RESEARCH ARTICLE

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Prognostic Factors for Advanced Epithelial Ovarian Cancer Following Primary Cytoreductive Surgery or Neoadjuvant Chemotherapy

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Abstract

Aim: To examine the association between clinicopathological factors and survival in advanced epithelial ovarian, tubal, and primary peritoneal cancers patients who had primary cytoreductive surgery (CRS) and those that received neoadjuvant chemotherapy (NAC). **Methods:** Women who had CRS or NAC between 2008-2017 were included. Association between clinical characteristics, pretreatment imaging, serum markers, surgical and pathological factors, and disease recurrence/progression/death was examined in multivariable analysis. **Results:** Two hundred and three women were recruited in this study (CRS 128 women and NAC 75 women). Median overall survival was 33.7 months for the CRS group and 27.9 months for the NAC group (p=0.04). Median progression-free survival was 14.9 months in the CRS group and 12.1 months in the NAC group (p=0.04). For the CRS group, factors independently associated with increased risk of death included primary peritoneal carcinoma (adjusted hazard ratio [aHR] 6.94), stable disease/progression at treatment completion (aHR 5.97), and initial tumor size of more than 12 cm (aHR 1.87). For the NAC group, stable disease/progression after complete treatment (aHR 6.45) and pre-treatment platelet to lymphocyte ratio of more than 310 (aHR 2.20) were significantly associated with an increased risk of death. **Conclusions:** NAC appeared to be a good alternative treatment for stage III/IV tubo-ovarian carcinoma. The worse survival outcome associated with primary peritoneal carcinoma and large initial tumor size in the patients who received CRS suggested that NAC could be an attractive option for those with these characteristics.

Keywords: Fallopian tube neoplasm- ovarian neoplasm- peritoneal neoplasm- prognostic factors

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Introduction

Ovarian cancer is the important cause of death from cancer globally. Typically, women with ovarian cancer present with advanced disease (stages III and IV). Surgery in combination with adjuvant chemotherapy is the foundation of the treatment of ovarian cancer. The aims of surgery include obtaining tissue for histological diagnosis and debulking (cytoreducing) tumors (Berek et al., 2021). Some early studies have shown that debulking cancer to less than one cm maximum residuum (optimal debulking), especially to no visible residual disease, is significantly associated with improved survival (Winter et al., 2007; Winter et al., 2008; Bookman et al., 2009; du Bois et al., 2009; Berek et al., 2021). However, some studies have suggested that the positive impact of cytoreduction on survival might depend on the stage and initial tumor volume (Hoskins et al., 1992; Crawford et al., 2005). It could not be concluded that the better survival outcome in patients with optimal cytoreduction results from the surgery or biologically more favorable disease (represented by lower stage and/or small tumor volume).

It should also be noted that a significant proportion of patients with advanced-stage epithelial ovarian cancer that undergo primary debulking surgery would have "suboptimal" cytoreduction with significant operative morbidity. These patients would have been suggested for neoadjuvant chemotherapy followed by debulking surgery. Neoadjuvant chemotherapy potentially leads to a higher chance of optimal cytoreduction and a decreased operative morbidity (Nishio and Ushijima, 2020). Naturally, the prognostic factors and survival outcomes for this group of advanced ovarian cancer patients would differ from those receiving primary cytoreductive surgery.

We conducted this study to examine the association between the clinical, surgical, and pathological factors and survival outcomes in patients with advanced-stage epithelial ovarian, fallopian tube, and primary peritoneal cancer who had primary cytoreductive surgery (CRS) and those that received neoadjuvant chemotherapy (NAC).

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Materials and Methods

In this retrospective cohort study, all women diagnosed with advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III/IV) epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer who had CRS or NAC at our institution between 2008-2017 were included. Exclusion criteria were non-epithelial ovarian cancer, borderline ovarian tumor, ovarian metastasis, and no recorded residual tumor status.

After approval by the Faculty of Medicine Research Ethics Committee (approval number OBG-2561-05735), the data of all eligible patients were reviewed. Clinical data included demographic characteristics, medical comorbidities, and findings on physical examination. Pretreatment imaging comprised pelvic ultrasonography or abdominal computerized tomography (CT) scan. Laboratory investigation consisted of serum inflammatory markers, i.e., neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), albumin to globulin ratio (AGR), and tumor marker (CA125). Surgical data included operative findings, operative procedures, and surgical outcomes. Pathological data involved histological type, grade, metastatic organs, presence of malignant ascites, and FIGO stage.

The primary outcome was an association between clinical, pretreatment imaging, serum inflammatory markers, CA125, surgical, and pathological factors and overall survival (OS) in patients with advanced (stage III and IV) ovarian cancer. The secondary outcome was an association between the above-mentioned potential predictors and progression-free survival (PFS). OS was defined by the duration from the first treatment date to either the date of death (for women who had died) or the last day of follow-up (for those alive). PFS was defined by the duration from the first treatment date to either the date of disease recurrence/progression (for patients with recurrent disease) or the last day of follow-up (for those without recurrence).

Statistical analysis was performed using Stata® program version 15 (StataCorp LP, College Station, Texas, USA). Categorical characteristics were compared between different primary treatment groups using Fisher's exact tests, and continuous variables were compared using the Mann-Whitney U test. The cut-off value of age, body mass index (BMI), CA125, AGR, NLR, PLR, tumor size, and duration between NAC and surgery were based on the ROC curve by the method proposed by Liu.(Liu, 2012) The association between the clinicopathological factors of interest and recurrence/progression/death was examined in univariable cox regression analysis. Factors with a P-value of < 0.25 and reliance on the proportional hazards (PH) assumption from the univariable analysis were subsequently included in a multivariable analysis that employed the Cox proportional hazard model. Survival curves were generated using the Kaplan-Meier method. The log-rank test compared the median OS / PFS in the CRS and NAC groups. The P-value of < 0.05 was considered statistically significant.

Results

After excluding three patients with secondary ovarian metastasis, and two with non-epithelial ovarian cancer, two hundred and three eligible women were recruited for this study. One hundred twenty-eight women received CRS, whereas 75 received NAC followed by interval debulking surgery (IDS).

General characteristics, including age and BMI, were comparable between the groups. Regarding the site of origin, a significantly higher prevalence of primary peritoneal cancer was observed in women that received NAC. For histology, high-grade serous carcinoma was more prevalent in the NAC group, while clear cell carcinoma was more common in the CRS group. A higher proportion of women in the NAC group had stage IV disease (33.3% vs. 19.6%). There was no difference in the distribution of tumor grade between the groups.

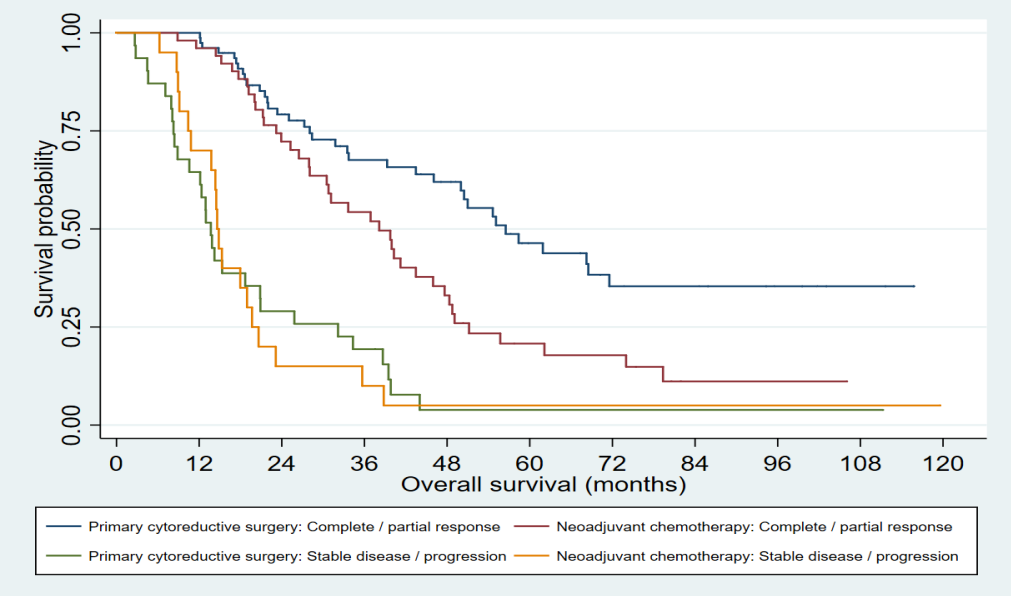

Figure 1. Kaplan-Meier Curve of Overall Survival According to Primary Treatment Group with Different Responses after Complete Treatment

Table 1. General Characteristics of Advanced Epithelial Ovarian Cancer Patients Classified by Primary Treatment

Characteristics	Number (%) or median (interquartile range)			P-value
	Overall (n=203)	CRS (n=128)	NAC (n=75)	
Age (year)	55 (48.0, 62.0)	55 (48.0, 61.0)	56 (48.0, 63.0)	0.44
BMI (kg/m^2) (n=202)	22.6 (20.3, 25.1)	22.7 (20.1, 24.8)	22.4 (20.7, 25.8)	0.49
ASA classification				0.69
1 & 2	179 (88.2)	112 (87.5)	67 (89.3)	
3	24 (11.8)	16 (12.5)	8 (10.7)	
Primary tumor site				<0.001
Ovary	149 (73.4)	102 (79.7)	47 (62.7)	
Fallopian tube	29 (14.3)	22 (17.2)	7 (9.3)	
Primary peritoneal cancer	25 (12.3)	4 (3.1)	21 (28.0)	
Cell type				<0.001
High grade serous	117 (57.6)	67 (52.3)	50 (66.7)	
Low grade serous	8 (3.9)	4 (3.1)	4 (5.3)	
Mucinous	7 (3.4)	7 (5.5)	0 (0.0)	
Endometrioid	14 (6.9)	6 (4.7)	8 (10.7)	
Clear cell	31 (15.3)	28 (21.9)	3 (4.0)	
Mixed	19 (9.4)	14 (10.9)	5 (6.7)	
Others	7 (3.4)	2 (1.6)	5 (6.7)	
Grade				0.85
1 & 2	21 (10.3)	14 (10.9)	7 (9.3)	
3	173 (85.2)	109 (85.2)	64 (85.3)	
Mixed / unknown	9 (4.5)	5 (3.9)	4 (5.4)	
Stage				0.01
IIIA	10 (4.9)	9 (7.0)	1 (1.3)	
IIIB	21 (10.3)	18 (14.1)	3 (4.0)	
IIIC	122 (60.1)	76 (59.4)	46 (61.3)	
IVA	23 (11.3)	13 (10.2)	10 (13.3)	
IVB	27 (13.3)	12 (9.4)	15 (20.0)	
CA-125 level (U/mL) (n=203)	750.0 (239.5, 2086.0)	534.9 (184.3, 1573.0)	1017.0 (450.8, 3050.0)	<0.001
Pretreatment NLR (n=201)	3.8 (2.7, 5.4)	3.7 (2.7, 5.7)	3.9 (2.6, 5.1)	0.75
Pretreatment PLR (n=201)	248.5 (170.9, 350.8)	215.8 (166.2, 329.9)	268.9 (197.1, 418.5)	0.01
Pretreatment albumin (n=194)	3.5 (3.0, 3.9)	3.6 (3.1, 3.9)	3.3 (2.9, 3.8)	0.02
Pre-treatment AGR (n=193)	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)	0.8 (0.7, 1.0)	0.04
Surgical status				<0.001
No residual tumor	45 (22.2)	27 (21.1)	18 (24.0)	
Optimal surgery ≤ 1 cm	54 (26.6)	23 (18.0)	31 (41.3)	
Suboptimal surgery > 1 cm	104 (51.2)	78 (60.9)	26 (34.7)	
Response after complete treatment				0.92
Complete response	70 (38.9)	42 (38.5)	28 (39.4)	
Partial response	58 (32.2)	36 (33.0)	23 (32.4)	
Stable of disease	5 (2.8)	4 (3.7)	1 (1.4)	
Progression	47 (26.1)	27 (24.8)	19 (26.8)	
Overall survival (month)	30.8 (23.9, 38.8)	33.7 (25.0, 46.1)	27.9 (20.6, 36.9)	0.04
Progression free survival (month)	12.2 (11.1, 14.8)	14.9 (9.2, 19.4)	12.1 (10.8, 13.8)	0.04

CRS, cytoreductive surgery; NAC, neoadjuvant chemotherapy; BMI, body mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; AGR, albumin to globulin ratio; Note: Fisher's exact test was used for categorical variables, and Mann–Whitney U test was used for continuous variables. Only overall survival and progression-free survival were assessed using Log-rank test.

Table 2. Association between Clinicopathological Factors and Death among Patients that Received Primary Cytoreductive Surgery

Characteristics	Overall survival			
	Univariable analysis		Multivariable analysis (n=109)	
	HR (95%CI)	P-value	aHR (95%CI)	P-value
Age		0.6		
≤ 57	1 (Ref)			
> 57	1.13 (0.72 to 1.76)			
BMI (kg/m^2)		0.6		
≤ 20	1 (Ref)			
> 20	1.13 (0.72 to 1.75)			
ASA classification		0.81		
1 and 2	1 (Ref)			
3	0.92 (0.46 to 1.85)			
Cell type		0.02*		
EM G1-G2	1 (Ref)			
HGSC and HGEM	2.75 (0.38 to 20.04)			
Mucinous	4.72 (0.55 to 40.42)			
Clear cell	4.74 (0.64 to 35.18)			
Others	1.55 (0.20 to 12.23)			
Grade		0.06		
1 and 2	1 (Ref)			
3	3.23 (1.17 to 8.87)			
Mixed / unknown	1.93 (0.43 to 8.63)			
Primary tumor site		0.12		<0.001*
Ovary	1 (Ref)		1 (Ref)	
Fallopian tube	0.61 (0.30 to 1.22)		0.88 (0.38 to 2.03)	
Primary peritoneal cancer	2.06 (0.75 to 5.69)		6.94 (2.23 to 21.61)	
Stage		0.4		
III	1 (Ref)			
IV	0.78 (0.43 to 1.41)			
CA125 level (U/mL)				
≤ 446	1 (Ref)	0.91		
> 446	1.03 (0.64 to 1.66)			
Pretreatment AGR		0.41		
≤ 0.8	1 (Ref)			
> 0.8	0.83 (0.52 to 1.30)			
Pretreatment NLR		0.15		
≤ 3.3	1 (Ref)			
> 3.3	1.41 (0.89 to 2.24)			
Pretreatment PLR		0.05*		
≤ 186	1 (Ref)			
> 186	1.58 (0.99 to 2.51)			
Ascites		0.66		
Absence	1 (Ref)			
Presence	1.13 (0.67 to 1.91)			
Pretreatment tumor size (cm)		0.16		0.02*
≤ 12	1 (Ref)		1 (Ref)	
> 12	1.37 (0.88 to 2.14)		1.87 (1.09 to 3.22)	

Table 2. Continued

Characteristics	Overall survival			
	Univariable analysis		Multivariable analysis (n=109)	
	HR (95%CI)	P-value	aHR (95%CI)	P-value
Complete surgical staging		0.17		
No	1 (Ref)			
Yes	0.6 (0.29 to 1.24)			
Surgical status				
No residual tumor	1 (Ref)	0.4		
Presence of residual tumor	1.27 (0.73 to 2.20)			
Number of adjuvant chemo-cycle				
≤ 6	1 (Ref)	<0.001*		
> 6	2.55 (1.53 to 4.26)			
Response after complete treatment		<0.001*		<0.001*
Complete / Partial response	1 (Ref)		1 (Ref)	
Stable / Progression	5.17 (3.10 to 8.63)		5.97 (3.48 to 10.27)	

HR, hazard ratio; aHR, adjusted hazard ratio; BMI, body mass index; EM, endometrioid adenocarcinoma; HGSC, high-grade serous adenocarcinoma; HGEM, high-grade endometrioid adenocarcinoma; AGR, albumin to globulin ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; Note: aHR was adjusted for cell type, grade, pretreatment NLR, pretreatment PLR, complete surgical staging, and number of adjuvant chemo-cycle. *, Statistically significant (P < 0.05)

Pre-treatment CA-125 level was significantly higher in the NAC group. Serum systemic inflammatory markers, except for NLR, differed significantly between the groups. A lower proportion of patients in the CRS group achieved optimal cytoreduction (no gross residual tumor or gross residual tumor of < 1 cm) compared to those in the NAC group (39.1% vs. 65.3%) (Table 1).

For the entire cohort, the median PFS was 12.2 months, 14.9 months in the CRS group, and 12.1 months in the NAC group (P = 0.04). Median OS was 30.8 months for the entire cohort, 33.7 months for the CRS group, and 27.9 months for the NAC group (P = 0.04).

Table 2 demonstrates an association between clinical, surgical, and pathological factors and death in the CRS group. In multivariable analysis, primary peritoneal carcinoma (aHR 6.94, 95% confidence interval [CI] 2.23-21.61), stable disease/progression at treatment completion (aHR 5.97, 95% CI 3.48-10.27), and initial tumor size of more than 12 cm (aHR 1.87, 95% CI 1.09-3.22) were independent predictors of poor OS. With regards to PFS, factors independently associated with increased risk of disease recurrence/progression were clear cell carcinoma (adjusted hazard ratio [aHR] 7.64, 95% CI 1.01-57.78), the number of adjuvant chemotherapy of more than six cycles (aHR 2.44, 95% CI 1.47-4.05), and presence of gross residual tumor (aHR 2.05, 95% CI 1.12-3.75).

Table 3 illustrates the association between clinical, surgical, and pathological factors and death in the NAC group. Factors independently associated with increased risk of death were stable disease/progression after complete treatment (aHR 6.45, 95% CI 3.36-12.40) and pre-treatment PLR level of more than 310 (aHR 2.20, 95% CI 1.28-3.78). The multivariable analysis identified no significant association between the factors of interest and recurrence/progression.

Discussion

In this non-randomized study, a higher prevalence of primary peritoneal cancer, high-grade serous carcinoma, stage IV disease, and a higher level of pre-treatment CA-125 were observed in the NAC group. This information reflected the more extensive nature of the disease in the NAC group, which was also the reason for patient allocation to the NAC group in the first place. Interestingly, a significantly higher rate of optimal cytoreduction was achieved in the patients who received NAC compared to those with CRS (approximately 25% difference). However, this higher achievement in cytoreduction in the NAC group did not result in consistent survival outcomes. Significantly more favorable PFS and OS were observed in the CRS group (three months longer median PFS and six months longer median OS). Disease status following treatment completion was consistently associated with PFS and OS both in patients with CRS and those with NAC.

In a randomized controlled study conducted by the European Organization for Research and Treatment of Cancer-Gynaecological Cancer Group (EORTC-GCG) and the National Cancer Institute of Canada (NCIC) Clinical Trials Group (Vergote et al., 2010), six hundred and seventy patients with stage IIIC or IV epithelial ovarian carcinoma, fallopian tube carcinoma, and primary peritoneal carcinoma were randomly assigned to receive either CRS or NAC. The proportion of patients with the residual tumor of one cm or less in diameter was 41.6% after primary debulking in the CRS group and 80.6% following interval debulking in the NAC group. Postoperative morbidity and mortality (death < 28 days after surgery) tended to be higher in the CRS group following primary debulking than in the NAC group

Table 3. Association between Clinicopathological Factors and Death among Patients that Received Neoadjuvant Chemotherapy Followed byInterval Debulking Surgery

Characteristics	Overall survival			
	Univariable analysis		Multivariable analysis (n=71)	
	HR (95%CI)	P-value	aHR (95%CI)	P-value
Age (year)		0.42		
≤ 60	1 (Ref)			
> 60	0.80 (0.47 to 1.37)			
BMI (kg/m^2)		0.72		
≤ 22	1 (Ref)			
> 22	1.10 (0.66 to 1.82)			
ASA classification		0.84		
1 & 2	1 (Ref)			
3	0.92 (0.39 to 2.14)			
Cell type		0.46		
EM G1-G2	1 (Ref)			
HGSC and HGEM	2.99 (0.40 to 22.24)			
Clear cell	4.93 (0.50 to 48.99)			
Others	2.25 (0.29 to 17.42)			
Grade		0.6		
1 & 2	1 (Ref)			
3	1.66 (0.58 to 4.74)			
Mixed / unknown	1.32 (0.33 to 5.33))			
Primary tumor site		0.62		
Ovary	1 (Ref)			
Fallopian tube	0.66 (0.23 to 1.84)			
Primary peritoneal cancer	0.82 (0.46 to 1.46)			
Stage		0.91		
III	1 (Ref)			
IV	0.97 (0.57 to 1.65)			
Ascites on pre-treatment CT		0.62		
No and minimal	1 (Ref)			
Moderate to massive	1.18 (0.62 to 2.24)			
CA125 level (U/mL)				
≤ 1000	1 (Ref)	0.74		
> 1000	1.09 (0.66 to 1.80)			
Pretreatment AGR		0.46		
≤ 0.8	1 (Ref)			
> 0.8	0.82 (0.48 to 1.39)			
Pretreatment NLR		0.06		
≤ 3.8	1 (Ref)			
> 3.8	1.65 (0.98 to 2.77)			
Pretreatment PLR		0.01*		<0.001*
≤ 310	1 (Ref)		1 (Ref)	
> 310	1.95 (1.15 to 3.28)		2.20 (1.28 to 3.78)	
Number of NAC cycle		0.21		
≤ 4	1 (Ref)			
> 4	1.55 (0.78 to 3.08)			

Table 3. Continued

Characteristics	Overall survival			
	Univariable analysis		Multivariable analysis (n=71)	
	HR (95%CI)	P-value	aHR (95%CI)	P-value
Interval between complete NAC and surgery (weeks)		0.72		
≤ 4	1 (Ref)			
> 4	0.84 (0.34 to 2.12)			
Surgical status		0.03*		
No residual tumor	1 (Ref)			
Presence of residual tumor	2.04 (1.09 to 3.82)			
Interval between surgery and postoperative chemotherapy (week)		0.81		
≤ 2	1 (Ref)			
> 2	0.93 (0.54 to 1.61)			
Number of postoperative chemotherapy cycles		0.11		
≤ 3	1 (Ref)			
> 3	1.53 (0.91 to 2.59)			
Response after complete treatment		<0.001*		<0.001*
Complete / Partial response	1 (Ref)		1 (Ref)	
Stable / Progression	6.21 (3.30 to 11.68)		6.45 (3.36 to 12.40)	

HR, hazard ratio; aHR, adjusted hazard ratio; BMI, body mass index; EM, endometrioid adenocarcinoma; HGSC, high-grade serous adenocarcinoma; HGEM, high-grade endometrioid adenocarcinoma; AGR, albumin to globulin ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; Note: aHR was adjusted for grade, pretreatment NLR, number of NAC cycle, surgical status, and number of postoperative chemo-cycle; *, Statistically significant (P < 0.05)

following interval debulking. Median PFS was 12 months in both groups. Median OS appeared comparable between the groups, 29 months in the CRS group and 30 months in the NAC group. Similarly, in a randomized controlled study (CHORUS trial) undertaken in 87 hospitals in the UK and New Zealand, 550 women with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer were randomly assigned to CRS or NAC (Kehoe et al., 2015). The rate of debulking to less than one cm residual disease was significantly higher in the NAC group, 73% vs. 41%. Grade 3 or 4 postoperative morbidities and deaths within 28 days following surgery were more prevalent in the CRS group, 24% vs. 14% for morbidity and 6% vs. <1% for mortality. Median PFS was 12.0 months for the NAC group and 10.7 months for the CRS group. Median OS was comparable between the groups, 22.6 months in the CRS group and 24.1 months in the NAC group. Recently, the long-term pooled data from these two studies were published.(Vergote et al., 2018) When considered separately, the median OS for these two studies was significantly different, 30.2 months for the EORTC study and 23.6 months for the CHORUS trials. In the pooled analysis, 612 patients were randomly assigned to receive CRS and 608 patients to receive NAC. There was no significant difference in median OS between the groups, 27.6 months for the NAC group and 26.9 months for the CRS group (HR 0.97, 95% CI 0.86–1.09; P = 0.59). In a subgroup analysis of women with stage IV disease, significantly better median OS was observed in the NAC group, 24.3 months vs. 21.2 months (HR 0.76, 95% CI 0.58-1.00, P = 0.05). Our survival outcomes with the median OS of 30.8 months for the entire cohort could be compared favorably to the survival outcomes from these large trials. Although the OS and PFS outcomes appeared inferior in the NAC group compared to those in the CRS group in our study, they could still be considered quite acceptable given the more aggressive disease in the patients enrolled in the NAC group. These findings supported the role of NAC as a valid treatment option for patients with stage III-IV tubo-ovarian cancer, especially in those with high tumor burden and poor performance status.

Multivariable analysis of the association between potential predicting factors and survival outcomes in both the CRS and the NAC groups consistently identified stable disease/progression after complete treatment as an independent predicting factor for OS (Figure 1). Recent evidence has suggested the role of genetic and epigenetic predisposition as a major determining factor for the biological characteristics and behavior of cancer cells. While mutations in the *BRCA1*, *BRCA2*, and *ADAMTS* gene family were associated with better treatment response and longer survival (Liu et al., 2015; Lisio et al., 2019; Fuh et al., 2020), *CCNE1* amplification and increased hypermethylation and stroma-related genes were related to chemotherapy resistance and poor survival outcomes (Chen et al., 2015; Patch et al., 2015). In addition, it has been reported that the C1/Mesenchymal molecular subtype of high-grade serous carcinoma was associated with a poorer response to platinum-based chemotherapy (Murakami et al., 2016). These findings suggested that intrinsic aggressiveness of the cancer cells is probably the major contributor to treatment resistance, resulting in poor survival outcomes regardless of treatment modality.

For the CRS group, apart from the status of disease after treatment completion, the primary peritoneal origin of cancer and tumor size of more than 12 cm were also independently associated with poorer OS. In a retrospective case-control study from Taiwan (Chao et al., 2013), survival outcomes of 38 women with advanced stage primary peritoneal serous papillary carcinoma were compared to those of 53 women with similar stage papillary serous ovarian cancer. While the PFS was comparable between the group, the OS was shorter in the primary peritoneal group (median OS 62.0 months vs. 77.5 months). However, it was noted that the patients in the primary peritoneal group were older and had a higher-grade disease, which likely contributed to the poorer outcome. Similar to that study, in the present study, the mean age of the patients with primary peritoneal cancer (61.25 years) appeared higher than those with primary ovarian (54.82 years) and fallopian tube cancer (55.77 years). Also, all patients with primary peritoneal cancer were classified as having grade 3 tumors. These factors could explain the poor OS outcome associated with primary peritoneal cancer. However, the small number of patients who had primary peritoneal cancer made the estimate imprecise and precluded definite conclusion regarding the true impact of the origin of cancer on survival in this group of patients. For the role of tumor size, in the exploratory analysis of the previously mentioned EORTC study (van Meurs et al., 2013), the size of the largest tumor of more than 4.5 cm was significantly associated with worse OS in patients both with stage IIIC (5-year OS 17% vs. 45%) and stage IV (5-year OS 2% vs. 13%). Furthermore, the additional analysis of the Gynecologic Oncology Group (GOG) study protocol 52 found that for optimally debulked (to one cm or less) stage III epithelial ovarian cancer, patients with initial extrapelvic disease of one cm or less had better survival outcomes than those with the larger-volume disease.(Hoskins et al., 1992) Our multivariable analysis data demonstrating the association between initial tumor size of 12 cm or more and poorer OS further substantiated these findings. In addition, our results supported the importance of intrinsic tumor biology aside from therapeutic interventions, including cytoreductive surgery and adjuvant chemotherapy as a predictor for treatment response and outcome.

The pre-treatment PLR level of more than 310 was significantly associated with a higher risk of death for the NAC group in our study. The prognostic role of systemic inflammatory markers such as serum albumin, NLR, PLR, and AGR in epithelial ovarian cancer has been recently assessed. In a meta-analysis of retrospective studies that addressed the prognostic role of NLR and PLR in all stages of epithelial ovarian cancer, despite some degree of heterogeneity, the group with higher NLR and PLR had worse overall survival with HR 2.21 (95% CI 1.95-2.52) and HR 2.53 (95% CI 2.16-61.65), respectively.(Zhu et al., 2018) Consistently, another meta-analysis of cohort studies showed that ovarian cancer patients with lower serum albumin had poorer overall survival. (Ge and Wang, 2018) However, the prognostic value of these markers has not been well evaluated in advanced-stage ovarian cancer patients receiving NAC. Our result in women with advanced-stage disease, who received NAC supported the prognostic role of PLR in this particular group.

Data on the impact of treatment characteristics, including number of NAC cycles, interval between complete NAC and IDS, the interval between IDS and postoperative adjuvant chemotherapy, and a number of adjuvant chemotherapy cycles on survival outcomes for patients who receive NAC, are conflicting (Colombo et al., 2014; Stewart et al., 2016; Altman et al., 2017; Xu et al., 2017; Chen et al., 2018; Lee et al., 2018; Phillips et al., 2018). We did not find any significant association between these parameters and OS (Table 3).

This study was based on long-term data from a single institution with uniform surgical treatment and chemotherapeutic regimens. Specialist gynecologic pathologists reviewed all pathological data. However, data were retrospective, and the sample may be too small to identify a significant association between certain characteristics/potential prognostic factors such as the status of debulking surgery and OS.

In conclusion, NAC appeared to be a reasonable alternative treatment for stage III/IV tubo-ovarian carcinoma, especially for patients with extensive disease and poor performance status. The worse survival outcome associated with primary peritoneal carcinoma and large initial tumor size in the patients who received CRS suggested that NAC could be an attractive option for those with these characteristics. The prognostic role of the systemic inflammatory markers in advanced-stage ovarian, tubal, and primary peritoneal cancer should be further explored.

Author Contribution Statement

Chalaithorn Nantasupha and Kittipat Charoenkwan made substantial contributions to the conceptualization and design of the study and data collection. Further, they were involved in drafting the manuscript and revising it. Tanarat Muangmool took part in statistical analysis, interpretation of the data, and manuscript revision. All authors read and approved the final manuscript.

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Ethical approval

The Faculty of Medicine Research Ethics Committee approved this study. (Approval number OBG-2561-05735)

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that they have no conflict of interest.

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