ORIGINAL ARTICLE

Effect of neoadjuvant chemotherapy on primary and metastatic tumour burden in epithelial ovarian cancer: a retrospective analysis of oncologic surgeries at a university hospital

Neoadjuvant chemotherapy in ovarian cancer

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ABSTRACT

Objective. To assess the effect of neoadjuvant chemotherapy (NACT) on pathological tumour burden in the primary tumour site and metastatic regions in patients with advanced epithelial ovarian cancer (EOC).

Materials and Methods. This retrospective study included FIGO stage III–IV EOC patients who underwent either primary debulking surgery (PDS) or NACT followed by interval debulking surgery (IDS). Tumor involvement in the ovaries (primary site) and other anatomical locations (metastatic sites) was recorded separately. Pre-treatment CA-125 levels and postoperative pathological findings were compared between groups.

Results. Seventy-six patients were evaluated (36 NACT+IDS, 40 PDS). Pre-treatment CA-125 levels were significantly higher in the NACT group. Although direct quantitative measurement of tumour burden was not performed, NACT-treated patients showed a marked decrease in CA-125 levels and a clinically evident reduction in tumour volume at IDS. Pathological assessment revealed lower tumour involvement in the ovaries after NACT, whereas metastatic site involvement remained comparable between the groups.

Conclusions. NACT may reduce primary tumour burden and facilitate cytoreductive surgery; however, its effect on metastatic regions appears limited. These findings support the possibility that biological heterogeneity may contribute to regional differences in chemotherapy response. Given the retrospective design, limited sample

size, and absence of standardized histopathologic response scoring or molecular profiling, prospective multicentre studies incorporating detailed molecular characterization are required to better elucidate NACT response patterns in EOC.

Key words

Epithelial ovarian cancer; neoadjuvant chemotherapy; cytoreductive surgery.

Introduction

Ovarian cancer (OC) is the fifth leading cause of cancer-related death among women [1]. Despite advances in treatment, five-year survival rates for advanced-stage OC have shown limited improvement over the past decade.

For FIGO stage III–IV patients, primary debulking surgery (PDS) is the standard initial treatment. Since the 2012 NCCN guideline recommended neoadjuvant chemotherapy (NACT) with interval debulking surgery (IDS) for high-risk surgical candidates, the use of NACT has increased [2–5]. NACT reduces surgical morbidity and improves optimal cytoreduction rates; however, randomized trials have not shown a clear advantage of NACT over PDS in progression-free or overall survival [2, 6–8].

Only a limited number of studies have evaluated the pathological response to NACT in epithelial ovarian cancer (EOC). These studies have employed various histopathologic assessment tools, such as pathological complete response (pCR) and chemotherapy response scoring (CRS), and have shown improved outcomes in patients achieving pCR. Nevertheless, pCR rates in EOC remain low, generally ranging from 0% to 4–14% [6, 8–11]. Accurate pCR assessment is difficult because IDS often requires extensive tissue removal. Moreover, no comprehensive study has compared NACT response between the primary tumor and different metastatic sites.

EOC exhibits biological and genetic heterogeneity, supported by its ability to spread through hematogenous, lymphatic, and direct invasion pathways. This heterogeneity may contribute to regional variations in chemotherapy response. Recent studies highlighting promising results with inhibitors targeting the BRAF and MEK pathways [12] and the established roles of BRCA1/2 mutations and homologous recombination deficiency (HRD) in mediating chemotherapy sensitivity [13], underscore the growing importance of tumor biology in guiding therapeutic decision-making.

Given that diverse metastatic pathways may reflect underlying molecular heterogeneity, which could influence regional chemotherapy response, this study aimed to evaluate the pathological effects of NACT separately in the primary tumor and in distinct metastatic sites.

Patients and Methods

This retrospective study included patients with advanced-stage epithelial ovarian cancer who were treated at the Department of Obstetrics and Gynecology, Hacettepe University,

between 01/01/2009 and 01/05/2017. Patients with a diagnosis of FIGO stage III–IV epithelial ovarian cancer were included in the study. The diagnosis was confirmed by biopsy, cytological evaluation, or histopathological examination of surgical specimens. Patients with non-epithelial ovarian tumors, incomplete clinical data, unavailable pathology specimens, or those whose initial surgery or pathological evaluation had been performed at another institution were excluded

Patients were divided into two groups: those who underwent interval debulking surgery (IDS) after neoadjuvant chemotherapy (NACT) and those who underwent primary debulking surgery (PDS). NACT consisted of paclitaxel plus carboplatin administered every three weeks according to standard protocols. Most patients received three cycles; however, four or more cycles were given when clinically indicated.

All surgical specimens were evaluated by gynecologic pathologists. The ovaries and fallopian tubes were considered the primary tumor site. Metastatic sites included the omentum, peritoneal surfaces, pelvic and paraaortic lymph nodes, peritoneal implants, and solid organ metastases. For each anatomical region, tumor involvement was recorded as present or absent. No quantitative scoring system was used; assessment was based on tumor positivity in the primary site and in metastatic regions.

Clinical, laboratory, surgical, and pathological data were retrieved retrospectively from the hospital's electronic medical record system. The study was approved by the Hacettepe University Faculty of Medicine Clinical Research Ethics Committee (Date: 16/05/2017, Approval No:GO 17/456-44). Owing to the retrospective design, additional informed consent was not required; all data were anonymized and evaluated in accordance with the principles of the Declaration of Helsinki. Demographic characteristics, CA-125 levels at diagnosis, surgical findings, and pathological outcomes were compared between groups. Tumor involvement in the primary and metastatic sites was analyzed separately for both groups.

Statistical analysis

Statistical analyses were performed using SPSS software (IBM SPSS Statistics for Windows, Version 23.0; IBM Corp., Armonk, NY, USA). The normality of distribution was assessed with the Kolmogorov–Smirnov test. Numerical variables with normal distribution were presented as mean ± standard deviation, whereas non-normally distributed variables were presented as median (min–max). Categorical variables were expressed as frequencies and percentages.

The Mann–Whitney U test was used for comparisons of non-normally distributed numerical variables. The Wilcoxon signed-rank test was applied for paired non-normally distributed variables. Pearson's chi-square test or Fisher's exact chi-square test was used for comparisons of categorical variables, as appropriate.

Results

Between 01/01/2009 and 01/05/2017, data from 383 patients who underwent surgery for ovarian cancer at our institution were identified through the pathology database. Of the 52 patients who had received neoadjuvant chemotherapy (NACT), 16 were excluded because IDS could not be completed or relevant data were unavailable. The study group (NACT–IDS) consisted of 36 patients, and the control group included 40 patients who underwent primary debulking surgery (PDS).

The demographic characteristics of the patients are presented in Table 1. The median CA-125 level at diagnosis was 1387 in the NACT–IDS group and 301.5 in the PDS group. CA-125 levels were significantly higher in the NACT group ($p < 0.001$). Among the patients receiving NACT, 8 received four or more cycles, while 28 received three cycles; no patient received fewer than three cycles. All patients were treated with a paclitaxel–carboplatin regimen.

Based on the final pathological evaluation, histologic diagnoses were categorized as serous epithelial carcinoma or other histologic subtypes. In the NACT–IDS group, 32 patients (88.9%) had serous histology and 4 patients (11.1%) had non-serous tumors. In the PDS group, 25 patients (62.5%) had serous histology and 15 patients (37.5%) had other histologic subtypes. Although serous tumours were more frequent in the NACT group, this difference was not statistically significant ($p = 0.08$) (Table 2).

CA-125 values for the NACT–IDS and PDS groups are presented in Tables 3, 4, and 5. At diagnosis, CA-125 levels were significantly higher in the NACT–IDS group compared with the PDS group ($p < 0.001$). In the NACT group, CA-125 levels measured after completion of chemotherapy were significantly lower than the baseline diagnostic values ($p < 0.001$). When preoperative CA-125 levels were compared, the NACT–IDS group had significantly lower values than the PDS group ($p < 0.001$).

Tumour involvement in the ovaries, omentum, peritoneum, and retroperitoneal lymph nodes was assessed in both groups (Table 6). Among the 36 patients in the NACT–IDS group, ovarian involvement was present in 20 patients (55.6%) and absent in 16 patients (44.4%). In the PDS group, ovarian involvement was observed in 37 of 40 patients (92.5%), while 3 patients (7.5%) had no ovarian disease. Ovarian involvement was significantly lower in the NACT–IDS group ($p < 0.001$).

There were no statistically significant differences between the two groups regarding tumour involvement of the peritoneum, omentum, pelvic lymph nodes, or paraaortic lymph nodes (Table 6)

Discussion

In this study, we evaluated the effect of neoadjuvant chemotherapy (NACT) on the primary tumour and metastatic sites in epithelial ovarian cancer (EOC). Although NACT substantially reduced overall tumour burden, our findings indicate that it did not achieve complete pathological response in most metastatic regions.

Previous studies have shown that NACT reduces postoperative morbidity without compromising survival and offers surgical advantages such as reduced blood loss, shorter operative time and hospitalization, and higher rates of optimal cytoreduction [14–16]. These benefits have largely been attributed to a decrease in tumour burden. Although we did not directly quantify tumour burden in our cohort, intraoperative assessments during interval debulking surgery revealed a notable reduction in tumour volume compared with initial surgical biopsies. In addition, CA-125 levels demonstrated a significant decline after NACT, further supporting its effect on tumour burden reduction.

The number of studies evaluating the pathological response to NACT in EOC is limited. Existing reports have used various scoring systems, including pathological complete response (pCR) and chemotherapy response scoring (CRS), to assess treatment response [2-4,5,7,9,14]. Although pCR has been associated with improved prognosis, pCR rates in ovarian cancer remain low, typically ranging between 0% and 4–14% [2–6, 7, 8, 10, 17]. Consistent with prior literature, no cases of pCR were observed in our study. This finding may be attributable to chemotherapy resistance arising from underlying biological heterogeneity.

To date, no comprehensive study has directly compared the response to NACT at the primary tumour site versus different metastatic regions. In our analysis, ovarian involvement was significantly lower in the NACT group, suggesting a more pronounced response in the primary tumour site. Although biological or vascular differences in the primary tumour region may contribute to this finding, further molecular and histopathological investigations are needed to clarify the underlying mechanisms.

In 2015, Böhn et al. introduced a chemotherapy response score (CRS) to evaluate treatment response in omental implants, demonstrating that higher CRS scores were associated with improved progression-free and overall survival. They also suggested that chemotherapy sensitivity may be more prognostically relevant than the extent of cytoreduction. [17]. However, that study did not extensively evaluate response patterns across the primary tumour and all metastatic sites. In our study, while the primary tumour demonstrated a more favourable response to NACT, persistent tumour positivity in metastatic regions indicates that assessing pathological response in each site separately may have clinical relevance. Given the capacity of EOC to metastasize through multiple pathways, different genetic variants may emerge in distinct metastatic locations, potentially contributing to varied levels of chemotherapy resistance. Indeed, recent studies highlight the roles of BRCA1/2 mutations and homologous recombination deficiency (HRD) in shaping chemotherapy sensitivity and may help explain regional differences in treatment response [13]. Similarly, molecular investigations of the BRAF and MEK pathways offer additional insight into resistance mechanisms observed in certain metastatic areas [12].

Sokolenko et al. examined tumour tissue before and after NACT in BRCA1-mutated patients and reported that, in 11 of 17 cases, post-treatment residual tumour consisted predominantly of cells retaining BRCA function [18]. The authors suggested that this pattern reflects clonal selection of BRCA-proficient, chemotherapy-resistant cells rather

than acquisition of new mutations [18]. This finding implies that continuing platinum-based therapy in tumours that have developed resistance may yield limited benefit. As cancer treatment is a dynamic process, adapting therapeutic strategies according to biological response may improve long-term outcomes. While NACT in our study did not achieve complete response in all tumour regions, this should not be viewed solely as treatment failure. Instead, early identification of chemotherapy resistance may offer an opportunity to modify treatment regimens and guide the development of more effective personalized therapies.

Conclusions. Our study demonstrates that although neoadjuvant chemotherapy (NACT) leads to a marked reduction in overall tumour burden, its effect on metastatic sites appears limited. Given its retrospective design, small sample size, and the absence of long-term follow-up and survival data, these findings should be interpreted with caution. Furthermore, the lack of detailed histopathologic response scoring and molecular profiling restricts a more comprehensive evaluation of the biological response to NACT.

To better understand the clinical relevance of the differing response patterns observed in primary and metastatic tumour sites, prospective multicentre studies incorporating molecular biomarkers (including BRCA/HRD status and other genetic alterations) and standardized histopathologic response scoring are needed. Such studies may help identify mechanisms of chemotherapy resistance at an earlier stage and contribute to the development of personalized treatment strategies, facilitating timely integration of emerging targeted therapies.

Compliance with Ethical Standards

Authors' Contributions
H.H.U.: Conceptualization, Data curation, Writing – original draft.
M.C.S.: Methodology, Formal analysis, Supervision, Writing – review & editing.
K.Y.: Investigation, Validation, Writing – review & editing.

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Study Registration
Not applicable.

Disclosure of Interests
The authors declare that they have no conflicts of interest.

Ethical Approval
This retrospective study was approved by the Institutional Review Board of Hacettepe University (Date: 16/05/2017, Approval No:GO 17/456-44). All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed Consent
This study was based on retrospective analysis of anonymized patient data. Informed consent was waived by the Institutional Review Board.

Data Sharing
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Table 1. Demographic characteristics of patients in the NACT-IDC and PDC groups

Characteristic	Study Group	Control Group
Age (median)	60	55,5
Menopausal status		
– Perimenopausal	9	9
– Postmenopausal	27	31
CA-125 at diagnosis (median)	1341,50	267,50
CA-125 at diagnosis (mean)	2881,21	783,69
Number of NACT cycles		
– 3 cycles	28	0
– 4 or more cycles	8	0

Table 2. Histological subtypes in patients undergoing NACT-IDC versus PDC

Histological Type	NACT Group	PDS Group	Pearson Chi-Square

Serous carcinoma	32 (%86,9)	25 (%62.5)	0.008
Other histologies	4 (%11,1)	15 (%37,5)	0.008

Table 3. CA-125 levels at diagnosis in NACT-IDC and PDC groups

CA-125	**NACT-IDC**	**PDS**	**p-value**
Minimum	152	7	
Maximum	19716	4575	
Median	1387	301,50	<0,001

Table 4. Pre- and post-NACT CA-125 levels in the NACT-IDC group

CA-125	**At Diagnosis**	**Post-NACT**	**p-value**
Minimum	152	4	
Maximum	19716	2464	
Median	1387	33,5	<0,001

Table 5. CA-125 levels before debulking surgery in NACT-IDC versus PDC groups

CA-125	**Post-NACT**	**PDS**	**p-value**
Minimum	4	7	
Maksimum	2464	4575	
Median	33,5	301,50	<0,001

Table 6. Tumor distribution in primary and metastatic sites between NACT-IDC and PDC groups

	Anatomical Site	**NACT Group**	**PDS Group**	**p-value**
Ovarian mass	Positive	20(%55,6)	37(%92,5)	<0,001

	Negative	16(%44,4)	3(%7,5)	<0,001
Omental mass	Positive	23(%63,9)	17(%42,5)	0,062
	Negative	13(%36,1)	23(%57,5)	0,062
Peritoneal mass	Positive	28(%77,8)	23(%57,5)	0,06
	Negative	8(%22,2)	17(%42,5)	0,06
Pelvic lymph node	Positive	9(%25)	11(%27,5)	0,805
	Negative	27(%75)	29(%72,5)	0,805
Paraaortic lymph node	Positive	12(%33,3)	12(%30)	0,755
	Negative	24(%66,7)	28(%70)	0,755