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ORIGINAL ARTICLE

Comparison of Neoadjuvant Chemotherapy Plus Interval Debulking Surgery and Primary Debulking Surgery in Patients with Stage III and IV Ovarian Carcinoma: A Multicenter Real Life Experience

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OBJECTIVE

The aim of the study is to compare treatment outcomes of the patients with federation of gynecology and obstetrics stages III and IV ovarian carcinomas, who underwent interval debulking surgery after neoadjuvant chemotherapy (NACT), and patients who underwent adjuvant chemotherapy after primary debulking surgery (PDS).

METHODS

Patients from four centers (n=183) were retrospectively evaluated. Of the patients, 91 (50%) were in the PDS group and 92 (50%) in the NACT group.

RESULTS

In the NACT group patients have advanced age, poor performance status, high levels of CA125, and advanced disease stage compared with the PDS group (p<0.050). Of the patients receiving NACT, 14 (15%)

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had a complete response, and 68 (74%) had a partial response. The R0 rate was higher in the PDS group (p=0.018). In univariate analysis, poor prognostic factors affecting OS were NACT in the treatment protocol (p<0.001), poor performance status (p<0.001), advanced age (<70 vs. ≥70, p=0.002), advanced clinical stage (p=0.042), and localization of the tumor with the largest diameter outside the omentum and ovary at the time of diagnosis (p=0.029). In the multivariate analysis, the presence of NACT (HR: 2.30, 95% CI: 1.25–4.23, p=0.007) and poor performance (HR: 2.52, 95% CI: 1.18–5.10, p=0.017) were independent poor prognostic factors for OS.

CONCLUSION

In the study, OS was better in the PDS group than in the NACT group. This result was thought to be associated with the NACT group having more disadvantageous characteristics (advanced age, poor performance, high CA125 level, advanced stage, etc.).

Keywords: Interval debulking; neoadjuvant chemotherapy; ovarian carcinoma; primary debulking.

INTRODUCTION

Epithelial ovarian cancer (EOC) is one of the most frequently diagnosed malignancies and the leading cause of death from a gynecological malignancy, accounting for more than 313,000 new cases annually and more than 207,000 deaths worldwide.[1] Approximately 70% of all patients are diagnosed in the advanced stage, especially the International federation of gynecology and obstetrics (FIGO) Stages IIIC and IV, due to the lack of specific symptomatology and screening procedures. Primary debulking surgery (PDS) followed by adjuvant chemotherapy with paclitaxel plus platinum-based chemotherapy is the standard treatment for advanced-stage ovarian cancer.[2,3] However, complete resection during cytoreductive surgery is strongly correlated with the longer survival of patients. Eventually, for these patients, most of whom are in the advanced stage, the probability of surgical success is reduced due to the diffuse nature of many metastatic foci, which often prevents complete cytoreduction, affecting the prognosis of the patients.[4] In terms of survival, it was shown that the patients with no macroscopic residual tumor (complete debulking; R0 resection) were better than the patients with minimal residual disease (optimal debulking; ≤1 cm, R1 resection) and those with residual disease (suboptimal debulking; >1 cm, R2 resection).[5]

In patients who are not good candidates for surgery due to the extensive spread of a tumor, neoadjuvant chemotherapy (NACT), followed by interval debulking surgery, are the standard treatment approach.[6,7] In retrospective studies, it was observed that the possibility of optimum debulking increased with NACT, and surgery-related complications decreased.[8,9] However, according to a meta-analysis, even though the increased maximal cytoreduction rate with NACT increased median survival, delayed surgery had a negative effect on the overall survival of the patient.[10] In patients who are receiving NACT, the number of chemotherapy cycles and the optimal time for interval debulking surgery are important parameters that might affect the survival outcomes of patients. In a retrospective analysis on this subject, delayed cytoreduction in patients who received 5 cycles or more of NACT was shown to have similar survival outcomes as patients who received 2–4 cycles of NACT.[11]

Another meta-analysis argued that there was no difference in PFS and OS between NACT and PDS groups and that the patient group that could benefit from NACT should be determined based on factors such as age, stage, performance status, and tumor histology.[12]

Other analyses in the literature show no difference in PFS and OS between the two groups.[10,13,14] Therefore, the aim of the present study is to compare the clinicopathologic characteristics and treatment outcomes in the patients with FIGO Stages 3 and 4 ovarian carcinomas receiving PDS and the patients receiving NACT.

MATERIALS AND METHODS

The patients with FIGO Stage III or IV, who were 18 years and over, admitted between 2009 and 2017, diagnosed with ovarian, tubal, or primary peritoneal serous carcinoma after exploratory laparotomy, laparoscopy, image-guided biopsy or surgery and subsequently treated with chemotherapy or surgery in four centers were included in the study. Of the patients included, 34 (18%) were receiving treatment at the Medical Faculty Hospital of Gazi University, 80 (44%) at Istanbul Dr. Lutfi Kirdar Kartal Training and Research Hospital, 42 (23%) at the Medical

Faculty Hospital of Hacettepe University, and 27 (15%) at Ankara Dr. Zekai Tahir Burak Women's Health Training and Research Hospital. The patient's performance status was evaluated according to the Eastern cooperative oncology group's (ECOG) performance criteria. Clinical staging was done according to the FIGO staging. Treatment response was assessed according to the criteria of the response evaluation criteria in solid tumors.

Patients who were diagnosed under 18 and could not receive treatment (surgery or chemotherapy) due to their general condition or performance related to their disease were excluded from the study.

Carboplatin/paclitaxel was administered to 95.6% (n=88) of the patients in the NACT group in cycles every 21 days, and 4% of the patients were administered another chemotherapy protocol chosen by the clinician, with a median of 3 cycles (min: 1–max: 9) NACT.

OS was defined as the date range from diagnosis to the date of the last follow-up or death, and PSF as the time to the last control date or date of death in those without progression (relapse/metastasis) or progression.

Ethics committee approval of the study was obtained from our institution.

Statistics

All data were analyzed using the SPSS version 22 (Chicago, IL, USA) statistical software. The comparison of clinicopathological features of NACT and PDS was examined by the Chi-square test or Fisher's exact tests. The Student t-test was used to compare continuous variables. The Mann–Whitney U-test was used for the groups which were not normally distributed. The survival rates were calculated according to the Kaplan–Meier method. A multivariate (Cox regression) analysis was used to evaluate the independent risk factors that affected survival. The value of $p \leq 0.05$ was considered to be significant. A correlation test was performed to determine the correlation between the level of CA125 and the survival times.

RESULTS

The clinicopathological characteristics of the groups are demonstrated in Table 1. Median age ($p<0.001$), median CA125 values ($p<0.001$), clinical stage ($p<0.001$), localization of the tumor with the widest diameter at diagnosis ($p<0.001$), histopathology ($p=0.038$), surgical resection status ($p=0.018$), pathological T stage ($p=0.024$), and the number of adjuvant chemotherapy cycles ($p<0.001$) were not equally distributed between the groups.

Complete response in 14 (15%) patients, partial response in 68 (74%) patients, stable disease in 6 (7%) patients, and progressed disease in 4 (4%) patients were detected in the NACT group. In the NACT group, the median CA125 level after CT was 41.22 (range, 0–4994).

In the NACT group, 49 (53%) patients underwent total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy and para-aortic and pelvic lymphadenectomy, 36 (40%) patients underwent debulking/cytoreductive surgery, and 7 (7%) patients underwent total hysterectomy. Bilateral salpingo-oophorectomy and omentectomy were performed. In the PDS group, surgically total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy and para-aortic and pelvic lymphadenectomy in 68 (75%) patients, debulking/cytoreductive surgery in 22 (24%) patients, and total hysterectomy in 1 (1%) patient, bilateral salpingo-oophorectomy, and omentectomy were performed ($p=0.01$).

The median follow-up period was 27 months (range 2–110), and the median and 2-year OS of all the patients were found as 49 months and 41%, respectively; and median and 2-year PFS as 19 months and 43%, respectively. In addition, a negative correlation was detected between the OS and PFS periods with the CA125 levels at diagnosis ($p=0.021$, $r=-0.173$ for OS; $p=0.002$, $r=-0.208$ for PFS).

In univariate analyses, prognostic factors affecting OS were the treatment protocol (NACT vs. PDS, $p<0.001$), ECOG PS ($p<0.001$), age (<70 years old vs. ≥70, $p=0.002$), clinical stage ($p=0.042$), and the localization of the tumor with the widest diameter at diagnosis ($p=0.029$). In the multivariate analysis, the presence of NACT (HR: 2.30, 95% CI: 1.25–4.23, $p=0.007$) and poor performance (HR: 2.52, 95% CI: 1.18–5.10, $p=0.017$) significantly increased risk of death. Table 2 shows the results of univariate and multivariate analyses for OS. Survival curves of the groups are shown in Figure 1 according to the treatment protocols and in Figure 2 according to ECOG PS. Only surgical resection status was statistically significant for PFS ($p=0.001$); however, no difference was found for the treatment protocol. No independent prognostic factor was detected for PFS in the multivariate analysis. Table 3 shows the prognostic factors affecting PFS. PFS curves of the groups are shown in Figure 3 according to the treatment protocol and Figure 4 according to the surgical resection status.

DISCUSSION

In the present study evaluating retrospectively the results of the patients, who received NACT and PDS in

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Table 1 Comparison of clinicopathological characteristics and treatment of the groups

	NACT n=92 (50%)		PDS n=91 (50%)		p
	n	%	n	%	
Median age					
Years (range)	60 (29–85)		51 (24–80)		**<0.001**
Age					
<70	75	82	85	94	**0.013**
≥70	17	18	6	7	
Median CA125 level (range) (IU/mL) at the time of diagnosis	1166 (97–11691)		354 (2–6468)		**<0.001**
ECOG PS					
ECOG 0–1	75	85	90	99	**<0.001**
ECOG 2 and above	13	15	1	1	
Clinical stage (FIGO)					
IIIC	75	82	91	100	**<0.001**
IV	17	18	–	–	
Location of the tumor with the largest size at the time of diagnosis					
Ovary	54	59	85	93	**<0.001**
Omental	22	24	5	6	
Others	16	17	1	1	
Histopathology					
Serous	87	95	78	86	**0.038**
Others	5	5	13	14	
Grade					
Well and moderately	12	13	12	13	0.928
Poor	80	87	79	87	
Peritoneal involvement	65	88	72	85	0.734
Involvement of Appendix	15	31	34	49	0.066
Malignant ascites cytology					
Negative	27	38	32	43	0.523
Positive	45	62	43	57	
Largest tumor size					
<5 cm	18	21	28	34	**0.041**
≥5 cm	69	79	55	66	
Pathological T stage					
T1–T2	4	5	16	18	**0.024**
T3	74	95	75	82	
Size of residual disease (cm)					
R0 (No gross)	45	49	63	69	**0.018**
R1 (≤1 cm)	32	35	20	22	
R2 (>1 cm)	15	16	8	10	
Median number of post-surgical chemotherapy cycles	3 (range, 1–9)		6 (range, 4–9)		**<0.001**
Chemotherapy regimen					
Carboplatin plus paclitaxel	91	99	88	97	0.306
Others	1	1	3	3	

NACT: Neoadjuvant chemotherapy; PDS: Primary debulking surgery; ECOG: Eastern Cooperative Oncology Group; PS: Performance status; FIGO: International Federation of Gynecology and Obstetrics

advanced-stage ovarian cancer, it was found that OS was worse in the patients who received NACT; however, there was no difference between the groups in terms of PFS. In addition, R0 resection was less provided in the NACT group. Adverse characteristics for OS were in the NACT group, poor performance, advanced clinical stage, over

Table 2 Prognostic factors affecting overall survival between the groups

Univariate analysis	The 2-year OS (%)	Median OS (month)	p
Treatment			
PDS	95	NR	**<0.001**
NACT	82	41	
Response of NACT			
Complete response	91	35	**0.467**
Partial response	89	43	
Stable disease	50	21	
Progressive disease	50	33	
ECOG PS			
ECOG 0–1	91	50	**<0.001**
ECOG 2 and above	69	33	
Clinical stage			
IIIC	91	49	**0.042**
IV	63	33	
Age			
<70	93	49	**0.002**
≥70	57	37	
Histopathology			
Serous	88	49	0.462
Others	94	53	
Cytology of malignant ascites			
Negative	92	NR	0.385
Positive	91	44	
Grade			
I-II	83	49	0.799
III	93	49	
Location of the tumor with the largest size at the time of diagnosis			
Ovary	77	43	**0.029**
Omental	91	50	
Others	92	35	
Largest tumor size			
<5 cm	83	43	0.751
≥5 cm	91	48	
Surgery resection			
R0	92	49	0.783
R1	92	49	
R2	83	NR	

Multivariate analysis	HR	CI %	p
ECOG			
ECOG 0–1	1		
ECOG 2 and above	2.52	1.18–5.40	**0.017**
Treatment			
PDS	1		
NACT	2.30	1.25–4.23	**0.007**

OS: Overall survial; PDS: Primary debulking surgery; NR: Not reached; NACT: Neoadjuvant chemotherapy; ECOG: Eastern Cooperative Oncology Group; PS: Performance status; HR: Hazard ratio; CI: Confidence interval

70 years of age, and localization of large tumors outside the ovary, respectively. Furthermore, poor performance and being in the NACT group were independent prognostic factors for OS. Only providing R0 resection was detected as a good prognostic factor for PFS.

In the study conducted by Schwartz et al.[15] to retrospectively analyze the results of 206 patients to whom PDS was applied and 59 patients receiving NACT, no statistically significant difference was found between the groups regarding median PFS and OS. Although the patients receiving NACT were older and had worse performance than the PDS group, survival outcomes were similar. However, in the current study, the unbalanced number of patients between the groups, the limited number of patients receiving neoadjuvant therapy, and the comparison of the results of the patients in the NACT group, who could only undergo surgery, should be considered in the evaluation.[15] The studies of European Organization for Research and Treatment of Cancer (EORTC) 55971 and CHORUS indicated that NACT was non-inferior when compared to PDS.[6,7] In the EORTC 55971, median survival was detected as 29 months in PDS and 30 months in NACT; and in the study of CHORUS, median OS was found as 22.6 months versus 24.1 months, respectively.[6,7] In a retrospective study by Kobal et al.,[16] PFS and OS data of the PDS (n=108) and NACT (n=49) groups were similar. It was shown that postsurgical complications were significantly lower in the NACT group. Median OS and PFS were found at 41.3 and 17.3 months, respectively, and 34.5 and 18.3 months in the NACT group. In another randomized study comparing NACT and PDS in terms of perioperative complications and survival in 171 patients with stage IIIC-IV epithelial ovarian, fallopian tube, or primary peritoneal cancer, and complete resection rates were found to be significantly higher in the NACT group. However, major post-operative complications were significantly higher in the PDS group. In this study, similar median PFS and OS were found between groups such as the EORTC55971 and

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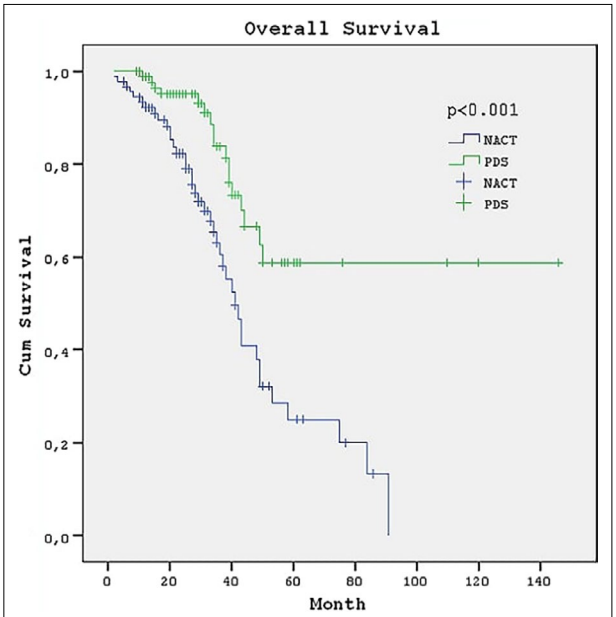

Fig. 1. Overall survival curves according to treatment protocol (NACT vs PDS).
NACT: Neoadjuvant chemotherapy; PDS: Primary debulking surgery.

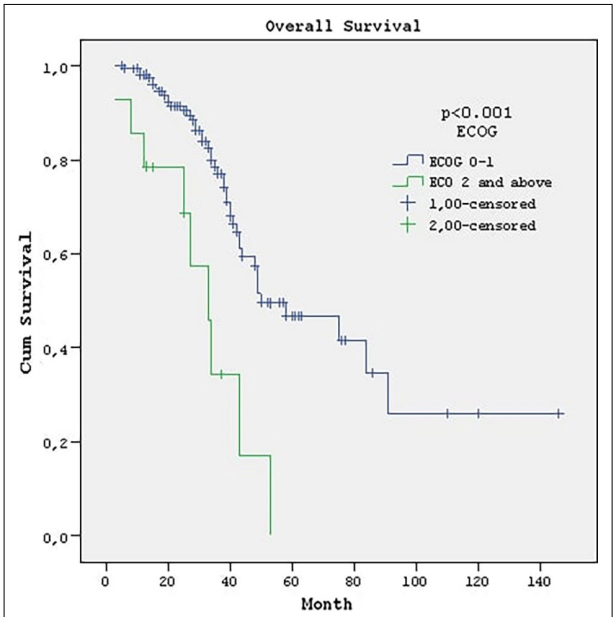

Fig. 2. Overall survival curves according to ECOG PS.
ECOG: Eastern Cooperative Oncology Group; PS: Performance status.

CHORUS studies.[17] In another randomized study, 301 patients were evaluated, but NACT could not be confirmed to be non-inferior to PDS, and it was interpreted that NACT may not always replace PDS.[18] However, the present study showed that the PDS group was longer OS compared with NACT, but not in PFS. It was observed that the median survival was not reached yet in the PDS group; however, the median PFS was 24 months, the median OS was 41 months, and the median PFS was 17 months in the NACT group. However, it should also be considered that the patients receiving NACT in the present study have worse clinical characteristics for OS (advanced age, poor performance, high CA125 level, advanced stage, extra ovarian spread of large tumors, and severe high histopathology).

It is known that the surgical resection status in patients with ovarian cancer, especially providing R0 resection, significantly affects the survival of the patients.[5,9,19] Can R0 resection be provided at a higher rate by giving chemotherapy to patients with advanced stage and high tumor burden before the surgery? Numerous studies investigated the answer to this question; however, the results of the studies are controversial.[6,7,16,20–25] The EORTC 55971 study was a multicenter, prospective, and randomized study that evaluated the treatment outcomes of NACT (n=334) and PDS (n=336). In the current study, including almost all Stages III and IV patients, the rate of residual disease of 1 cm after surgery was higher in the NACT group (80.6% vs. 41.6%). In the multivariate analysis, the most potent independent factor predicting survival was the absence of residual tumors after surgery.[6] Similar to EORTC 55971 study, the CHORUS study is a multicenter, randomized, and controlled non-inferior study that compares the results of PDS (n=276) and NACT (n=274). In the present study, the incidence of a residual tumor of 1 cm and less after the surgery was 41% in the PDS group and 73% in the NACT group, and the rate of the patients to whom R0 resection was provided was found to 17% and 39%, respectively.[7] In the study by Kobal et al.,[16] R0 resection was found to be 53.7% in the PDS group and 77.6% in the NACT group. In addition, the correlation between residual disease and survival was revealed in the study. In another study in which 285 patients were analyzed retrospectively, residual tumor burden was evaluated as an independent factor significantly affecting survival.[9] In the present study, surgical resection status was isolated as a prognostic factor that affects PFS. However, this significance was not in question for OS. It was observed that as the residual tumor was reduced, PFS recovered. In the NACT group, less R0 resection was observed compared to PDS (48.9% vs. 69.2%, respectively); however, a higher pT3 stage was seen after the surgery. However, it should be considered that the extra ovarian localization of large tumors was higher in the NACT group. It seems

Table 3 Prognostic factors affecting progression-free survival between groups

Univariate analysis	The 2-year PFS (%)	Median PFS (month)	p	Univariate analysis	The 2-year PFS (%)	Median PFS (month)	p
Treatment				Cytology of malignant ascites			
NACT	33	17	0.111	Negative	55	26	0.057
PDS	51	24		Positive	33	16	
Response of NACT				Grade			
Complete response	40	16	**0.318**	I-II	50	21	0.318
Partial response	33	18		III	42	19	
Stable disease	25	16		Location of the tumor with the largest size at the time of diagnosis			
Progressive disease	–	5					
ECOG PS				Ovary	28	16	0.199
ECOG 0–1	44	20	0.301	Omental	43	20	
ECOG 2 and above	29	16		Others	39	16	
Clinical stage				Largest tumor size			
IIIC	43	19	0.338	<5 cm	34	17	0.430
IV	32	16		≥5 cm	46	20	
Age				Surgery resection			
<70	45	20	0.106	R0	54	26	**0.001**
≥70	20	16		R1	20	13	
Histopathology				R2	29	16	
Serous	41	19	0.394				
Others	46	24					

PFS: Progresion free survival; NACT: Neoadjuvant chemotherapy; PDS: Primary debulking surgery; ECOG: Eastern Cooperative Oncology Group; PS: Performance status

reasonable that fewer R0 resections were performed in the NACT group with higher tumor burden, worse performance, and older age compared to the younger PDS group with better clinical features.

In a retrospective analysis evaluating the potential predictive markers for survival and optimal cytoreduction of the patients, who underwent interval debulking surgery only after NACT, it was found that CA125 reduction kinetics and ascites regression were associated with interval debulking and the survival outcomes.[24] In the current study, CA125 levels at diagnosis were significantly higher in the NACT group than in the PDS group concerning the tumor burden. Furthermore, a negative correlation was found between all patients' CA125 levels at diagnosis and OS and PFS periods. In the study, the NACT group did not evaluate ascites regression; however, the correlation between malignant ascites at diagnosis and OS and PFS was investigated. Malignant ascites at diagnosis showed an almost statistically significant effect on PFS but not on OS. Furthermore, the presence of malignant ascites between the groups was similar.

Cioffi et al.[26] examined the effects of patient age in 102 patients who received NACT. In the study, the patients were examined in two groups, aged under 70 years old and over, and they showed that the patients over 70 years old were more suitable for NACT due to higher comorbidity and poor performance. In the patients aged 70 and over, median PFS and OS were significantly lower in the present study (median PFS; 9 months vs. 13 months and median OS; 21 months vs. 29 months, respectively). In addition, advanced age, stage IV disease, ascites, and residual disease greater than 1 cm were associated with OS, lower PFS, a high American Society of Anesthesiologists score, and residual disease greater than 1 cm.[26] In the present study, there were more patients over 70 years old in the NACT group compared to PDS. In the study, even though worse median OS was isolated in patients over 70, this correlation was not found in PFS. As in other studies, NACT seems to be used more in the treatment option in advanced and elderly patients in the current study.

In the evaluation of a subgroup analysis of the EORTC 55971 study, clinical and pathological characteristics that could be potential biomarkers were investigated.[20] The largest metastatic tumor size and stage of disease were found to be statistically significantly correlated with 5-year survival. It was shown that stage IIIC patients with metastatic tumors of ≤45 mm benefited more from primary surgery, and Stage IV patients

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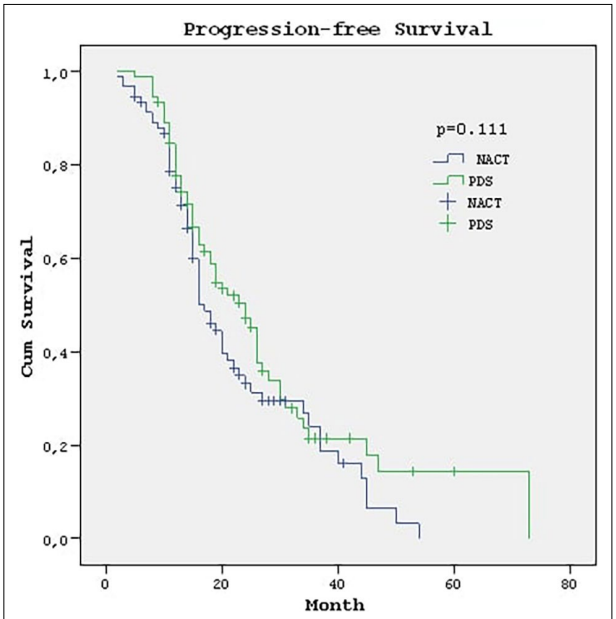

Fig. 3. Progression-free survival curves according to treatment protocol.
NACT: Neoadjuvant chemotherapy; PDS: Primary debulking surgery.

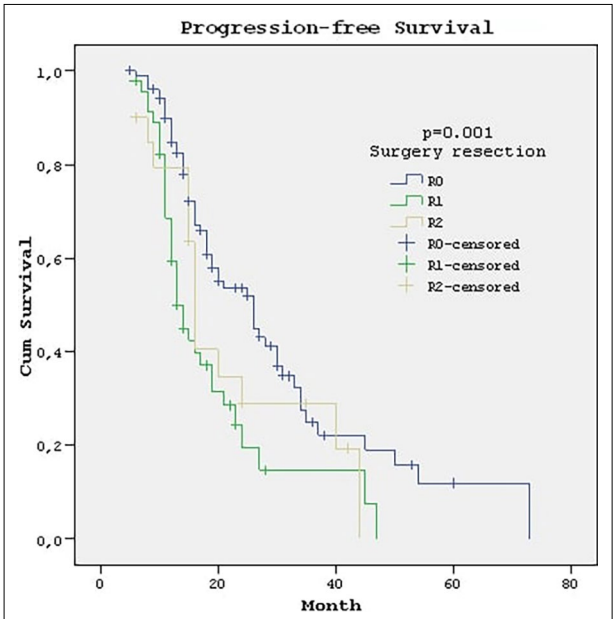

Fig. 4. Progression-free survival curves according to surgery resection status.

with metastatic tumors of >45 mm benefited more from NACT. Furthermore, the patients with stage IIIC and large tumors and those with stage IV and less common diseases benefited equally from both treatments. Survival outcomes of PDS and NACT treatment groups in the EORTC 55971 study were similar; however, Stage IIIC patients with small tumors had better survival with PDS, and Stage IV patients with large tumors had better survival with NACT.[23] Depending on this analysis, the current study observed that the patients with large tumor sizes and advanced stages were mainly treated with NACT. In the present study, when the patients were examined in two groups with the largest tumor size of >5 cm and <5 cm, any correlation was not found between the largest tumor size and OS and PFS, unlike other studies. In addition, the extra ovarian spread of the large tumors was more common in the NACT group.

In a meta-analysis study including 21 studies conducted between 1989 and 2008, data of the patients with Stages IIIC and IV EOC, who received NACT, were compared with PDS. According to this meta-analysis, patients receiving NACT were evaluated as those with poor risk factors and a low chance of achieving optimal cytoreduction.[14] In the National Cancer Database study conducted in 2016, which included 62,727 patients with Stages IIIC and IV EOC, demographic characteristics, medical comorbidities, cancer characteristics, and treatment characteristics of the patients were evaluated.[27] Of the patients, 6922 (11%) received NACT, and 31280 (50%) had PDS. It was observed that NACT was used more in stage IV than in stage IIIC (13% and 9%, respectively). In addition, the use of NACT increased over time. Variables associated with the increased use of NACT were detected as the patients older than 50 had more comorbid diseases and those with Stage IV and high-grade epithelial ovarian carcinoma.[27] Likewise, it was observed in the present study that the patients in the NACT group were older, had more advanced stages, had poor performance, and had a low chance of complete resection after the surgery.

CONCLUSION

Consequently, the present study determined that the OS of the NACT group was worse, and R0 resection could be achieved less than the PDS group. This result was suggested to be related to the selection of patients with poor characteristics in the NACT group. However, NACT may continue to be an alternative treatment option in patients who do not have a chance for PDS that results in complete resection due to advanced age, comorbidities, or tumor extent since no difference was shown in PFS results between the groups. It was also thought that this result would be different in a study in which the clinicopathological characteristics of the groups were similar.

Major limitations of the study are retrospective design and quality of surgery was not controlled, the effect of surgery is greater in the choice of treatment of patients. In addition, the side effects of the treatments (surgery, chemotherapy) administered to the patients and their effects on quality of life were not evaluated in the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declared no conflict of interest.

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