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ORIGINAL RESEARCH

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Comparison of neoadjuvant chemotherapy versus primary cytoreductive surgery in stage III–IV epithelial ovarian cancer: a retrospective study

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Abstract

Background: The aim of this study was to compare survival outcomes, short-term post-operative morbidity and mortality in patients undergoing primary debulking surgery (PDS) and receiving neoadjuvant chemotherapy (NACT). **Methods**: This study is a single center retrospective clinical study. We evaluated 196 patients with advanced stage epithelial ovarian cancer (EOC). The treatment approach was based on the patient's performance status (PS), preoperative radiological evaluation and diagnostic laparoscopic evaluation. Overall survival (OS) and progression-free survival (PFS) were compared for stage III–IV and IIIC alone according to the amount of residual tumor which determines the prognosis. Kaplan-Meier method was used for survival curves and Long-Rank test was used for survival comparisons. Pearson Chi-square test was used to compare categorical variables. **Results**: Out of 196 patients, 127 (64.7%) underwent PDS and 69 (35.2%) received NACT due to the comorbities, poor PS and unresectable tumor burden. In both groups most of the patients had stage IIIC and serous histology. NACT group had significantly older age, poorer PS, higher rates of recurrence and mortality. Complete and optimal cytoreduction were similar in both groups (PDS: 43.3% and 40.2% versus NACT: 33.3% and 50.7%, respectively). Complete resection was observed to prolong PFS and OS in PDS. In patients with stage IIIC, the effect of PDS on OS is superior. Because of the low number of patients in stage IVA–B, OS and PFS were found insignificant in both groups. The 30-day post-operative complication rate was higher in the NACT group ($p < 0.001$). **Conclusions**: PDS should be preferred initial treatment for patients with III–IV EOC. NACT should be considered for patients who are not medically fit for surgery and/or for whom complete cytoreduction is not feasible.

Keywords

Epithelial ovarian cancer; Survival; Residual tumor; Morbidity

1. Introduction

Epithelial ovarian cancer (EOC) is the primary cause of mortality from gynecological cancers. Approximately 70% of patients are diagnosed at an advanced stage, according to the International Federation of Gynecology and Obstetrics (FIGO) classification, which categorizes stages as IIIC and IV. The standard treatment for patients with advanced disease is primary debulking surgery (PDS) followed by platinum-based chemotherapy [1]. The objective of surgical intervention is to reduce the intra-abdominal tumor burden to the greatest extent possible and patients who have no residual disease (RD) at the conclusion of surgery demonstrate superior survival rates compared to those with visible residual lesions [2]. In order to minimize the risk of a patient developing a recurrence of disease, several surgical techniques have been proposed which are designed to be highly invasive; including the removal of all visible disease on the diaphragm, the colon, spleen, pelvis and elsewhere in the abdomen [2]. Nevertheless, a number of studies have indicated that patients presenting with an initial high disease burden are likely to have a worse prognosis, despite optimal resection with aggressive surgery [3].

In recent decades, the use of neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) in patients with advanced EOC has been proposed as an alternative treatment to increase the likelihood of optimal debulking by decreasing surgery-related complications and mortality. The question is whether the necessary delay to surgery that comes with NACT might decrease survival [4]. Two randomized clinical trials comparing PDS followed by chemotherapy and NACT followed by IDS demonstrated comparable survival outcomes with a low incidence of post-operative morbidity when NACT and IDS were employed [5, 6]. Both trials have demonstrated that NACT is not inferior to PDS for overall

survival (OS) and progression-free survival (PFS) with lower surgery-related morbidity and mortality; however, they have been criticized for low rates of R0 resection and low survival rates in the PDS arm. On the other hand, two meta-analysis reported opposite results in the IDS arm [7, 8]. In the results of the two randomized trials, SCORPION [9] and JCOG0602 [10], they both concluded that post-operative complications were lower in the NACT arms.

The feasibility of surgical resection of a tumor is contingent upon a number of factors, including the patient's age, the stage of the disease, the extent of the disease burden, the presence of comorbidities, the location of metastatic sites, the patient's performance status (PS) and the surgeon's experience. The use of both serum biomarkers and computed tomography (CT) imaging to identify tumor spread has limitation to predict optimal debulking (RD $\leq$1 cm) preoperatively, in this case laparoscopy prior to debulking surgery can offer to evaluate peritoneal cavity, enhanced visualization of upper abdomen, surface of the spleen, liver and diaphragm. Fagotti and colleagues [11] demonstrated that using laparoscopic Predictive Index Value (PIV) score is a reliable procedure for the assessment of the optimal cytoreduction. They suggested that if PIV score is 8–12 that is associated with suboptimal cytoreduction due to high tumor load, NACT may be preferred to avoid unnecessary exploratory laparotomy.

It is beyond dispute that the optimal survival outcome is achieved when all visible disease is removed during cytoreductive surgery [12, 13]. Therefore, selection of the appropriate patients with especially stage IIIC or IV ovarian cancer for PDS or IDS is important and remains subject of continuing debate by considering balance between the benefits and risks. The goal of this paper is to utilize and compare survival, recurrence, mortality and short-term post-operative morbidity rates in PDS and IDS groups.

2. Materials and methods

2.1 Patients

A cohort of patients diagnosed with advanced (FIGO stage III–IV) EOC which includes primary peritoneal and primary fallopian tube cancers, was identified and treated with either PDS or NACT followed by IDS at the Department of Obstetrics and Gynecology in Ankara University Faculty of Medicine between 2002 and 2017. A comprehensive review of the medical records of all patients was conducted, and the relevant demographic, clinical, surgical, pathological and follow-up information was obtained from electronic hospital Avicenna database and patient files, retrospectively. A total of 196 patients with complete information on grade, stage, histology, recurrence, morbidity, mortality, survival and amount of residual tumor after PDS and IDS were enrolled in the study. Patients with early-stage disease and non-epithelial tumors were excluded. We distributed the patients underwent PDS followed by 6 cycles of adjuvant chemotherapy or to 3–4 cycles of NACT, then IDS, followed by 3–4 more cycles of completion chemotherapy. Patients were followed up until March 2019.

2.2 Study design

Preoperatively clinical evaluation consisted of general and gynecological examination, PS, blood tests, serum Cancer Antigen 125 (CA-125) levels, electrocardiogram (ECG), thoracoabdominopelvic computerized tomography (CT) scan (in case of need positron emission tomography-computerized tomography (PET-CT) was used). Patients who were assigned to receive primary chemotherapy underwent either histological or cytological confirmation of their diagnosis by performing laparoscopy or fine-needle aspiration of ascites and pleural effusion before starting chemotherapy. The reasons for NACT involved the advanced spread of disease, co-morbidity and poor PS. Patients in stage IVA were included only in the event of a positive pleural effusion. Stage IVB with isolated resectable liver and/or splenic parenchymal involvement patients underwent PDS. An American Society of Anesthesiologists (ASA) score of 3 or greater was defined as poor PS.

The objective of debulking surgery was to remove the tumor in order to achieve complete debulking, with the aim of achieving no macroscopic RD. This included the resection of the uterus, both fallopian tubes, the ovaries, the omentum, both pelvic and para-aortic lymph nodes and the complete resection of all visible tumor tissue. Radical procedures included splenectomy, partial hepatectomy, bowel resection and anastomosis if indicated, cholecystectomy, appendectomy, diaphragmatic stripping and peritonectomy. The necessity for an ostomy was determined by surgeons based on the location and spread of the disease, the number of bowel resections, and the specific clinical conditions of the patient. The extent of RD was determined by the size of the single largest lesion and classified into 3 categorizes: R0-maximal cytoreduction (no gross RD), optimal cytoreduction (RD $\leq$1 cm), or suboptimal cytoreduction (RD $>$1 cm).

Both neoadjuvant and post-operative chemotherapy used a combination of paclitaxel (175 mg/m^2) and carboplatin (area under curve (AUC) 5–6). The administration of these agents was conducted on a three-week schedule. IDS was not allowed in patients having progressive disease under NACT, and chemotherapy was changed to a second line schedule then if there was response or stable disease, then IDS was performed. Some patients received NACT weekly. For patients who underwent PDS treatment, the stage of their disease was determined through a pathology report and an intra-operative examination. Patients were monitored on a three-monthly basis for a period of two years, after which they were observed every six months for a further three years, and then annually thereafter.

The clinical response to chemotherapy and disease progression were evaluated in accordance with the Response Evaluation Criteria In Solid Tumors (RECIST) and the Gynecologic Cancer Intergroup (GCIG) criteria [14]. The recurrence time was detected by serum CA-125 levels and/or CT scans. In the case of CT scans, the progression time was defined as the initial appearance of new lesions. In the context of serum CA-125 levels, the progression time was defined as the first date on which the serum CA-125 levels exceeded the upper limit of normal [14, 15]. Upon the subsequent confirmation of a rise in CA-125 levels by CT scan, the progression time was defined

as the date of the CA-125 rise.

Post-operative complications and length of hospitalization within 30 days of surgery were assessed. Progression-free survival was defined as the time interval from the date of completion of treatment to the earliest date of progression, recurrence of disease or death from any cause. Overall survival time was started from the first dose of NACT or date of PDS to either March 2019 or the date of death, whatever the cause. Patients death were abstracted through March 2019.

2.3 Outcomes

The main endpoint for comparing the PDS group and the NACT group was survival. The principal secondary efficacy endpoints were the amount of RD following surgery, PFS, treatment-related morbidity and mortality.

2.4 Statistical analysis

All statistical analysis was conducted and evaluated by using the Statistical Package for the Social Sciences (SPSS) 21.0 software package (IBM Corp., Armonk, NY, USA). Categorical variables are presented with numbers and percentages, while numerical variables are presented with prevalence measures such as the standard deviation, mean, median and range. The Pearson Chi-square test was employed to assess the comparability of categorical variables, whereas the Mann-Whitney U test was utilized to evaluate the discrepancy between independent groups in numerical variables where the assumption of normality was not provided. The Kaplan-Meier method was used to estimate OS and PFS rates. The log-rank test was used to compare survival rates between the two groups. For all tests, a p-value of < 0.05 was deemed to be statistically significant.

3. Results

Between 2002 and 2017, a total of 196 patients with advanced EOC were involved in present study. Sixty nine of them received ACT and 127 underwent PDS. All patients having NACT underwent IDS following 3 or 4 cycles of chemotherapy. Table 1 presents comparisons of the pathological and clinical characteristics of patients who received NACT and PDS. At diagnosis, the median age was significantly different between the NACT and PDS groups, 61 (range 41–79) and 54 years (range 21–81) ($p < 0.001$), respectively. Most patients in both groups had FIGO stage IIIC disease (62.2%) and serous carcinoma histology (86.2%). Patients who received NACT were overall older with more co-morbidities compared with the PDS group. Seventy seven percent (n = 98) of patients who had PDS and 55% (n = 38) of patients who received NACT had preoperative performance status ASA-1. The PDS arm was significantly more likely to have better PS ($p = 0.002$). The two groups demonstrated no statistically significant differences for poor PS (ASA-3). Approximately 14% of the patients exhibited stage IV disease, while 7% exhibited poor PS, totally.

In our study, pelvic and para-aortic lymph node dissection was performed in 62 of 69 patients (89.8%) who received NACT followed by IDS. The findings of our paper also showed that the patients with no RD who underwent PDS had so much better survival outcomes than the patients who received NACT (79 months versus 68 months, $p < 0.001$). With regard to adverse events within 30 days of surgery, the incidence of complications was found significantly lower in the PDS group, with a morbidity rate of 25.9% compared to 63.7% in the NACT group ($p < 0.001$).

Totally, only 2 patients died within 30 days, one due to intra-operative hemorrhage and the other due to pulmonary failure after surgery. Both deceased patients were in PDS arm compared with none in NACT arm. Median length of hospitalization after surgery was significantly longer in the NACT group than the PDS group (median, 5 days versus 4 days; $p = 0.011$).

Optimal cytoreduction was succeeded in 51 patients (40.2%) in the PDS group versus 35 patients (50.7%) in the NACT group. Complete cytoreduction was obtained in 55 women (13.3%) allocated to PDS versus 23 women (33.3%) in NACT. Despite different radicality of surgery, a comparison of complete and optimal debulking rates between the PDS and NACT groups revealed no significant differences ($p = 0.322$) (Table 1).

The median OS for stage III and IV EOC was remarkably longer for the PDS group than the NACT group (67 months versus 38 months, $p < 0.001$) with 5-year survival rates of 55.9% versus 30.1%, respectively (Fig. 1). Statistics for PFS were significantly in favour of the PDS group with medians of 19 months versus 7 months for the NACT group ($p < 0.001$) (Fig. 2). In stage III patients, the effect of PDS on survival was superior, with a median OS of 70 months for PDS and 38 months for NACT and statistically significant ($p < 0.001$). Furthermore, patients with stage III disease who received NACT exhibited a significantly reduced median PFS compared to those treated with PDS (median, 7 months versus 20 months; $p < 0.001$).

A subgroup analysis was conducted to compare survival outcomes between PDS and NACT based on RD. The volume of RD was prognostic factor in both groups. Median survivals for R0 and optimal debulking surgery were, respectively, 68 and 38 months in patients who received NACT compared with 79 and 72 months in patients who underwent PDS, which were significantly higher in PDS ($p < 0.001$) (Fig. 3). Furthermore, our findings indicated that NACT was related to a significantly decreased OS within the subgroup of patients with stage IIIC for complete and optimal cytoreductive surgery compared with PDS ($p < 0.001$). The median progression-free survivals according to RD between PDS and NACT were as follows: R0, 23 versus 10 months; RD <1 cm, 19 versus 7 months, respectively ($p < 0.001$) (Fig. 4). Considering patients with stage IIIC with complete and optimal cytoreduction, the median PFS was 39 and 23 months in the PDS group which was significantly higher compared to 11 and 7 months in the NACT group ($p < 0.001$).

With regards to adverse events within 30 days after surgery, complications in total was found lower in PDS, significantly (morbidity rates, PDS: n = 33, 25.9% and NACT: n = 44, 63.7%, $p < 0.001$) (Table 2). Specifically, the most common complication was wound infection for NACT arm (n = 7, 10.1%) and ileus for PDS arm (n = 6, 4.7%). In total, in order of frequency, wound infection occurred in 5.1% (n = 10), ileus

TABLE 1. Patient, tumor and procedural characteristics of cytoreductive surgery.

Treatment arm	PDS (N = 127)	NACT (N = 69)	*p*-value
Median age (range)	54 (21–81)	61 (41–79)	<**0.001**
Stage. n (%)			
IIIA	16 (12.6%)	8 (11.5%)	
IIIB	15 (11.8%)	7 (10.1%)	
IIIC	78 (61.4%)	44 (63.7%)	-
IVA	2 (1.6%)	3 (4.3%)	
IVB	16 (12.6%)	7 (10.1%)	
Histology. n (%)			
Serous	104 (81.9%)	65 (94.2%)	
Endometrioid	3 (2.4%)	2 (2.8%)	
Clear cell	4 (3.1%)	2 (2.8%)	
Mucinous	3 (2.4%)	-	-
Undifferentiated	4 (3.1%)	-	
Mixed epithelial	8 (6.3%)	-	
Malign brenner	1 (0.8%)	-	
ASA. n (%)			
1	98 (77.2%)	38 (55.0%)	**0.002**
2	22 (17.3%)	27 (39.1%)	**0.002**
3	7 (5.5%)	4 (5.7%)	
Residual disease. n (%)			
Complete	55 (43.3%)	23 (33.3%)	
Optimal	51 (40.2%)	35 (50.7%)	0.322
Suboptimal	21 (16.5%)	11 (9.0%)	
Recurrence. n (%)			
Yes	95 (74.8%)	67 (97.1%)	**0.003**
No	32 (25.2%)	2 (2.8%)	
Overall mortality			
Yes	75 (59.1%)	57 (82.6%)	<**0.001**
No	52 (40.9%)	12 (17.3%)	
Length of hospitalization			
Median	4	5	**0.011**
Range	1.0–23.0	1.0–24.0	
Bowel resection. n (%)	23 (18.0%)	12 (17.0%)	0.900
Ostomies	11 (8.6%)	6 (8.6%)	0.993

PDS: primary debulking surgery; NACT: neoadjuvant chemotherapy; ASA: American Society of Anesthesiologists. Bold numbers indicate significance.

in 5.1% (n = 10), mood disturbance in 4.5% (n = 9), deep venous trombosis (DVT) in 4.5% (n = 9), pulmonary embolism (PE) in 3.5% (n = 7), abscess in 3.5% (n = 7) and as incisional hernia, which were more common in the NACT group. Table 3 presents the post-operative complications which were classified according to level of the life threat based on Clavien-Dingo Complication Scale. In particular, 1 case of enterocutaneous fistula, 2 acute kidney failure were reported in NACT and 1 rectovaginal fistula was occurred in PDS. Bowel resection rate was 17.3% (n = 12) in NACT and 18.1% (n = 23) in PDS (p = 0.900); additionally, ostomies were performed in 8.6% of women having PDS as in NACT (p = 0.993).

Another notable results were that in case of rate of recurrence and deaths. Until March 2019, recurrence (67 patients (97.1%) in NACT arm and 95 patients (74.8%) in PDS arm) and deaths (57 patients (82.6%) in NACT arm and 75 patients (59.1%) in PDS arm) were higher significantly in patients who received NACT (p = 0.003 and $p < 0.001$; respectively) (Table 1).

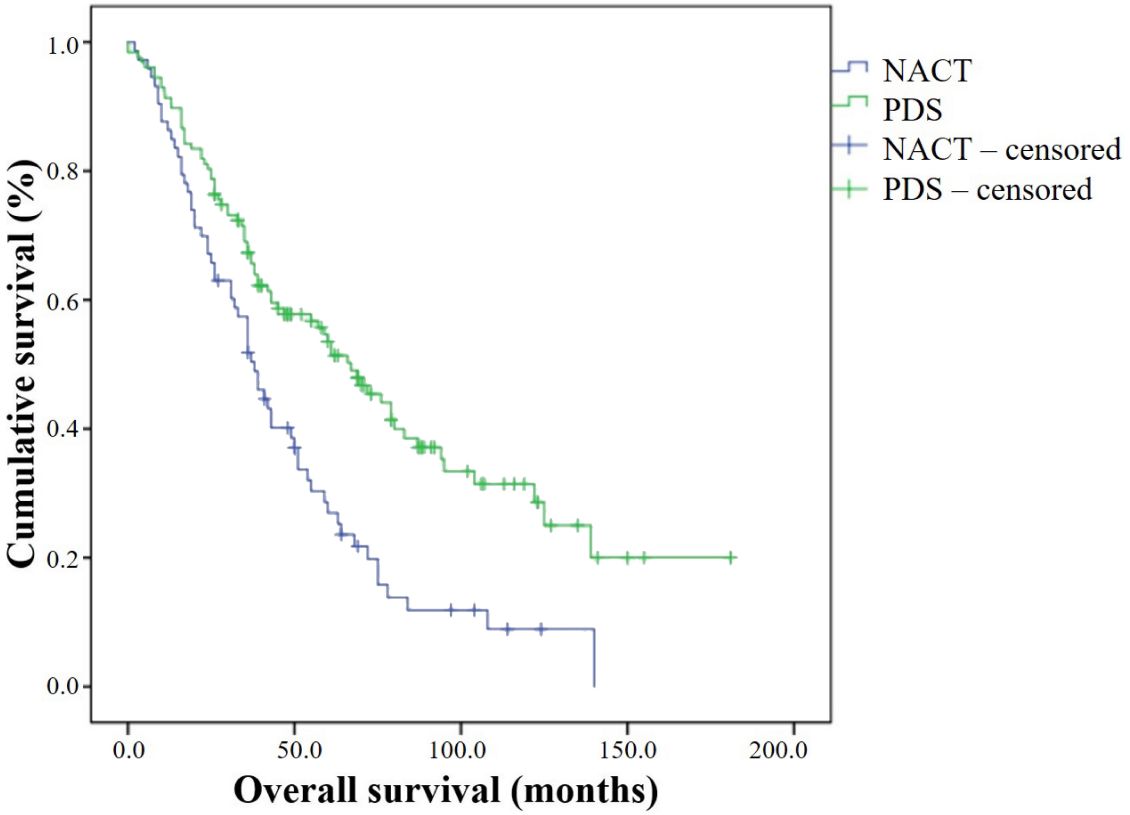

FIGURE 1. Kaplan-Meyer plots for overall survival in PDS and NACT. PDS: primary debulking surgery; NACT: neoadjuvant chemotherapy.

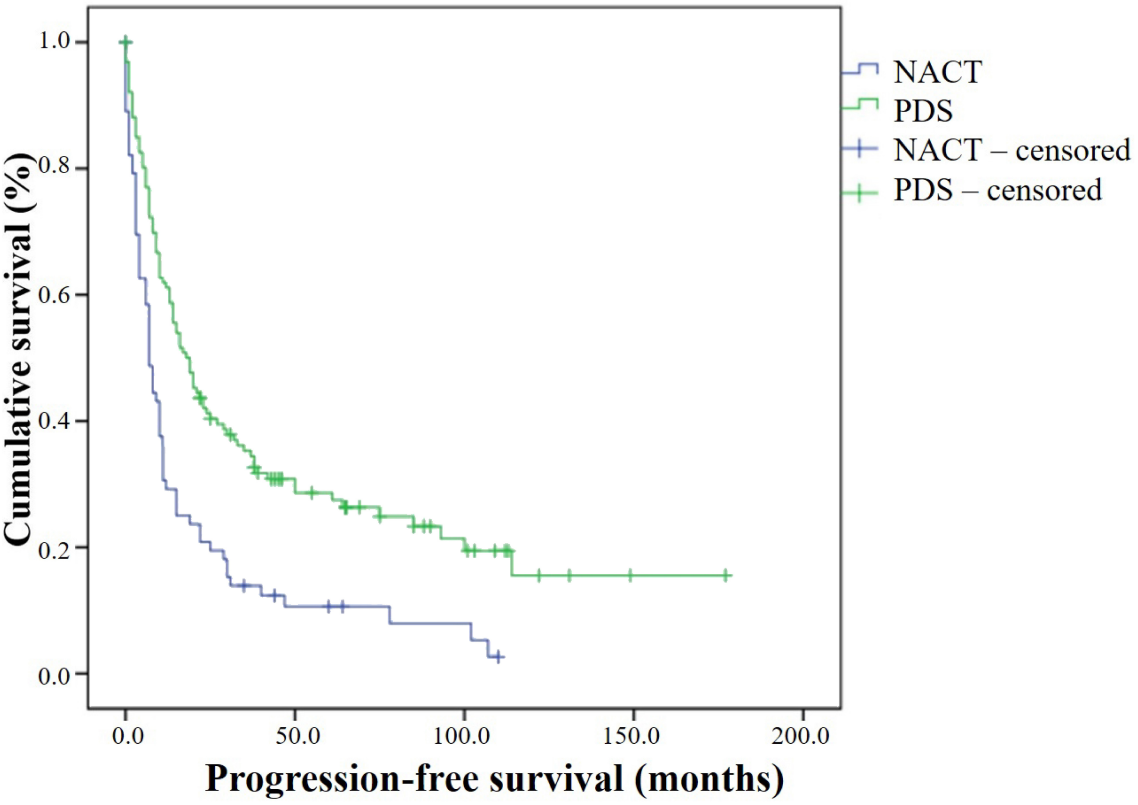

FIGURE 2. Kaplan-Meyer plots for progression-free survival in PDS and NACT. PDS: primary debulking surgery; NACT: neoadjuvant chemotherapy.

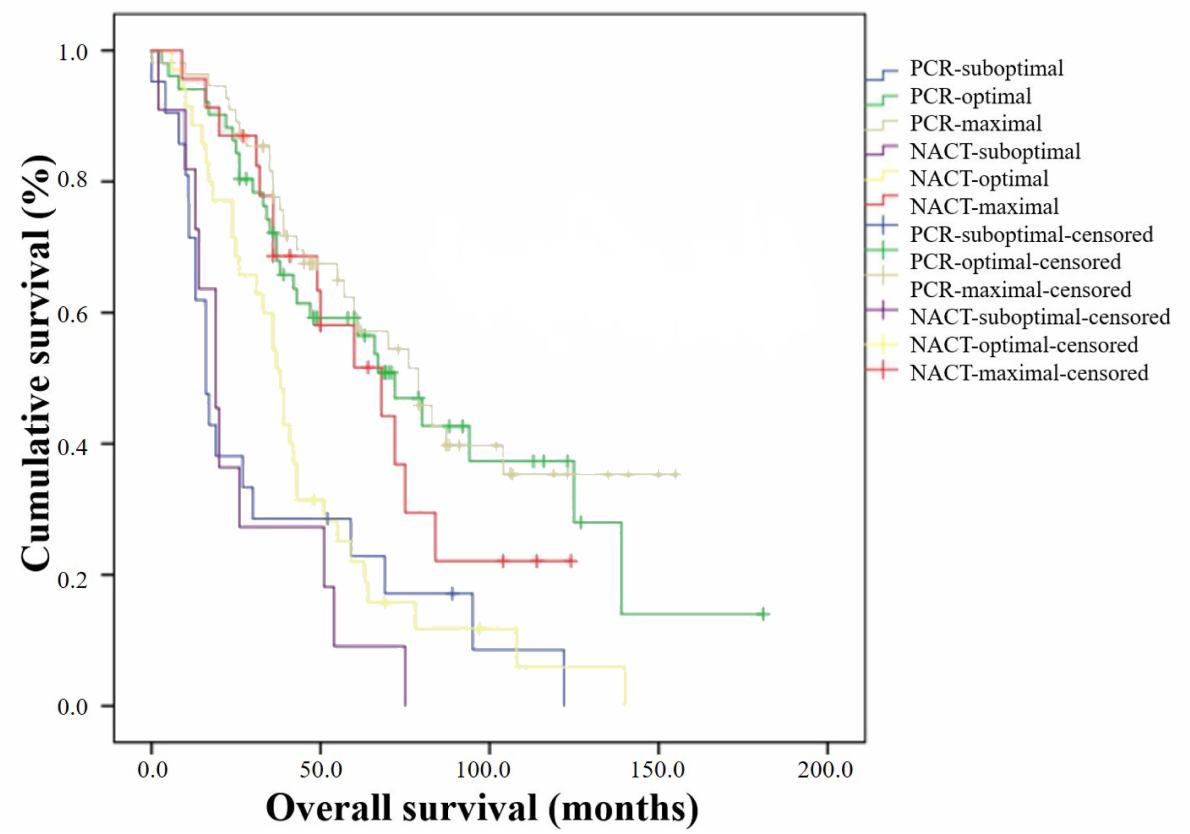

FIGURE 3. Median overall survival by residual disease of patients in NACT and PDS. NACT: neoadjuvant chemotherapy; PCR: primary cytoreductive.

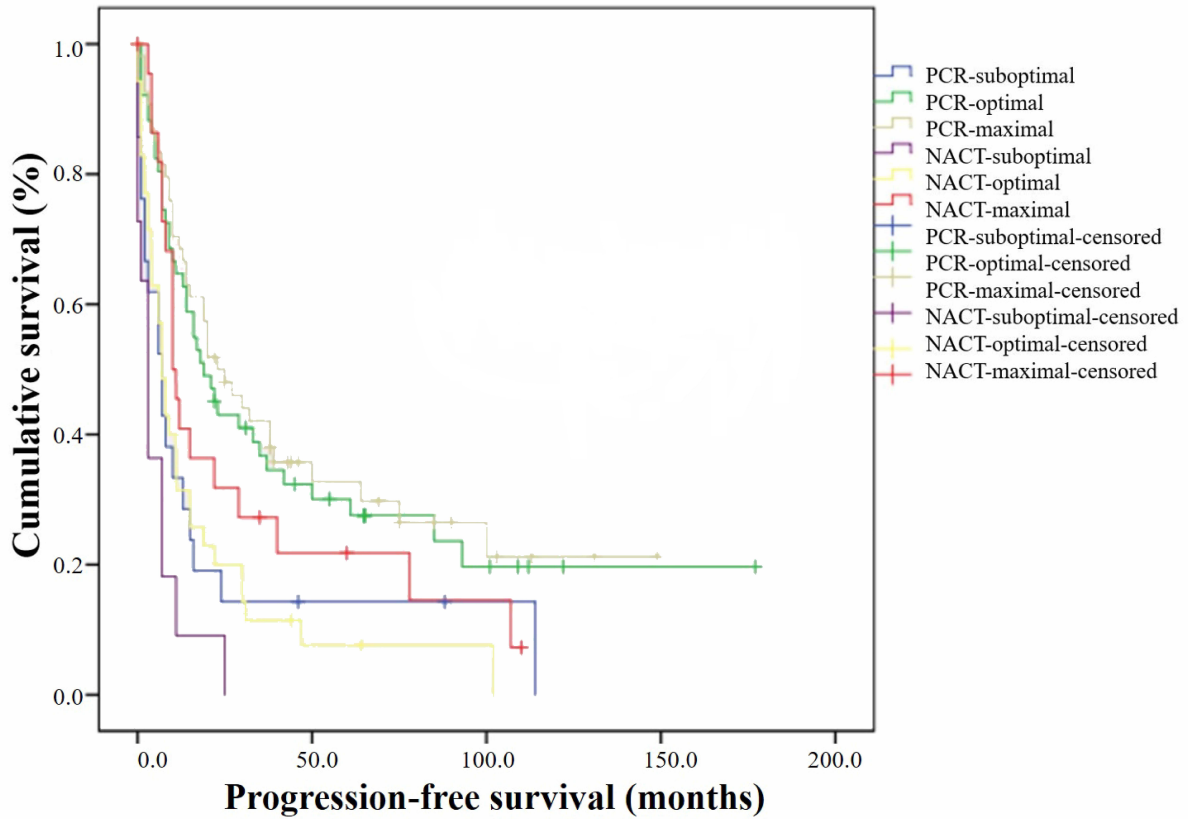

FIGURE 4. Median progression-free survival by residual disease of patients in NACT and PDS. NACT: neoadjuvant chemotherapy; PCR: primary cytoreductive.

TABLE 2. Post-operative complications within 30 days after surgery.

Post-operative complications	PDS (N = 127)	NACT (N = 69)	*p*-value
Average morbidity rate. (%)	2.1%	5.2%	<**0.001**
Ileus	6 (4.7%)	4 (5.7%)	-
Wound infection	3 (2.3%)	7 (10.1%)	-
Deep venous trombosis	4 (3.1%)	5 (7.2%)	-
Mood disturbance	3 (2.3%)	6 (8.6%)	-
Abscess	4 (3.1%)	3 (4.3%)	-
Incisional hernia	4 (3.1%)	3 (4.3%)	-
Pulmonary embolism	2 (1.5%)	5 (7.2%)	-
Post-operative fever	2 (1.5%)	3 (4.3%)	-
Sepsis	2 (1.5%)	3 (4.3%)	-
Cerebrovascular event	2 (1.5%)	2 (2.8%)	-
Acute renal failure	-	2 (2.8%)	-
Fistula	1 (0.7%)	1 (1.4%)	-
Total	33 (25.9%)	44 (63.7%)	

PDS: primary debulking surgery; NACT: neoadjuvant chemotherapy. Bold number indicate significance.

TABLE 3. Post-operative complications within 30 days after surgery according to the Clavien-Dindo Scale.

Post-operative complications	PDS (N = 127)	NACT (N = 69)
Grade I	2 (1.5%)	3 (4.3%)
Grade II	10 (7.8%)	18 (26.0%)
Grade III	15 (11.8%)	11 (15.9%)
Grade IIIA	10 (7.8%)	7 (10.1%)
Grade IIIB	5 (3.9%)	4 (5.7%)
Grade IV	6 (4.7%)	12 (17.3%)
Grade IVA	4 (3.1%)	9 (13.0%)
Grade IVB	2 (1.5%)	3 (4.3%)
Grade V	2 (1.5%)	-

PDS: primary debulking surgery; NACT: neoadjuvant chemotherapy.

4. Discussion

The efficacy of PDS in the treatment of advanced ovarian, primary fallopian tube, or primary peritoneal cancer is well documented. Over the past four decades, numerous investigators have put forth the use of NACT followed by IDS in patients with advanced EOC. However, the results of these investigations have yielded disparate findings regarding the debulking rate due to RD, intra- and post-operative complications and survival [16]. In 1989, NACT was proposed as a potential treatment for advanced, unresectable ovarian tumors [17]. Vergote and colleagues [17] conducted a comparative analysis of the crude survival rates of patients treated before the introduction of NACT in 1989 and afterwards. The retrospective analysis demonstrated that the administration of NACT to a specific subgroup of patients was more efficacious than the administration of primary surgery to all patients [17]. A meta-analysis published by Bristow and Chi and colleagues [17, 18] in 2006 deduced that NACT was associated with a worse prognosis than PDS. A substantial number of investigators concurred that NACT could be an appropriate treatment option for patients with lesions that could be optimally resected [4, 19].

In our retrospective study, we compared PDS followed by chemotherapy and NACT followed by IDS in women with advanced EOC. Patients with stage IVB in the PDS group were selected by only isolated parenchymal liver and/or splenic metastases. Compared with PDS, a survival non-inferiority of NACT was not confirmed in this study. The findings of our study indicate that PDS is associated with a significantly higher survival outcome and lower post-operative complication rates and mortality. These disagree with previous phase III randomized studies; EORTC55971, CHORUS and SCORPION trials [5, 20, 21]. Moreover, NACT failed to show any superiority of PFS in comparison of PDS. Our findings also demonstrated

that PDS improved survival in women with stage IIIC disease significantly, but not for stage IV disease. It is noteworthy that the primary chemotherapy arm was more likely to have a longer length of hospital stay.

The median OS of up to 67 months reported in this study for PDS, in comparison with 41 months in the SCORPION, 29 months in the EORTC and about 23 months in the CHORUS trials [5, 20, 21]. Moreover, the results also showed the superiority of PDS for PFS in our study. Unlikely the above-mentioned trials which showed that NACT is not inferior to PDS [5, 20, 21], in our study, PDS got the advantage over NACT. The possible explanations for the low OS and PFS in the NACT might be based on the older median age, poorer PS and low number of patients. Similiarly, Narasimhulu and colleagues observed that 3-year OS was higher for PDS (64.1% *vs.* 42.6%, $p = 0.001$) [22]. Additionally, another two studies showed similiar results which demonstrated PFS was significantly longer in PDS [12, 13]. On the other hand, in 2020, the JCOG trial demonstrated that compared with PDS, a survival non-inferiority of NACT was not confirmed in this study [23]. The median OS was 49.0 in the PDS group and 44.3 months in the NACT group. They suggested that NACT may not always be a substitute for PDS [23].

The most significant prognostic factor for survival is the extent of residual tumor following PDS or IDS. Vergote and colleagues [19] highlight the crucial question of how to select patients for primary surgery or primary chemotherapy with the objective of achieving complete tumor removal. In the current study the rate of R0 cytoreduction was not significantly different for PDS and NACT groups which were 43.3% and 33.3%, respectively ($p = 0.322$). Unlikely this result was lower compared to NACT groups of the EORTC and CHORUS studies (51% and 39%) were significantly higher than that of their PDS groups (19% and 17%) [5, 20]. Nevertheless, the results of the EORTC study may not be generalisable, given that R0 was achieved in only 19% of patients. Notably, one institution achieved R0 rates of 62%, whereas the other six enrolling institutions had rates of R0 of approximately 10% [3]. Angioli and colleagues [16] showed initial benefit of diagnostic laparoscopy to select the patients for primary chemotherapy or primary surgery and reported that the rate of R0 cytoreduction which was higher in PDS group compared to NACT (96% versus 80%, respectively) directly affects the OS (87% versus 60%, respectively). In 2023, the Dutch study reported similiar result which demonstrated that R0 cytoreduction was significantly higher in PDS than NACT (69.7% *vs.* 62.1%, $p = 0.001$, respectively) [24]. Interestingly, in present study, although the results demonstrated no significant difference for R0 and optimal cytoreduction between groups, median OS and PFS were remarkedly superior in PDS compared to NACT. Similarly, another single institution cohort study, Mayo Clinic Rochester, found that the rate of successful cytoreduction procedure were found to be comparable between the PDS and NACT (complete: 62.5% versus 66.7%, $p = 0.47$ and optimal: 95.3% versus 98%, respectively, $p = 0.36$) but 3-year OS with successful cytoreduction were significantly higher for the PDS group ($p = 0.007$ and $p = 0.02$) [22]. However, in previous prospective randomized trials showed that even maximal cytoreduction rates in the PDS arm are low compared to NACT arm significantly affects the PFS and OS results [5, 21, 25]. On the other hand, in 2014, Rosen and colleagues [2] found that although the R0 resection rate was 41.5% in the PDS group and 50.1% in the NACT group ($p = 0.03$), the median OS was superior in PDS (PDS: 41.1% and NACT: 8.6%, $p < 0.0001$). Similarly, in another multi-institutional randomized clinical trial study, although the R0 resection rate in stage IIIC–IV was superior in the NACT group than the PDS group (38.6% and 20.8%), median OS was 33 months and 43 months for stage IIIC and 31 months and 36 months for stage IV, respectively ($p = 0.04$) [26]. Survival in stage IIIC was more significant in the PDS group but not stage IV [26]. Correlatively, compared to R0 and optimal cytoreduction after surgery in patients with stage IIIC, PDS were significantly associated with better survival benefits in our study. Nevertheless, there was no significant difference for OS and PFS among patients with IV disease ($p = 0.208$). This may be the reason for the small number of patients at this stage of the disease. The possible reason why the OS and PFS rates in our study are different from the literature is that the previous studies are multicentre and especially the maximal cytoreduction rates in the PDS arm vary greatly between countries, which may cause PDS to be negatively affected in terms of PFS and OS.

As we know so far risk of recurrence directly with the extent of RD after surgery [2]. Successful complete resection has a favourable effect on the prognosis even after the occurrence of recurrent disease. Although there was no difference for optimal and maximal cytoreduction between both groups in our study, recurrence rate was found remarkably greater in NACT than PDS. This finding supports the importance of the RD after surgery.

Another endpoint was 30-day post-operative complications in our study. Our results demonstrated that the NACT procedure was associated with significantly higher morbidity rates. Especially, wound infection, mood disturbance, deep venous trombosis, pulmonary embolism and ileus were the more common complications compared to PDS arm; this outcome may be due to: older age and higher co-morbidities. Post-operative adverse events probably affected the length of hospital stay which was notably superior in NACT arm. By contrast, several studies have reported lower early post-operative complications in NACT [5, 20, 21]. Similarly, in the SCORPION trial [14], whom peri-operative complications were graded on a I–IV scale according to the Memorial Sloan Kettering Cancer Center, post-operative adverse events grade III–V was significantly lower in the NACT group (52.7% versus 5.7%, $p = 0.0001$) in comparison to the JCOG0602 study, which demonstrated a reduction in the frequency of post-operative complications [27]. In SCORPION trial, the most common complication was grade III and consisted of pleural effusion which was significantly higher in PDS arm ($p = 0.0001$) [14]. Three grade IV and two grade V complications were observed in only PDS arm. Unlikely, in our study, the most common grade of complication was II and consisted of wound infection in the context of NACT. The PDS group exhibited the highest incidence of grade 3 complications, with ileus representing the most prevalent among these adverse events. On the other hand, grade IV complication was observed in a total of two patients,

all of whom were in the PDS group as well as SCORPION trial. The SCORPION [14] and the JCOG0602 [27] studies also found that the length of hospitalization was shorter in favour of NACT. On the other hand, another cohort study, which is inconsistent with the literatures, showed similar short term outcomes [22]. Extend of the surgery, high tumor burden, surgical complexity and post-operative care may affect post-operative complications.

Our study has limitations including that the data was retrospective and from a single center, not a randomized trial, a potential selection bias and heterogenous group of ovarian cancer (*i.e.*, stage IIIA and IIIB, non-serous histology). We did not observe aggressive surgery effect. In addition, the number of patients was small in NACT group and stage IV in both groups. The present study's strength lies in its ability to demonstrate that older age and poor PS are another important factors that affect survival even if the RD is similar in both groups.

5. Conclusions

In conclusion, maximal cytoreduction is generally accepted as one of the strongest predictors of survival outcome in patients with advanced stage EOC [8]. In cases in which treatment planning cannot be decided as a result of preoperative radiological examination before PDS and NACT, diagnostic laparoscopy should be performed based on the Fagotti scoring system to more precisely understand the extent of the disease and the possibility of resectability. In current study, patients were distributed into either a PDS group or an NACT group based on the results of a preoperative radiological examination, their performance status, and the presence of co-morbidities. In instances where a definitive treatment plan could not be established, diagnostic laparoscopy was conducted in accordance with the Fagotti PIV to gain a more precise understanding of the extent of the disease and the potential for resectability. The proposed advantages of NACT include increased optimal RD rate, less aggressive surgery, less blood loss, lower morbidity, reduced length of hospital stay, better quality of life and selection of patients with platinum-resistant disease [28]. Generally, patients with stage IIIC should receive PDS as standard treatment. The results of our study demonstrated that women with no RD who underwent PDS exhibited significantly superior survival outcomes compared to women who received NACT. We agree with the position of Chi and colleagues [15] that the objective of PDS should be removal all visible tumor. Furthermore, if necessary, more aggressive surgical techniques should be employed [15]. We respectfully disagree with Vergote and colleagues [19] that NACT and PDS have a similar outcome. We recommend that NACT may be preferred in patients with poor PS, high unresectable tumor burden and who cannot undergo R0 resection in stage IIIC–IV.

AVAILABILITY OF DATA AND MATERIALS

The data underpinning the findings of this study can be obtained from the corresponding author, TS, upon a reasonable request.

AUTHOR CONTRIBUTIONS

UFO—project development, management/editing. ST—management/editing. TS—data collection, data analysis, manuscript writing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the institutional Ethics Committee of Ankara University Faculty of Medicine (approval number: 09-575-18). Consents were obtained from all participants included in the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Colombo N, Gadducci A, Landoni F, Lorusso D, Sabbatini R, Artioli G, *et al.* Consensus statements and treatment algorithm to guide clinicians in the selection of maintenance therapy for patients with newly diagnosed, advanced ovarian carcinoma: results of a Delphi study. Gynecologic Oncology. 2023; 175: 182–189.

[2] Rosen B, Ferguson S, Laframboise S, Dodge J, Bernardini M, Murphy J, *et al.* The impacts of neoadjuvant chemotherapy and of debulking surgery on survival from advanced ovarian cancer. Gynecologic Oncology. 2014; 134: 462–467.

[3] Horowitz NS, Miller A, Rungruang B, Richard SD, Rodriguez N, Bookman MA, *et al.* Does aggressive surgery improve outcomes? Interaction between preoperative disease burden and complex surgery in patients with advanced-stage ovarian cancer: an analysis of GOG 182. Journal of Clinical Oncology. 2015; 33: 937–943.

[4] Thrall MM, Gray HJ, Symons R, Weiss NS, Flum DR, Goff BA. Neoadjuvant chemotherapy in the medicare cohort with advanced ovarian cancer. Gynecologic Oncology. 2011; 123: 461–466.

[5] Kehoe S, Hook J, Nankivell M, Jayson GC, Kitchener H, Lopes T, *et al.* Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. The Lancet. 2015; 386: 249–257.

[6] Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, *et al.*; European Organization for Research and Treatment of Cancer-Gynaecological Cancer Group; NCIC Clinical Trials Group. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. The New England Journal of Medicine. 2010; 363: 943–953.

[7] Bristow RE, Chi DS. Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis. Gynecologic Oncology. 2006; 103: 1070–1076.

[8] Kang S, Nam BH. Does neoadjuvant chemotherapy increase optimal cytoreduction rate in advanced ovarian cancer? Meta-analysis of 21 studies. Annals of Surgical Oncology. 2009; 16: 2315–2320.

[9] Fagotti A, Vizzielli G, Ferrandina G, Fanfani F, Galotta V, Chiantera V, *et al.* Survival analyses from a randomized trial of primary debulking

surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer with high tumor load (SCORPION trial). Journal of Clinical Oncology. 2018; 36: 5516.

[10] Onda T, Satoh T, Saito T, Kasamatsu T, Nakanishi T, Takehara K, *et al.* Comparison of survival between upfront primary debulking surgery versus neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomized trial: JCOG0602. Journal of Clinical Oncology. 2018; 36: 5500.

[11] Lee YJ, Chung YS, Lee J, Nam EJ, Kim SW, Kim YT, *et al.* Role of diagnostic laparoscopy in deciding primary treatment in advanced-stage ovarian cancer. Journal of Clinical Oncology. 2023; 34: e17.

[12] Chandy RG, Thomas V, Sebastian A, Mani T, Thomas A, Joel A, *et al.* Survival outcomes of epithelial ovarian cancer treated at a tertiary level hospital in India. Indian Journal of Cancer. 2023; 60: 475–485.

[13] Ehmann S, Shay K, Zhou Q, Iasonos A, Sonoda Y, Gardner GJ, *et al.* Outcomes and long-term follow-up by treatment type for patients with advanced-stage ovarian cancer managed at a tertiary cancer center: a memorial sloan kettering cancer center team ovary study. Gynecologic Oncology. 2023; 169: 118–124.

[14] Fagotti A, Ferrandina G, Vizzielli G, Fanfani F, Galotta V, Chiantera V, *et al.* Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): final analysis of peri-operative outcome. European Journal of Cancer. 2016; 59: 22–33.

[15] Chi DS, Musa F, Dao F, Zivanovic O, Sonoda Y, Leitao MM, *et al.* An analysis of patients with bulky advanced stage ovarian, tubal, and peritoneal carcinoma treated with primary debulking surgery (PDS) during an identical time period as the randomized EORTC-NCIC trial of PDS *vs.* neoadjuvant chemotherapy (NACT). Gynecologic Oncology. 2012; 124: 10–14.

[16] Angioli R, Innocenza P, Marzio AZ, Ludovico M, Natalina M, Marco C, *et al.* Diagnostic open laparoscopic in the management of advanced ovarian cancer. Gynecologic Oncology. 2006; 100: 455–461.

[17] Van Meurs HS, Tajik P, Hof MHP, Vergote I, Kenter GG, Mol BWJ, *et al.* Which patients benefit most from primary surgery or neoadjuvant chemotherapy in stage IIIC or IV ovarian cancer? An exploratory analysis of the european organisation for research and treatment of cancer 55971 randomised trial. European Journal of Cancer. 2013; 49: 3191–3201.

[18] Chi DS, Bristow RE, Armstrong DK, Karlan BY. Is the easier way ever the better way? Journal of Clinical Oncology. 2011; 29: 4073–4075.

[19] Vergote I, Trope CG, Amant F, Ehlen T, Reed NS, Casado A. Neoadjuvant chemotherapy is the better treatment option in some patients with stage IIIc to IV ovarian cancer. Journal of Clinical Oncology. 2011; 29: 4076–4078.

[20] Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, *et al.* Neoadjuvant chemotherapy or primary surgery in stage IIIc–IV ovarian cancer. The New England Journal of Medicine. 2010; 363: 943–953.

[21] Fagotti A, Ferrandina MG, Vizzielli G, Pasciuto T, Fanfani F, Gallotta V, *et al.* Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850). International Journal of Gynecological Cancer. 2020; 30: 1657–1664.

[22] Narasimhulu DM, Thannickal A, Kumar Amanika, Weaver AL, McGree ME, Langstraat CL, *et al.* Appropriate triage allows aggressive primary debulking surgery with rates of morbidity and mortality comparable to interval surgery after chemotherapy. Gynecologic Oncology. 2021; 160: 681–687.

[23] Onda T, Satoh T, Ogawa G, Saito T, Kasamatsu T, Nakanishi T, *et al.* Comparison of survival between primary debulking surgery and neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomised trial. European Journal of Cancer. 2020; 130: 114–125.

[24] Tewarie NMS, Van Driel WJ, Van Ham M, Wuters MW, Kruitwagen R; Participants of the Dutch Gynecological Oncology Collaborator Group. Postoperative outcomes of primary and interval cytoreductive surgery for advanced ovarian cancer registered in the dutch gynecological oncology audit (DGOA). Gynecologic Oncology. 2021; 162: 331–338.

[25] Vergote I, Coens C, Nankivell M, Kristensen GK, Parmar MKB, Ehlen T, *et al.* Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials. The Lancet Oncology. 2018; 19: 1680–1687.

[26] Meyer LA, Cronin AM, Sun CC, Bixel K, Bookman MA, Cristea MC, *et al.* Use and effectiveness of neoadjuvant chemotherapy for treatment of ovarian cancer. Journal of Clinical Oncology. 2016; 34: 3854–3863.

[27] Onda T, Satoh T, Saito T, Kasamatsu T, Nakanishi T, Nakamura K, *et al.* Comparison of treatment invasiveness between upfront debulking surgery versus interval debulking surgery following neoadjuvant chemotherapy for stage III/IV ovarian, tubal, and peritoneal cancers in a phase III randomised trial: Japan Clinical Oncology Group Study JCOG0602. European Journal of Cancer. 2016; 64: 22–31.

[28] Morrison J, Haldar K, Kehoe S, Lawrie TA. Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer. Cochrane Database of Systematic Reviews. 2007; CD005343.

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