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Original Article

Precision chemotherapy duration in advanced ovarian cancer: neoadjuvant cycle optimization and differential treatment adaptation by cytoreduction outcome

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Abstract: This retrospective study evaluated the impact of neoadjuvant chemotherapy (NACT) cycle number and total chemotherapy (TCT) cycle number on survival and surgical outcomes in patients with advanced epithelial ovarian cancer undergoing interval debulking surgery (IDS). A total of 115 patients with FIGO stage III-IV ovarian cancer treated with NACT followed by IDS were included and categorized by NACT cycle number (2-4 vs. ≥ 5) and TCT cycle number (≤ 9 vs. > 9). The number of NACT cycles showed no significant association with progression-free survival (PFS, 19.0 vs. 23.0 months, HR = 0.780, 95% CI [0.457-1.332], *P* = 0.363), overall survival (OS, 42.0 vs. 74.0 months, HR = 0.572, 95% CI [0.277-1.182], *P* = 0.131), or surgical outcomes, including optimal debulking rate (84.7% vs. 75.0%, *P* = 0.192) and combined surgery rate (33.9% vs. 32.1%, *P* = 0.841). In the suboptimal debulking group (n = 23), patients who received more than 9 TCT cycles had significantly improved OS (40.0 vs. 16.0 months, HR = 0.046, 95% CI [0.006-0.364], *P* = 0.004) and a trend toward better PFS (15.0 vs. 9.0 months, HR = 0.143, 95% CI [0.020-1.030], *P* = 0.054). In the high-grade serous carcinoma (HGSC) subgroup (n = 81), survival outcomes were significantly influenced by cytoreduction status (OS: not reached vs. 26.0 months, P < 0.001), while neither NACT nor TCT cycles showed a significant survival benefit. Overall, the number of NACT cycles did not appear to influence survival or surgical outcomes in patients undergoing NACT followed by IDS. Optimal cytoreduction remained the most important prognostic factor, whereas extended TCT cycles may offer a survival benefit in patients with suboptimal cytoreduction.

Keywords: Ovarian neoplasms, neoadjuvant therapy, cytoreduction surgical procedures, chemotherapy, adjuvant, treatment outcome

Introduction

Ovarian cancer (OC) ranks as the eighth most frequently diagnosed cancer and the fifth leading cause of cancer-related death among women worldwide [1]. Approximately 75% of patients are diagnosed at an advanced stage, requiring both debulking surgery and systemic treatment [2]. In the management of stage III and IV ovarian cancer, primary debulking surgery (PDS) is regarded as the standard of treatment [3]. Recent study has highlighted the significant impact of achieving optimal PDS on patient survival [4, 5]. However, achieving optimal debulking at diagnosis may be challenging due to metastatic distribution, tumor burden, the potential morbidity associated with surgery, and patient comorbidities. Therefore, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is considered as an alternative strategy with a non-inferior survival outcome for patients with advanced ovarian cancer [6-10]. In our clinical practice, NACT is typically administered for three to four cycles before IDS. However, when complete cytoreduction appears unlikely at the planned inter-

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val, additional preoperative cycles may be given, thereby increasing total chemotherapy (TCT) exposure.

At present, there is no consensus on the optimal number of NACT cycles [11-22]. The primary aim of this retrospective cohort study was to evaluate the association between the number of NACT cycles, TCT exposure, and key clinical outcomes including surgical cytoreduction and survival. The secondary aim was to identify other prognostic factors relevant to survival in advanced OC.

Materials and methods

Study design, population, and diagnostic evaluation

This retrospective study analyzed data from Kaohsiung Chang Gung Memorial Hospital (CGMH) patient database (Jan 2008-Dec 2021) for FIGO 2014 stage III-IV epithelial OC treated with NACT followed by IDS. Patients with non-epithelial tumors, primary debulking surgery, incomplete records, or progression during NACT were excluded. The study was approved by the Institutional Review Board of CGMH (IRB No. 202301253B0), and the requirement for informed consent was waived due to the retrospective nature of the study and the use of de-identified clinical data. In our clinical practice, for patients with a clinical suspicion of ovarian cancer, comprehensive diagnostic assessments are arranged, including abdominal, pelvic and chest computed tomography scanning or a chest X ray for evaluation. Additional investigations, such as gastrointestinal evaluations, PET/CT, or MRI, were performed as clinically indicated. Treatment decisions regarding PDS or NACT are guided by the Leuven criteria together with the attending's assessment [23]. Histologic confirmation prior to NACT is achieved through tumor biopsy obtained via diagnostic laparoscopy or laparotomy, or through ascites cytology collected by paracentesis.

NACT and IDS protocol

For patients receiving NACT, three to four cycles of treatment are administered initially, followed by imaging studies and serum CA125 evaluations to assess treatment response. If the assessment suggests a likelihood of achieving optimal debulking, a shared decision-making discussion is held with the patient to determine whether to proceed with IDS. For those not suitable for IDS clinically, chemotherapy is continued, and the possibility of surgery is continuously evaluated after another 3 to 6 cycles. The standard NACT regimen consisted of carboplatin (AUC 5-6) and paclitaxel (175 mg/m^2) administered every 3 weeks, with dose modifications made based on patient tolerance and toxicity profiles. Alternative regimens were used in a small proportion of patients due to toxicity or intolerance. IDS was performed by experienced gynecologic oncologists with the goal of achieving optimal cytoreduction (residual disease < 1 cm). Postoperatively, we followed NCCN guidelines recommendation for a minimum of six total chemotherapy cycles, including at least three postoperative cycles, with the actual number of cycles individualized according to clinical assessment, treatment response, and individual tolerance. In this study, we used the mean TCT for further survival analysis.

Data collection, variable definitions, and statistical endpoints

Data obtained from medical records encompassed various factors such as age at diagnosis, FIGO stage, histological type, number of NACT cycles and regimen, residual disease status post-IDS, combined surgery with other specialist for tumor resection, intraoperative estimated blood loss, adjuvant chemotherapy cycles, adjuvant Bevacizumab usage, total number of chemotherapy cycles, the date of last adjuvant chemotherapy, and the date of expiration or last visit. Combined surgery was defined as multidisciplinary cytoreductive procedures performed in collaboration with colorectal surgeons, urologists, or general surgeons when bowel, bladder, ureteral, or other organ resections were required to achieve optimal debulking. Standard and extended NACT cycles were defined as two to four cycles or five or more cycles, respectively, while the TCT cycles threshold was set at nine or fewer cycles, or more than nine cycles. Optimal debulking was characterized by a residual tumor size of less than 1 cm. Progression-free survival (PFS) was calculated from completion of primary treatment to progression or death, whichever came first, and overall survival (OS) from diagnosis to death or last follow-up.

Table 1. Clinicopathological characteristics of all patient (N = 115)

Age, mean (SD)	58.03 (10.75)
FIGO stage, n (%)	
III	66 (57.4)
IV	49 (42.6)
Histological type, n (%)	
High grade serous	81 (70.4)
Low grade serous	7 (6.1)
Clear cell	7 (6.1)
Endometrioid	7 (6.1)
Mucinous	2 (1.7)
Carcinosarcoma	3 (2.6)
Others*	6 (5.2)
Cannot access	2 (1.7)
Regimen of Neoadjuvant chemotherapy, n (%)	
Carboplatin + Paclitaxel	111 (96.5)
Others	4 (3.5)
Neoadjuvant chemotherapy cycle, n (%)	
2-4	59 (51.3)
≥ 5	56 (48.7)
Mean (SD)	4.92 (2.06)
Residual disease after IDS, n (%)	
Optimal	92 (80.0)
Suboptimal	23 (20.0)
Combined surgery at IDS, n (%)	
Yes	38 (33.0)
No	77 (67.0)
Adjuvant chemotherapy, n (%)	
Yes	110 (95.7)
No	5 (4.3)
Mean† (range, SD)	4.68 (1-22, 2.39)
Bevacizumab add in adjuvant chemotherapy, n (%)	
Yes	32 (29.1)
No	78 (70.9)
Total chemotherapy cycle, n (%)	
≤ 9	66 (57.4)
> 9	49 (42.6)
Mean (range, SD)	9.4 (4-30, 3.06)
Median (IQR)	9 (8-10)

*Others include: Adenocarcinoma 4 (3.5%), mixed type 1 (0.9%), Small cell carcinoma 1 (0.9%), †N = 110.

Statistical analysis

We conducted data analysis using SPSS 25.0 software (IBM corporation). The baseline characteristics were compared using Chi-square test for categorical variables, with Fisher's exact test applied when any expected cell count was less than 5. Independent two-sample t-test for continuous variables. Univariate prognosis factors were compared using the log-rank and χ^2 tests. The Cox proportional hazard regression model was used to determine the independent contributions of the prognostic variables in a multivariate analysis. Survival curves were performed with the Kaplan-Meier method. Differences were considered statistically significant at $P < 0.05$.

Results

Patient characteristics and treatment overview

From a total of 1,082 ovarian cancer patients treated at our hospital between 2008 and 2021, 115 women met the study criteria (stage III = 57.4%, stage IV = 42.6%; mean age 58 years, SD = 10.75), and their characteristics are summarized in **Table 1**. The patient selection process is shown in **Figure 1**.

High-grade serous carcinoma (HGSC) accounted for approximately 70% of all cases. Nearly all patients (96.5%) received carboplatin-paclitaxel NACT, with a mean of 4.92 cycles (SD = 2.06). Among them, 59 patients (51.3%) received 2-4 cycles, and 56 patients (48.7%) received ≥ 5 cycles of NACT, defined as standard and extended NACT prior to IDS, respectively. Optimal cytoreduction was achieved in 92 patients (80%). 38 patients (33%) underwent combined surgery during IDS. Most patients (95.7%) received adjuvant chemotherapy, and 32 patients (29.0%) received bevacizumab in combination. A total of 66 patients (57.4%) completed 9 or fewer cycles of chemotherapy, while 49 patients (42.6%) underwent more than 10 cycles of chemotherapy.

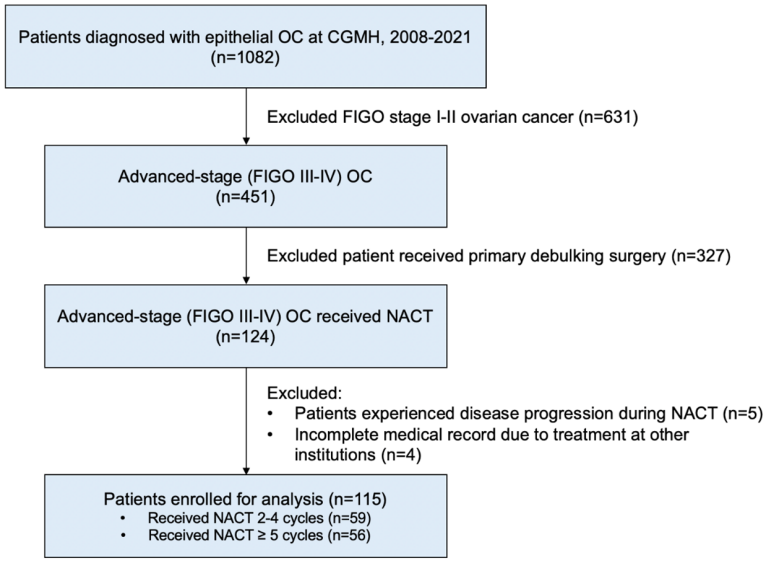

Figure 1. Flow diagram of patient selection for the NACT-IDS cohort.

Comparison between standard and extended NACT groups

Table 2 summarizes the clinicopathological characteristics of patients who received either standard or extended NACT. Overall, the two groups were well-balanced with no significant differences in age (mean 56.8 vs. 59.2 years, $P = 0.109$), FIGO stage distribution (Stage III 62.7% vs. 51.8%, $P = 0.236$), histological type (HGSC: 69.5% vs. 71.4%, $P = 0.820$), and treatment regimens (carboplatin-paclitaxel 94.9% vs. 98.2%, $P = 0.619$). Surgical outcomes showed no significant differences between groups, including optimal debulking rates (84.7% vs. 75.0%, $P = 0.192$) and combined surgery rates (33.9% vs. 32.1%, $P = 0.841$). Post-operative management was similar, with comparable rates of adjuvant chemotherapy (98.3% vs. 92.9%, $P = 0.351$) and bevacizumab use during adjuvant treatment (27.1% vs. 28.6%, $P = 0.714$). Specifically, more patients in the extended NACT group received > 9 total cycles (62.5% vs. 23.7%), which is expected given the predefined grouping criteria.

Prognostic factors for survival outcomes

Univariate and multivariate analyses of prognostic factors for all enrolled patients are presented in **Table 3**. On univariate analysis, only optimal cytoreduction was significantly associated with improved survival outcomes (PFS 25.0 vs. 11.0 months; OS 92.0 vs. 27.0 months; both P < 0.001). Multivariate analysis confirmed optimal debulking as the most significant independent prognostic factor for both PFS (HR = 4.088, 95% CI [2.233-7.483], $P < 0.001$) and OS (HR = 6.726, 95% CI [3.264-13.860], $P < 0.001$). Additionally, bevacizumab use during adjuvant chemotherapy was independently associated with improved PFS (HR = 0.545, 95% CI [0.298-0.998], $P = 0.049$), though not with OS ($P = 0.235$). FIGO stage, histological subtype, number of NACT cycles (2-4 vs. ≥ 5, **Figure 2A**), TCT cycles (≤ 9 vs. > 9), and combined surgery at IDS showed no significant impact on either PFS or OS in both univariate and multivariate analyses.

Prognostic factors for patients with suboptimal debulking surgery

Subgroup analysis of patients with suboptimal cytoreduction (n = 23) revealed different prognostic patterns (**Table 4**). On univariate analysis, extended TCT (> 9 cycles) was associated with a significantly longer PFS (15 vs. 9 months; $P = 0.003$) and a longer OS (40 vs. 14 months; $P = 0.103$). Extended NACT was associated with marginal improvements in PFS (12 vs. 11 months; $P = 0.08$) and OS (33 vs. 17 months; $P = 0.054$). The addition of bevacizumab to adjuvant chemotherapy suggested a potential benefit in OS (33 vs. 23 months; $P = 0.086$).

Multivariate analysis indicated that extended TCT independently improved OS (HR = 0.046; 95% CI [0.006-0.364]; $P = 0.004$) (**Figure 2B**) and showed a trend toward longer PFS (HR = 0.143; 95% CI [0.020-1.030]; $P = 0.054$). By contrast, extending the number of NACT cycles offered no survival advantage (**Figure 2C**). Notably, patients requiring combined surgery at IDS had worse OS (HR = 5.650; 95% CI [1.189-26.849], $P = 0.029$), which may reflect the increased disease complexity and surgical burden in these patients.

Table 2. Clinicopathological characteristics of patient who received 2-4 cycles versus ≥ 5 cycles of neoadjuvant chemotherapy

	NACT 2-4 (N = 59)	NACT ≥ 5 (N = 56)	*p* value
Age, n			0.109
Mean (SD)	56.8 (9.3)	59.2 (12.0)	
Median (range)	58.7 (35-72.8)	60 (19-79.2)	
FIGO stage, n (%)			0.236
III	37 (62.7)	29 (51.8)	
IV	22 (37.3)	27 (48.2)	
Histological subtype, n (%)			0.820
HGSC	41 (69.5)	40 (71.4)	
Others	18 (30.5)	16 (28.6)	
Regimen of Neoadjuvant chemotherapy, n (%)			0.619
Carboplatin + Paclitaxel	56 (94.9)	55 (98.2)	
Others	3 (5.1)	1 (1.8)	
Neoadjuvant chemotherapy cycle, n			
Mean (SD)	3.47 (0.568)	6.45 (1.95)	
Median (range)	4 (2-4)	6 (5-12)	
Residual disease after IDS, n (%)			0.192
Optimal	50 (84.7)	42 (75.0)	
Suboptimal	9 (15.3)	14 (25.0)	
Combined surgery at IDS, n (%)			0.841
Yes	20 (33.9)	18 (32.1)	
No	39 (66.1)	38 (67.9)	
Adjuvant chemotherapy, n (%)			0.351
Yes	58 (98.3)	52 (92.9)	
No	1 (1.7)	3 (5.4)	
Missing	0	1 (1.8)	
Mean (SD)	4.73 (1.6)	4.29 (3.19)	0.102
Bevacizumab add in adjuvant chemotherapy, n (%)			0.714
Yes	16 (27.1)	16 (28.6)	
No	42 (71.2)	36 (64.3)	
Total chemotherapy cycle, n (%)			< 0.001
≤ 9	45 (76.3)	21 (37.5)	
> 9	14 (23.7)	35 (62.5)	
Mean (SD)	8.2 (1.68)	10.66 (3.65)	0.024
Median (IQR)	9 (7-9)	10 (9-11)	< 0.001
Intraoperative estimated blood loss, ml*			
Median (IQR)	235 (138-578)	215 (100-400)	0.296

*The record of blood loss is available for 112 patients, of whom 58 belong to the NACT 2-4 group, while the remaining 54 belong to the NACT ≥ 5 group.

High-grade serous carcinoma subgroup analysis

Given that HGSC comprised the majority of cases in our cohort (70.4%, n = 81), we performed a separate analysis to evaluate prognostic factors specifically in this histological type (Table S1). Consistent with the overall cohort, optimal cytoreduction remained the most critical prognostic factor, significantly influencing both PFS (24.0 vs. 13.0 months, $P < 0.001$) and OS (not reached vs. 26.0 months, $P < 0.001$) in HGSC patients. Neither the number of NACT cycles (**Figure 2D**) nor TCT cycles showed significant impact on survival outcomes. PFS was comparable between stan-

Table 3. Univariate and Multivariate analysis of factors associated PFS and OS in all patients included in the study (N = 115)

	PFS					OS				
	Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis		
	PFS (months)	*p* value	HR	95% CI	*p* value	OS (months)	*p* value	HR	95% CI	*p* value
FIGO stage		0.246	1.275	0.800-2.033	0.307		0.303	1.393	0.750-2.587	0.294
III	24.0					58.0				
IV	19.0					44.0				
Histological subtype		0.360	1.408	0.807-2.455	0.228		0.344	0.641	0.334-1.228	0.180
HGSC	21.0					63.0				
Others	23.0					52.0				
Neoadjuvant chemotherapy cycle		0.300	0.780	0.457-1.332	0.363		0.216	0.572	0.277-1.182	0.131
2-4	19.0					42.0				
≥ 5	23.0					74.0				
Residual disease after IDS		< 0.001	4.088	2.233-7.483	< 0.001		< 0.001	6.726	3.264-13.860	< 0.001
Optimal	25.0					92.0				
Suboptimal	11.0					27.0				
Combined surgery at IDS		0.847	1.093	0.663-1.801	0.728		0.428	1.649	0.845-3.217	0.142
Yes	20.0					44.0				
No	24.0					63.0				
Bevacizumab add in adjuvant chemotherapy		0.702	0.545	0.298-0.998	0.049		0.587	0.589	0.246-1.411	0.235
Yes	24.0					44.0				
No	20.0					63.0				
Total chemotherapy cycle		0.321	0.729	0.411-1.294	0.280		0.929	0.694	0.325-1.483	0.346
≤ 9	20.0					70.0				
> 9	23.0					52.0				

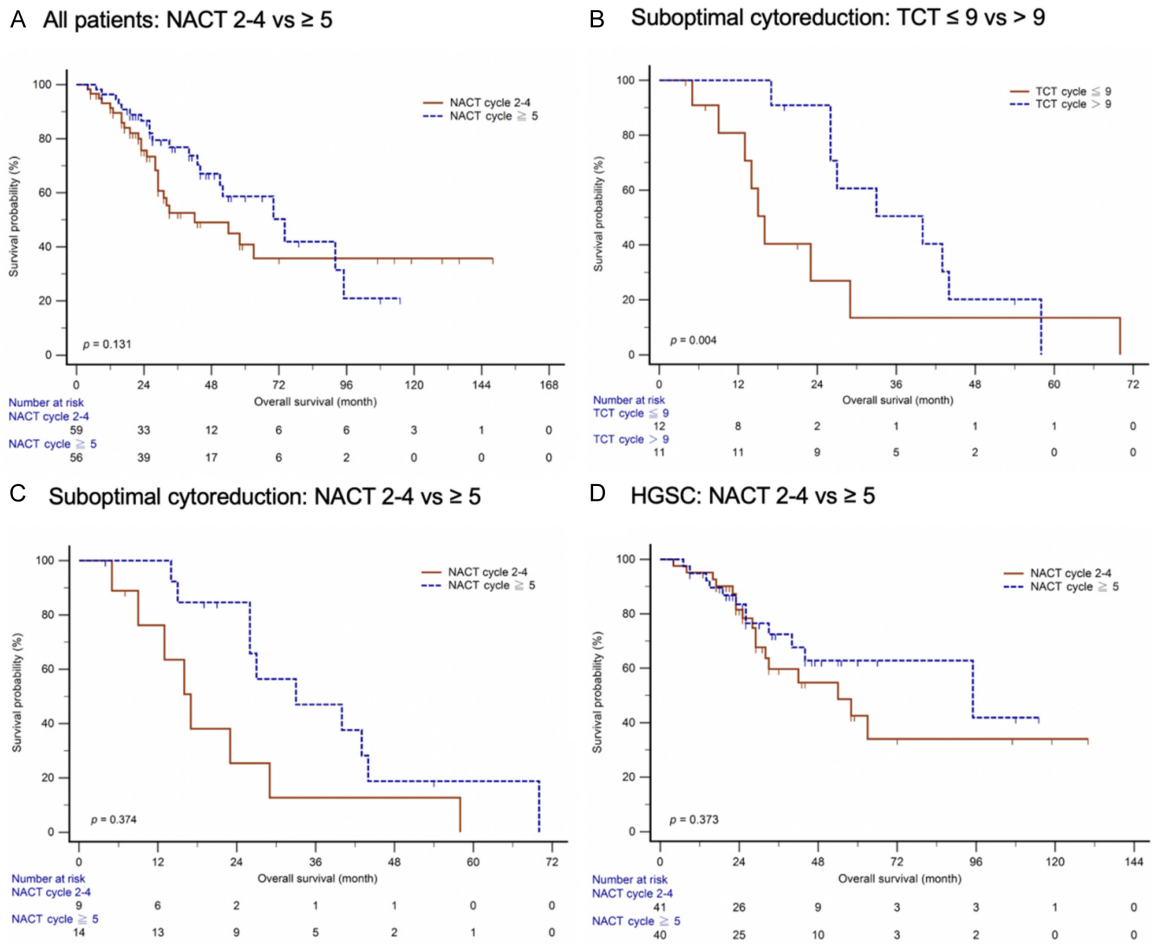

Figure 2. Overall survival stratified by NACT cycles and TCT cycles (Kaplan-Meier curves): (A) entire cohort, NACT 2-4 vs. ≥ 5 cycles; (B) patients with suboptimal IDS cohort, TCT ≤ 9 vs. > 9 cycles; (C) patients with suboptimal IDS, NACT 2-4 vs. ≥ 5 cycles; (D) patients with HGSC, NACT 2-4 vs. ≥ 5 cycles.

dard and extended NACT groups (21.0 vs. 21.0 months, P = 0.631), and TCT duration did not significantly affect PFS (19.0 vs. 24.0 months, P = 0.140) or OS (95.0 vs. 58.0 months, P = 0.684).

FIGO stage showed a trend toward significance for OS (Stage III: not reached vs. Stage IV: 44.0 months, P = 0.068), while bevacizumab use demonstrated a marginal trend toward improved PFS (not reached vs. 20.0 months, P = 0.059).

Discussion

For patients with advanced epithelial OC unsuitable for PDS, NACT is an alternative treatment; however, the optimal cycle number remains undefined due to the lack of standardized protocols.

Current recommendations and practice patterns

The NCCN guidelines (2025, version 3) recommend 3-4 cycles of NACT as standard treatment, with potential extension to 4-6 cycles based on clinical judgment. In randomized controlled trials (RCTs) focusing on the comparison of survival outcomes between NACT-IDS and PDS, the number of administered NACT cycles typically ranges from 3 to 4, followed by adjuvant chemotherapy totaling 6 to 8 cycles [6-9]. These variations in treatment duration reflect the flexibility of clinical practice and highlight the ongoing uncertainty regarding the optimal number of preoperative chemotherapy cycles.

In this study, the distribution of standard versus extended NACT was balanced (51.3% vs. 48.7%). Baseline characteristics including age,

Table 4. Univariate and Multivariate analysis of factors associated PFS and OS in patient underwent suboptimal debulking surgery (N = 23)

	PFS					OS				
	Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis		
	PFS (months)	*p* value	HR	95% CI	*p* value	OS (months)	*p* value	HR	95% CI	*p* value
FIGO stage		0.715	1.376	0.500-3.789	0.536		0.519	1.406	0.376-5.259	0.612
III	12.0					26.0				
IV	11.0					33.0				
Histological subtype		0.387	0.757	0.224-2.556	0.654		0.979	0.351	0.087-1.417	0.142
HGSC	13.0					26.0				
Others	10.0					27.0				
Neoadjuvant chemotherapy cycle		0.080	1.506	0.264-8.586	0.645		0.054	2.214	0.384-12.751	0.374
2-4	11.0					17.0				
≥ 5	12.0					33.0				
Combined surgery at IDS		0.791	1.712	0.500-5.865	0.392		0.390	5.650	1.189-26.849	0.029
Yes	8.0					26.0				
No	11.0					27.0				
Bevacizumab add in adjuvant chemotherapy		0.212	0.651	0.158-2.678	0.552		0.086	0.190	0.026-1.380	0.101
Yes	14.0					33.0				
No	11.0					23.0				
Total chemotherapy cycle		0.003	0.143	0.020-1.030	0.054		0.103	0.046	0.006-0.364	0.004
≤ 9	9.0					16.0				
> 9	15.0					40.0				

FIGO stage, histology, and chemotherapy regimen were comparable, suggesting that the use of extended NACT likely reflected individual tumor response or clinical judgment, such as suboptimal tumor shrinkage or elevated perioperative risk. A total of 95.7% of patients received adjuvant chemotherapy following IDS. The higher total chemotherapy exposure in the extended NACT group reflects the grouping definition, as patients receiving ≥ 5 preoperative cycles accumulated more total cycles.

Conflicting evidence on NACT duration and survival outcomes

Current studies focused on the effect of different NACT cycles on survival outcomes have yielded inconsistent results. Some studies reported no significant difference in survival between standard and extended NACT cycles [11-16]. For instance, a French multicenter study reported both PFS (23.2 months vs. 22.5 months, HR 1.21, 95% CI [0.92-1.59], $P = 0.31$) and OS (64.0 months vs. 49.2 months, HR 1.81, 95% CI [0.89-3.71], $P = 0.09$) did not differ significantly between patients receiving < 4 cycles and ≥ 5 cycles [11]. Similar findings were reported in a large-scale study by Yao et al. involving 572 patients showed comparable PFS (24.0 months vs. 27.0 months, HR = 0.91, $P = 0.55$) and OS (41 vs. 43 month, HR = 1.11, $P = 0.51$) regardless of NACT duration [12].

In contrast, other reports suggested that extended NACT cycles may lead to inferior survival outcomes. Bristow et al. conducted a large meta-analysis in 2006 involving 835 patients treated with NACT-IDS, demonstrating that each incremental chemotherapy cycle was associated with a 4.1-month reduction in median survival time (95% CI [8.1 to -0.1], $P = 0.046$) [17]. A retrospective multicenter study by Thomas et al., which included 928 cases, reported worse PFS (17.6 vs. 11.5 months, HR = 1.42; 95% CI [1.22-1.67]; $P < 0.0001$) and OS (51.2 vs. 44.3 months, HR = 1.29; 95% CI [1.06-1.56]; $P = 0.0095$) in patients who received more than four cycles of NACT [18].

The inconsistent findings reported across previous studies may partly reflect differences in patient selection. In many retrospective cohorts, the decision to extend NACT is influenced by anticipated resectability, chemotherapy tolerance, and overall clinical condition. As a result, prolonged NACT may be more frequently administered to patients with more advanced disease, making it difficult to separate the effect of treatment duration from underlying disease severity. Our analysis is subject to similar limitations.

Impact of extended NACT and bevacizumab on survival outcomes

In our single-center cohort, nearly half of the patients received more than four NACT cycles. Under consistent treatment protocols and standardized surgical procedures, we found that extended NACT was not independently associated with either improved or worsened PFS or OS in multivariate analysis. In addition, the use of bevacizumab in adjuvant chemotherapy was significantly associated with prolonged PFS, with a median extension of approximately four months, this finding aligns with results from the GOG-0218 trial, in which bevacizumab administered during and after chemotherapy improved PFS without affecting OS [24]. Notably, GOG-0218 enrolled patients who underwent primary debulking surgery, whereas our data indicate that the PFS advantage of bevacizumab also applies to NACT-IDS cases, warranting prospective evaluation.

Extended NACT and surgical feasibility: evidence and limitations

A 2021 Cochrane review reported that, compared with PDS, NACT followed by IDS reduced stoma formation (RR 0.43, 95% CI 0.26-0.72), bowel resection (RR 0.49, 95% CI 0.26-0.92), and postoperative mortality (RR 0.18, 95% CI 0.06-0.54) [10]. However, the review did not stratify outcomes according to the number of NACT cycles. In this context, a randomized controlled trial of 30 patients published in 2020, Kumari et al. showed that administering six-as opposed to three-cycles of NACT significantly increased the rate of optimal cytoreduction and reduced peri-operative morbidity [20]. By contrast, a retrospective multicenter cohort of 501 patients, Lecointre et al. reported no significant difference in surgical morbidity (15.8% vs. 10.7%, $P = 0.12$) or postoperative complications (23.6% vs. 19.8%, $P = 0.34$) between standard and extended NACT regimens, with comparable complete-cytoreduction rates in both groups (P = 0.28) [11]. While optimal cytoreduction is an established prognostic determi-

nant in PDS, its survival impact after NACT remains uncertain. In a retrospective cohort of 572 patients undergoing NACT followed by interval debulking surgery, Yao et al. reported that patients who achieved complete cytoreduction had significantly longer overall survival than those with any macroscopic residual disease, independent of the number of NACT cycles administered [12]. In contrast, a 2020 retrospective study of 199 patients by Liu et al. showed that extended NACT was associated with significantly shorter PFS (8.2 vs. 14.6 months; HR 2.20, 95% CI 1.45-3.33; P < 0.001) and OS (28.9 months vs. not reached; HR 2.78, 95% CI 1.37-5.63; P = 0.016), despite comparable complete-resection rates [21]. Similarly, Colombo et al. reviewed 367 cases and observed no survival advantage with extended NACT, even though the rate of complete cytoreduction was numerically higher than with standard IDS (64.9% vs. 61.5%; P = 0.712) [22]. Overall, the available evidence fails to demonstrate a consistent surgical or survival advantage from extending NACT beyond the conventional three to four cycles.

In our cohort, extending the number of NACT cycles did not significantly increase the rate of optimal debulking. Specifically, optimal cytoreduction was achieved in 84.7% of patients in the standard NACT group and 75.0% in the extended group (P = 0.192), indicating no statistical improvement despite additional cycles. These results indicate that factors such as baseline tumor burden or response to initial chemotherapy may have a greater impact on surgical feasibility than the number of NACT cycles alone. Multivariate analysis identified optimal cytoreduction as an independent predictor of both PFS and OS, regardless of NACT duration. In addition, extended NACT was not associated with reduced surgical complexity, as reflected by similar rates of combined procedures and intraoperative blood loss between groups. Extending NACT beyond four cycles was therefore not associated with improved surgical or survival outcomes.

Survival impact of NACT and TCT in suboptimal IDS

In our cohort, patients who achieved optimal cytoreduction at IDS had better survival outcomes than those with residual disease. However, optimal cytoreduction was not always feasible, particularly in patients with extensive disease burden or limited response to initial chemotherapy. To further explore the relationship between treatment response and surgical outcomes, patients were stratified according to IDS status.

In optimal surgery group, neither the number of NACT cycles nor TCT cycles significantly influenced PFS or OS. By contrast, in the suboptimal surgery group, the number of NACT cycles remained unrelated to survival outcomes, while receiving more than nine total chemotherapy cycles was associated with longer overall survival and a favorable trend in PFS. These findings should be interpreted cautiously given the small sample size and exploratory nature of this subgroup.

The number of TCT cycles is determinated by both NACT and post-IDS chemotherapy cycles, the latter of which vary widely in practice. The ideal number of chemotherapy cycles post-IDS, ensuring both treatment efficacy and safety, has yet to be determined. In a retrospective study by Chung et al., receiving fewer than six TCT cycles was associated with worse PFS and OS. Among patients who completed at least six cycles, survival did not differ by the number of NACT cycles administered (1 to 3 vs. more than 4) [25]. In contrast, Altman et al. reported no association between the total number of chemotherapy cycles (categorized as 0 to 6 cycles and ≥ 7 cycles) and overall survival [26]. In our cohort, the observed survival advantage associated with > 9 cycles in patients with suboptimal cytoreduction may be attributable to additional postoperative chemotherapy in the presence of residual disease. Notably, patients who underwent suboptimal debulking without combined surgical procedures had better OS, which may reflect a lower baseline disease burden or less aggressive tumor behavior. Conversely, those requiring combined procedures likely had more extensive dissemination and may have experienced delays in initiating adjuvant therapy due to postoperative recovery.

Although extended NACT may still be considered when surgical feasibility remains uncertain, routine prolongation beyond four cycles does not appear to offer additional benefit. Among patients with residual disease following IDS, the survival advantage associated with higher TCT exposure may be attributable to

additional postoperative chemotherapy rather than prolonged preoperative NACT. In this subgroup, proceeding with IDS as scheduled and ensuring adequate postoperative treatment may offer greater benefit than postponing surgery by extending NACT.

Impact of NACT and TCT cycle number on survival in patient with HGSC

Serous carcinoma represents the predominant histologic subtype of OC, accounting for 42.97% of newly diagnosed cases worldwide [27]. In our cohort, serous tumors comprised 76.5% of patients, of which 70.4% were HGSC. Despite its prevalence, the optimal number of NACT cycles for this subgroup has not been clearly established. Given the known heterogeneity in chemosensitivity across ovarian cancer histologies [28], we performed a subgroup analysis focusing solely on HGSC patients to minimize histology-related confounding and better evaluate the prognostic value of NACT and TCT exposure.

Within this subgroup, survival outcomes were primarily associated with the extent of cytoreduction achieved at IDS, whereas neither the number of NACT cycles nor TCT exposure showed a measurable impact on PFS or OS. Extending chemotherapy beyond the standard number of cycles did not improve survival outcome. Future studies incorporating molecular or genomic stratification, such as BRCA mutation status or homologous recombination deficiency, may help identify patients who could benefit from individualized treatment intensity or chemotherapy duration.

Limitation

The strengths of our retrospective study include the concurrent evaluation of both NACT cycle number and TCT cycle number in relation to survival and surgical outcomes. In addition, subgroup analyses were performed in patients with suboptimal IDS and those with HGSC, the most common histologic subtype.

This study has several limitations. First, the modest sample size may limit statistical power and generalizability. Second, the absence of BRCA mutation data limited assessment of its prognostic and predictive relevance. Third, the retrospective design may be subject to selection bias and limits causal inference, and objective baseline measures reflecting tumor burden or early chemotherapy response were not consistently available for analysis.

Prospective validation is required to better define the association between chemotherapy exposure and survival outcomes. Ongoing trials such as the CHRONO trial (NCT03579394) and the ROCOCO trial (NCT03693248) are expected to provide further insights into the optimal number and timing of NACT cycles in advanced ovarian cancer. As of this writing, neither trial has yet reported final results.

Conclusion

In this retrospective cohort study of patients with advanced OC treated with NACT followed by IDS, the number of NACT cycles was not associated with survival or surgical outcomes. Among those who underwent suboptimal debulking, patients receiving more than nine total chemotherapy cycles showed longer survival; however, this observation was based on a small subgroup and warrants cautious interpretation. Across the entire cohort and within the HGSC subgroup, optimal cytoreduction remained the most important predictor of both PFS and OS.

Disclosure of conflict of interest

None.

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Table S1. Univariate analysis of factors associated PFS and OS in patient with High grade serous carcinoma (N = 81)

	PFS		OS	
	(month)	*p* value	(month)	*p* value
FIGO stage		0.321		0.068
III	24.0		NR*	
IV	19.0		44.0	
Neoadjuvant chemotherapy cycle		0.631		0.373
2-4	21.0		54.0	
≥ 5	21.0		95.0	
Residual disease after IDS		< 0.001		< 0.001
Optimal	24.0		NR*	
Suboptimal	13.0		26.0	
Combined surgery at IDS		0.802		0.923
No	20.0		63.0	
Yes	24.0		44.0	
Bevacizumab add in adjuvant chemotherapy		0.059		0.388
Yes	NR*		44.0	
No	20.0		58.0	
Total chemotherapy cycle		0.140		0.684
≤ 9	19.0		95.0	
> 9	24.0		58.0	

*NR = Not-reached.