, non-high-grade serous carcinoma histology (HR, 3.79; 95% CI, 1.67–8.62) and any residual disease (HR, 2.26; 95% CI, 1.21–4.24) were significantly associated with a higher risk of death. The patients were also categorized based on the residual diseases (R0, R0–0.5 cm, R0.5–1.0 cm, R > 1.0 cm) to evaluate the presence of a linear trend (Table 1). As a result, residual disease was found to be an independent prognostic factor associated with higher risks of progression and death.

Finally, the patients were also categorized into quartiles based on the time intervals (≤37, 38–42, 43–50, and >50 days) to evaluate the presence of a linear trend (Table 3). Consequently, patients with longer time intervals were found to have higher risks of recurrence and death (P for trend: 0.006 and <0.001, respectively). Patients in the highest quartile (>50 days) had the highest risks of recurrence (HR, 1.93; 95% CI, 1.16–3.20) and death (HR, 2.06; 95% CI, 1.05–4.02), as compared to patients in the lowest quartile (≤37 days). Table 2 shows the comparison of the patients' demographic and clinical characteristics according to the time interval quartiles.

4. Discussion

In this study, we investigated whether the timing of POAC initiation after NAC has any prognostic relevance in patients with advanced ovarian cancer. Our results indicated that patients who receive POAC within 42 days after completing NAC derive a greater survival benefit. Furthermore, decreasing time intervals were associated with significant improvements in survival.

NAC followed by IDS and POAC is a potentially advantageous treatment option for patients with large tumor burdens, multiple comorbidities, or stage IV disease [25]. Although the European Organization for Research and Treatment of Cancer (EORTC) 55,971 [5] and Chemotherapy OR Upfront Surgery (CHORUS) [6] trials led to the adoption of NAC in clinical practice, neither trial evaluated the role of the time interval between completion of NAC and initiation of POAC. Recent study protocols from the International Collaborative Ovarian Neoplasm (ICON8) [26] and Study of Upfront Surgery Versus Neoadjuvant Chemotherapy in Patients With Advanced Ovarian Cancer (SUNNY) [27] recommend surgery within 4 and 6 weeks after NAC, respectively, and both protocols recommend POAC initiation as soon as possible after IDS.

Regarding the time to surgery after NAC, the accepted practice is to perform surgery when the neutropenic window is overcome, normally resulting in a 3–4-week interval. However, it is unclear if a delay in surgery influences the efficacy of the previous systemic treatment for ovarian cancer. To our knowledge, there are no studies on the optimal time intervals between NAC and surgery in patients with ovarian cancer;

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Table 2
Univariate and multivariate analyses for progression-free and overall survival using a Cox proportional hazards model.

Variables	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age, years								
≤57	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
>57	0.93 (0.67–1.31)	0.712	1.13 (0.78–1.64)	0.531	1.52 (0.94–2.45)	0.086	1.86 (1.08–3.29)	0.026
ASA score								
1–2	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
3–4	1.23 (0.82–1.83)	0.322	1.26 (0.81–1.96)	0.314	1.54 (0.83–2.83)	0.171	1.49 (0.75–2.98)	0.256
FIGO stage								
III	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
IV	1.62 (1.07–2.44)	0.022	1.66 (1.03–2.67)	0.038	0.90 (0.54–1.52)	0.701	1.13 (0.59–2.17)	0.713
Histology								
HGSC	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Non-HGSC	2.26 (1.27–4.02)	0.006	2.13 (1.11–4.08)	0.023	3.87 (2.01–7.47)	<0.001	3.79 (1.67–8.62)	0.001
Residual disease								
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Any residual	1.63 (1.15–2.31)	0.006	1.71 (1.17–2.49)	0.006	1.94 (1.17–3.21)	0.011	2.26 (1.21–4.24)	0.011
Radical surgery								
No	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
Yes	1.33 (0.94–1.87)	0.109	1.12 (0.77–1.63)	0.547	1.16 (0.72–1.87)	0.550	1.06 (0.61–1.87)	0.827
Time interval[a], days								
≤42	1 (Reference)		1 (Reference)		1 (Reference)		1 (Reference)	
>42	1.46 (1.02–2.00)	0.040	1.41 (0.98–2.03)	0.063	1.98 (1.22–3.23)	0.006	2.03 (1.16–3.54)	0.013

ASA, American Society of Anesthesiologists; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HGSC, high-grade serous carcinoma; HR, hazard ratio; IDS, interval cytoreductive surgery; PFS, progression-free survival; OS, overall survival.
[a] The time interval was defined as the time between the end of neoadjuvant chemotherapy to the initiation of postoperative adjuvant chemotherapy.

however, several retrospective studies investigated the appropriate time to surgery after NAC in patients with breast cancer [10–12]. Omarini et al. [10] researched the optimal time interval between the completion of neoadjuvant systemic therapy and breast surgery, and found that breast cancer patients treated within 21 days experienced better survival outcomes. In contrast, Sanford et al. [12] showed that breast cancer patients with intervals between NAC and surgery of up to 8 weeks had equivalent survival outcomes. Gao et al. [11] investigated the timing of surgery after neoadjuvant chemoradiation in patients with clinical stage IIIA N2 non-small cell lung cancer and found that the OS appeared to be significantly lower in patients who underwent surgery beyond 6 weeks after receiving neoadjuvant therapy.

Furthermore, some retrospective studies have attempted to identify the optimal time interval between surgery and initiation of adjuvant chemotherapy, and concluded that unnecessary delays ought to be avoided [13,14]. Mahner et al. investigated the prognostic effect of the time to chemotherapy after surgery in patients with advanced ovarian cancer stratified by residual disease, and provided evidence that early initiation of chemotherapy may slightly improve survival in patients who undergo complete cytoreduction [14]. Tewari et al. estimated that the survival of patients with advanced ovarian cancer may be adversely affected when chemotherapy initiation exceeds 25 days following surgery [13]. Other studies failed to show that the time to chemotherapy initiation after surgery was a determinant prognostic factor in patients with advanced ovarian cancer [28,29]. Furthermore, animal models have shown that removal of the primary tumor can stimulate residual tumor growth; earlier initiation of chemotherapy offered a significant advantage in preventing systemic relapse, as well as in growth suppression of the residual tumor [30–32].

In clinical practice, the interval between completion of NAC and initiation of POAC is influenced by multiple factors. As described above, the time interval was defined as the combination of the time to surgery (the completion of NAC to IDS) and the time to postoperative chemotherapy (IDS to initiation of POAC) in the present study. Our subgroup analyses evaluating the 2 factors separately showed that the time to surgery might influence the survival to a greater extent than the time to chemotherapy. Concerning the time to surgery after NAC, a frequently encountered obstacle is the difficulty in scheduling surgery in a timely fashion after NAC due to organizational shortcomings. IDS requires a long operative time as well as a multidisciplinary team involving gynecologic oncologists, general surgeons, urologists, and thoracic surgeons; hence, scheduling a date for surgery can be difficult and is a major reason for

Table 3
Multivariate Cox regression of progression-free survival and overall survival, and P for trend according to the time interval quartile values.

Time interval, days[b]	N	PFS[a]		OS[a]	
		HR (95% CI)	P for trend	HR (95% CI)	P for trend
≤37	54	1 (Reference)	0.006	1 (Reference)	<0.001
38–42	49	1.20 (0.70–2.03)		0.77 (0.33–1.83)	
43–50	48	1.27 (0.78–2.06)		1.23 (0.63–2.66)	
>50	43	1.93 (1.16–3.20)		2.06 (1.05–4.02)	

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.
[a] The multivariate analysis was adjusted for age, ASA score, FIGO stage, histology, residual disease, and radical surgery.
[b] The time interval was defined as the time between the end of neoadjuvant chemotherapy to the initiation of postoperative adjuvant chemotherapy.

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delays. Furthermore, the time required for patients' recovery from the side effects of chemotherapy, mainly hematological toxicities, can also delay surgery. Some patients also have comorbidities and conditions during chemotherapy that may lead to delays. As for the time to chemotherapy after surgery, the prolonged recovery time required by patients who undergo intensive surgery and postoperative complications are the main reasons for delays. Although we cannot determine from the patients' medical records how the clinicians' preferences affect the time intervals, such preferences may also be an important factor, because there were no significant differences in the patient characteristics according to the time interval in this study. Even if there are no chemotherapy-induced toxicities or postoperative complications, some clinicians prefer to schedule IDS after >4 weeks have elapsed, and to start POAC 3 weeks after IDS.

A limitation of our study was that it was retrospective and dependent on medical records, as well as the fact that it was based on a single institution experience. Moreover, the study lacked information about the patients' physical statuses. Although physical status can be a significant factor in determining the initiation of chemotherapy and surgery, only the pretreatment ASA score was considered in our study. Lastly, our study evaluated all-cause mortality rather than cancer-specific mortality; therefore, the patients could have died of other factors not related to ovarian cancer. It was difficult to distinguish between mortality from ovarian cancer and that from cancer-related complications or comorbidities.

Despite these limitations, the major strength of this study is that it is the first to examine the effects of the time interval between NAC and POAC in patients with advanced-stage ovarian cancer. A prospective study on this topic would be unethical and difficult to perform. Our results demonstrate that a significant correlation may exist between survival outcomes and the time intervals between the completion of NAC and initiation of POAC, and that a delay in POAC initiation beyond 42 days after NAC may lead to worse survival outcomes. Further studies are warranted to validate our findings and to provide additional information on the relationships between NAC, the initiation of POAC, and the survival outcomes of the patients.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Disclosure

The authors have no disclosures.

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