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Original article

Neoadjuvant chemotherapy followed by interval debulking surgery versus primary debulking surgery in advanced ovarian carcinoma

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Background: Ovarian cancer represents the sixth most commonly diagnosed cancer among women in the world and causes more deaths per year than any other cancer of the female reproductive system. Most patients with epithelial ovarian carcinoma present with advanced disease (International Federation of Gynecology and Obstetrics (FIGO) stage IIIc or IV). Primary debulking surgery (PDS) followed by chemotherapy is the standard treatment for ovarian cancer. Neoadjuvant chemotherapy followed by interval debulking surgery (IDS) could be an alternative treatment for these patients.

Objective: In the current work, we compared between primary debulking surgery and neoadjuvant chemotherapy followed by interval debulking surgery with the overall and progression free survival as primary end points and surgical morbidity as a secondary end point.

Methods: a prospective randomized study was conducted on 50 patients with histopathologically proven epithelial ovarian cancer with advanced stage (IIIb /IIIc). The patients were randomly assigned either to primary debulking surgery followed by chemotherapy (paclitaxel-carboplatin) (PDS group; $n = 25$) or to three to six courses of neoadjuvant chemotherapy (paclitaxel-carboplatin) followed by interval debulking surgery in all patients who achieved response or even stable disease (NACT group; n=20/25).

Results: Optimal cytoreduction was performed in 52% in PDS group & 55% in NACT group with insignificant P value (0.84). The results of surgical parameters of cytoreduction in both groups showed no significant differences as regard the mean operative duration, the blood loss rates (number of transfused blood units), and the length of postoperative hospital stay. Moreover, there was no difference between the postoperative complications in both groups. The median overall survival time was not statistically different ($P = 0.55$) in both treatment arms (29 vs 30 months, respectively). Longer median progression free survival in the NACT group in comparison to the PDS group (22 vs 19 months, respectively) was detected, but it didn't reach statistical significance (P=0.11).

Conclusions: Despite that primary cytoreductive surgery is considered the standard of care for advanced ovarian carcinoma, neoadjuvant chemotherapy is not inferior to primary cytoreductive surgery for patients with advanced stage ovarian carcinoma.

Key words: Ovarian Cancer-Neoadjuvant Chemotherapy-Oncosurgery.
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INTRODUCTION

Ovarian cancer represents the sixth most commonly diagnosed cancer among women in the world and causes more deaths per year than any other cancer of the female reproductive system[1]. Most patients with epithelial ovarian carcinoma present with advanced disease (International Federation of Gynecology and Obstetrics (FIGO) stage IIIc or IV)[2]. Primary debulking surgery (PDS) followed by chemotherapy is the standard treatment for ovarian cancer. The goal of PDS is optimal cytoreduction, usually defined as surgery with residual disease (RD) < 1 or < 2 cm in diameter[3]. There is agreement that one of the most important prognostic factors for survival in the treatment of ovarian cancer is the amount of residual tumor after cytoreduction[4]. Unfortunately, optimal cytoreduction for advanced ovarian cancer is achieved in only 30-60% of the patients at most institutions[5]. One reason for this low rate is that patients with advanced ovarian cancer are often poor candidates for aggressive surgery because of low performance status (PS) caused by massive ascites, pleural effusion and large abdominal tumors at time of primary surgery[3]. An alternative treatment for these patients could be neoadjuvant chemotherapy (NAC)[6], followed by interval debulking surgery (IDS) and further chemotherapy for patients with low PS and those with apparently unresectable tumors evaluated

with computed tomography (CT) or laparoscopy[3]. Several retrospective studies revealed comparable results by the NAC setting treatments with standard treatment[7-9], and few prospective feasibility studies[10-12] revealed promising results by NAC setting treatment. Taking into account these favorable outcomes, several prospective clinical trials compared this treatment with the standard treatment for advanced ovarian cancer[2,3]. In the current work, we compared between primary debulking surgery followed by adjuvant chemotherapy and neoadjuvant chemotherapy followed by interval debulking surgery with the overall and progression free survival as primary end points and surgical morbidity as a secondary end point.

PATIENTS AND METHODS

From September 2008 to July 2011, a prospective randomized study was conducted at the department of clinical oncology and nuclear medicine and the surgical oncology department in the oncology centre, Mansoura University on 50 patients with histopathologically proven epithelial ovarian cancer with advanced stage (IIIb /IIIc) according to the (FIGO) staging. All patients' performance status ranged between 0 to 2 according to World Health Organization (WHO) performance status[13], with the absence of serious disabling comorbidity that would contraindicate primary cytoreductive surgery or platinum-based chemotherapy.

All patients were subjected to informed consent, physical examination, evaluation of performance status, a complete blood count, measurement of renal and liver function tests, serum CA125 levels, and radiological studies (including CT of the abdomen and pelvis).

The patients were randomly assigned either to primary debulking surgery followed by at least six courses of paclitaxel-carboplatin chemotherapy (PDS group; *n*=25) or to three to six courses of neoadjuvant paclitaxel-carboplatin chemotherapy (NACT group; *n*=25) followed by interval debulking surgery in all patients who achieved response or even stable disease (NACT group; *n*=20/25), followed in turn by two to three courses of the same chemotherapy to a total number of 6-8 cycles. Five patients were excluded from interval debulking surgery as they had progressive disease.

All patients received paclitaxel-carboplatin regimen consisting of paclitaxel (175 mg/m^2 infused over 3 h) and an area under the curve 6 of carboplatin (repeated every 3 weeks).

The clinical response to neoadjuvant chemotherapy was evaluated after the third cycle by clinical examination, serum CA 125 level, and computed tomography (CT) scan. Tumor response was classified according to the WHO criteria[14], while surgicopathologic response was evaluated after IDS.

The standard surgery was defined as total abdominal hysterectomy with bilateral salpingoophorectomy, appendectomy, total infragastric omentectomy, peritonectomy of the pelvis, paracolic gutters, anterolateral diaphragmatic area, and pelvic, common iliac, and infrarenal paraaortic lymphadenectomy.

Optimal cytoreduction (residual disease < 1cm) was performed in (13/25) in PDS group and (11/25) in NACT group, while the suboptimal cytoreduction was performed in (12/25) in PDS group and (9/25) in NACT group. However, in both groups extended surgery beyond the standard was needed in some cases, in which an additional organ was resected in order to achieve more cytoreduction.

The surgical aspects of cytoreduction was evaluated in both groups as regards the mean operative duration, the blood loss rates (number of transfused blood units), and the length of postoperative hospital stay. Moreover, the postoperative complications in both groups were reported.

Statistical Methods:

The statistical analysis of data was done by using SPSS (SPSS, Inc, Chicago, IL) program statistical package for social science version 16.

To test the normality of data distribution, K-S (Kolmogorov-Smirnov) test was done, only significant data revealed to be nonparametric. However all tested data revealed to be parametric. The description of the data done in form of mean (+/-) SD for quantitative data, while frequency & proportion for qualitative data. The analysis of the data was done to test statistical significant difference between groups. For quantitative data, student t-test was used to compare between two groups. Chi square test was used for qualitative data. Kaplan- Meier survival curve was used to estimate survival. *P* is significant if < or = 0.05 at confidence interval 95%. Life tables, log rank test, Cox regression and hazard ratio were used to test the effect of different risk factors on survival

RESULTS

In the present randomized study, 25 patients were subjected to primary cytoreductive surgery (PDS group) and 20/25 patients who showed either response or stable disease after neoadjuvant chemotherapy were subjected to interval debulking surgery (NACT group).

Patients characteristics were evenly distributed between the two groups (Table 1).

The median number of neoadjuvant chemotherapy cycles was 3.5 (range 3-6, mean 4). Response to chemotherapy in NACT group was evaluated according to WHO criteria (Table 2) where (52%) responded to NACT according to clinical examination, serum CA125 level and abdomino - pelvic CT. These three parameters returned to normal (complete response) in one patient (4%), partial response in 12 patients (48%), 7 patients (28%) had stable disease and 5 cases (20%) progressed during chemotherapy and did not underwent surgical interference, while surgicopathologic response to NACT was shown in Table (5).

Optimal cytoreduction was performed in (13/25) in PDS group & (11/25) in NACT group, while the suboptimal cytoreduction was performed in (12/25) in PDS group & (9/25) in NACT group with insignificant *P* value (0.84). The main surgical procedures of both groups are summarized in (Table 3).

The extended non-standard surgery was performed in 9 patients (36 %) in PDS group, and 6 patients (30 %) in NACT group. The most common organ added to resection was the small intestine with primary anastomosis (in 9 patients), partial cystectomy was done in 4 patients, colectomy was done in 2 patients.

The results of surgical parameters of cytoreduction in both groups showed no significant differences as regard the mean operative duration, the blood loss rates (number of transfused blood units), and the length of postoperative hospital stay. Moreover, there was no difference between the postoperative complications in both groups (Table 4).

The median overall survival time was 29 months (confidence interval CI: 27.15 – 30.85) (range: 9–32 months) in the PDS group and 30 months (CI: 28.81 –31.19) (range: 10–32 months) in the NACT group with an insignificant *P* value ($P = 0.55$) (Figure 1).

The median progression free survival was 19 months (CI: 7.43 – 30.57) (range: 6–30 months) in the PDS group and 22 months (CI: 10.39 – 33.61) (range: 7–32 months) in the NACT group with an insignificant *P* value ($P = 0.11$) (Figure 2).

Univariate and Multivariate analysis were performed for overall survival in both treatment groups together, and included the following variables (age, pathologic type, stage, grade, treatment arm and residual size). By univariate analysis, age ($P = 0.04$), grade ($P < 0.001$) stage ($P = 0.008$), pathological type ($P = 0.002$) and residual size ($P < 0.001$) were found to affect survival significantly, while residual size (in favour of residual size <1 cm, $P < 0.001$) was the only significant variable which affected survival by multivariate analysis (Table 6).

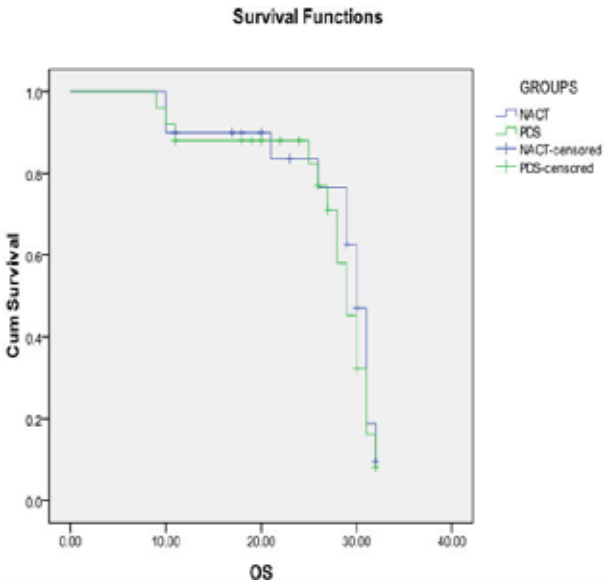

Figure 1: The Overall survival.

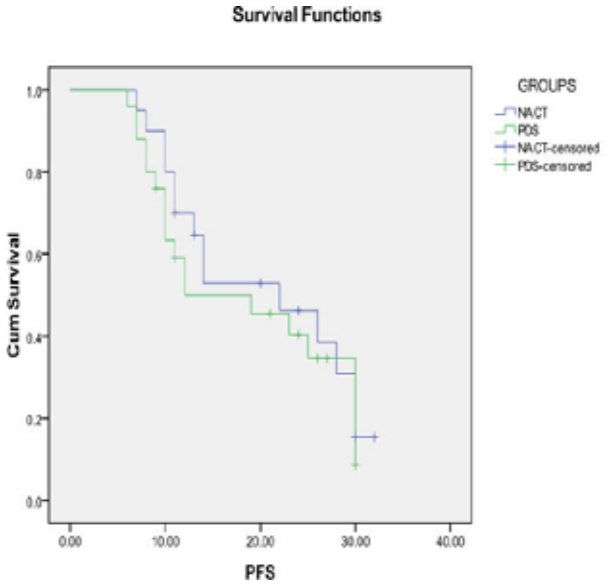

Figure 2: Progression free survival.

Table 1: Patient characteristics.

Characteristics	PDS group (*n* = 25)	NACT group (*n* = 25)	*P*
Age (years)			
Median	53	55	0.27
Range	36 – 72	24 – 72	
PS			
0	7 (28%)	5 (20%)	0.51
1	15 (60%)	14 (56%)	
2	3 (12%)	6 (24%)	
FIGO stage			
IIIB	6 (24%)	7 (28%)	0.75
IIIC	19 (76%)	18 (72%)	
Grade			
I	7 (28%)	4 (16%)	0.88
II	14 (56%)	15 (60%)	
III	4 (16%)	6 (24%)	
Histological type			
Serous	9 (36%)	13 (52%)	
Mucinous	10 (40%)	8 (32%)	0.56
Undifferentiated	5 (20%)	4 (16%)	
Endometrioid	1 (4%)	-	

PS = Performance status, FIGO = International Federation of Gynecology and Obstetrics

Table 2: Clinical response to NACT.

Response	No	%
Overall response	13	52%
Complete response	1	4%
Partial response	12	48%
Stable disease	7	28%
Progressive disease	5	20%

Table 3: The main surgical procedures.

	PDS Group (25)	NACT Group (25)	Total (50)	*P* value
Cytoreduction:				
Optimal	13 (52%)	11 (44%)	24 (48%)	
Suboptimal	12 (48%)	9 (36%)	21 (42%)	0.84
No surgical interference	-	5(20%)	5(10%)	
The extended resection:	9 (36%)	6 (30%)	15 (33.3%)	
Small Intestine	5 (20%)	4 (20%)	9 (20%)	0.94
Urinary Bladder	2 (8%)	2 (10 %)	4 (8.8%)	
Colon	2 (8%)	0 (0%)	2 (4.4%)	

Table 4: The surgical parameters & complications of cytoreduction.

	PDS Group (25)	NACT Group (20)	*P* value
Operative duration (minutes)			
Mean ± SD	187.2 ± 61.17	206.5 ± 72.18	0.66
Range	90 - 460	90 - 980	
Intraoperative blood transfused units			
Mean ± SD	1 ± 1.22	1.15 ± 1.42	0.71
Range	0 - 4	0 - 4	
Hospital stay (days):			
Mean ± SD	13.08 ± 5 .61	13.3 ± 4.69	0.89
Range	6 - 27	5 - 25	
Complications:			
Wound infection (6 patients)	4 (16%)	2 (10%)	0.84
DVT (2 patients)	1 (4%)	1 (5%)	

SD = standard deviation.

DISCUSSION

In this randomized trial, primary debulking surgery followed by chemotherapy was compared to neoadjuvant chemotherapy followed by interval debulking surgery in women with advanced ovarian cancer. We found that survival after neoadjuvant chemotherapy followed by interval debulking surgery was similar to survival with the standard approach of primary surgery followed by chemotherapy.

Chemotherapy used for all patients was paclitaxel–carboplatin. The planned number of neoadjuvant chemotherapy cycles varied from three to six, which was similar to previous published studies, where the number of cycles ranged from 2 to 10[7,15,16].

However, in the treatment of NACT and IDS, the number of chemotherapy cycles given after IDS is limited (usually two to three cycles) to a total number of 6-8 cycles, and this was in accordance with Onda *et al*.[3] who gave three to four cycles after IDS.

Our study showed response rate to neoadjuvant chemotherapy of 52%, which is lower when compared with that of Ansquer *et al*.[6] (80%), Hegazy *et al*.[17] (66.7%) and Yan *et al*.[18] (69%) which may be due to different patients' characteristics. Optimal cytoreduction was performed in 52% in PDS group & 55% in NACT group, while the suboptimal cytoreduction was performed in 48% in PDS group & 45% in NACT group with insignificant *P* value (0.84). These results compare favorably with Surwit *et al*.[15], who reported 55% of cytoreduction to less than 1 cm, higher percent of optimal cytoreduction was obtained by Jacob *et al*.[7] (77%), Ansquer *et al*.[6] (72%) and Hegazy *et al*.[17] (72.2%).

The results of surgical parameters of cytoreduction in both groups showed no significant differences as regard the mean operative duration, the blood loss rates (number of transfused blood units), and the length of postoperative hospital stay. Moreover, there was no difference between the postoperative complications in both groups. Conversly, Schwartz *et al*.[19], reported that the morbidity of debulking surgery seems to be decreased after neoadjuvant chemotherapy with less blood loss ($P < 0.001$), shorter intensive care unit stay ($P = 0.01$), and shorter postoperative hospitalization ($P < 0.001$), also Ansquer *et al*.[6] described lower morbidity of debulking surgery after neoadjuvant chemotherapy with less than 50% of patients receiving blood transfusions and a median hospital stay of 10 days. Similarly, Hegazy *et al*.[17] claimed that debulking surgery in NACT group was less aggressive than in the conventional group with less blood loss rates, shorter intensive care stay and shorter postoperative hospitalization.

The median overall survival time was not statistically different in both treatment arms (29 vs 30 months in the PDS and NACT group, respectively) ($P = 0.55$) which is similar to that reported by Hegazy *et al*.[17] (28 vs 25 months) and Vergote *et al*.[2] (29 vs 30 months), Yan *et al*.[18] (43 vs 34 months) and Kuhn *et al*.[10] showed significant longer median survival time in the neoadjuvant group (42 vs 23 months), conversely, Ghaemmaghami *et al*.[20] reported longer survival in the primary cytoreductive surgery group in comparison to the neoadjuvant group. Our study showed longer median progression free survival in the NACT group in comparison to the PDS group (22 vs 19 months, respectively) but this difference is statistically insignificant (P=0.11), similarly, Hegazy *et al*.[17] reported longer but insignificant median progression free survival (22 vs 19 months) (P=0.4) in the NACT group, conversely, Yan *et al*.[18] described significant longer median progression free survival in the primary cytoreductive surgery group in comparison to neoadjuvant chemotherapy group (18 vs 8 months, respectively) ($P < 0.05$).

So, among patients with advanced (stage IIIb or IIIC) ovarian carcinoma, survival after neoadjuvant chemotherapy followed by interval debulking surgery is similar to survival after primary debulking surgery followed by chemotherapy. This result is consistent with the conclusions of a recent meta-analysis of 21 nonrandomized trials[21].

On multivariate analysis, the overall survival was found to be affected significantly by residual size (P<0.001) only, which is similar to Bristow *et al*.[4] and Vergote *et al*.[2]. Conversely, Hegazy *et al*.[17] reported that the overall survival was not affected by any of these variables in both treatment groups, whereas the progression free survival was affected only by the residual size in the conventional group and by the tumor type (P=0.02) and the degree of optimal debulking (P=0.01) in the NACT group.

CONCLUSION

Despite that primary cytoreductive surgery is considered the standard of care for advanced ovarian carcinoma, neoadjuvant chemotherapy is not inferior to primary cytoreductive surgery for patients with stage IIIb/ IIIC ovarian carcinoma. No significant advantages of neoadjuvant therapy or primary debulking surgery were observed with respect to survival and postoperative morbidity. These findings must be confirmed by larger prospective randomized trials evaluating the efficacy

and morbidity of primary surgery versus neoadjuvant chemotherapy followed by interval debulking surgery.

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