

Interval debulking Surgery after Neoadjuvant Chemotherapy for Advanced Ovarian Carcinoma, Impact on Patients' Survival

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Objective: The standard management of advanced epithelial ovarian carcinoma (EOC) is complete tumor cytoreduction followed by chemotherapy. This study prospectively evaluated the outcomes of interval debulking surgery (IDS) after neoadjuvant chemotherapy (NACT) in terms of pathological response, surgical outcome, and patients' survival.

Patients and methods: The study was carried out between January 2018 and December 2021, 72 patients with a denovo stage III-IV EOC were enrolled in the study, they received IDS after platinum based NACT to achieve a complete surgical debulking to no macroscopic residual disease (R0) or optimal debulking to < 1cm residual disease (R1). Patients' characteristics, operative details, complications, overall survival (OS) and the progression free survival (PFS) were analyzed.

Results: Complete pathological response (CPR) was reported in 8 patients (11.1%). The complete debulking surgery was achieved in 39 patients (54.2%) while optimal debulking was done in 33 patients (45.8%). PFS was better in patients with complete pathological response (CPR) 44.54 months than patients with Micro/ Macro pathological response (Micro/ Macro PR) 33.39 month, P = 0.018. PFS was 39.02 months for patients undergone complete cytoreduction versus 31.47 months for patients undergone optimal cytoreduction, P = 0.010. While OS was 45.09 months for patients undergone complete cytoreduction versus 35.97 months for patients undergone optimal cytoreduction, P = 0.004.

Conclusion: Combination of NACT and IDS in advanced ovarian carcinoma can result in better pathological response, surgical resection outcome and decreased minimal residual disease leading to improved OS and PFS.

Key words: Advanced ovarian carcinoma, Interval debulking surgery, Neoadjuvant chemotherapy, Overall survival, Progression free survival.

Introduction

In 2020, the newly diagnosed cases with ovarian cancer worldwide were 313,959 with 207,252 reported deaths and this represents 1.6% of newly diagnosed cancer cases and 2.1% of cancer related deaths for all types of cancer.¹ While In Egypt, the newly diagnosed cases with ovarian cancer were 2787 with 1839 reported deaths during the last year.²

Among the several types of ovarian carcinoma, the epithelial ovarian carcinoma (EOC) has the highest incidence rate, 95% of ovarian cancers.³ In 1975, Griffiths.⁴ reported that the integration of primary debulking surgery (PDS) followed by Adjuvant chemotherapy (Platinum and taxane-based) is the cornerstone of EOC treatment. However, if there are contraindications for PDS (Like locally advanced disease where optimal debulking is not feasible) neoadjuvant chemotherapy could be received followed by interval debulking surgery then adjuvant chemotherapy.³

Debulking of ovarian tumor was described in 1934,⁵ basically to improve outcome of radiotherapy before recent advances in chemotherapy. As a result of minimal benefits, these data were of a limited clinical application till Griffiths' publication clarified that better survival rates were observed in patients with less residual tumor diameter.⁴

The Gynecologic Oncology Group (GOG),⁶ defined

optimal debulking as residual implants ≤ 1 cm. The key for diagnosis is an image guided core biopsy of the tumor primary or any metastatic lesions of ovarian carcinoma.⁷

The combination of neoadjuvant chemotherapy (NACT) followed by interval debulking (IDP), has gained a lot of interest as NACT adds many benefits lowering surgery related morbidity as radical surgical resection is performed with better outcome for minimal residual disease. NACT followed by interval debulking was reported to have comparable survival outcomes to primary surgery.⁸ IDS can allow removal of poorly vascularized tumor where chemotherapeutic agents have poor access. It can also remove chemoresistant clones, which are less susceptible to chemotherapy.⁹

Some retrospective studies showed that IDS was found to have a better outcome if proceeded by NACT (73%-81%), but the available prospective evidence regarding survival benefits and the complete pathologic response (CPR) after NACT is still not so clear.^{10,11}

Since the optimal cytoreduction represents an indicator for surgical outcome, in patients receiving NACT, pathologic response is an indicator of chemotherapy response and sensitivity hence, survival outcome.¹²

The lack of prospective studies on the survival benefits, pathological response together with surgical outcome of NACT followed by IDS protocol necessitates the initiation of the current study.

Patients and methods

This prospective study was conducted between January 2018 and December 2021 and included 72 patients with denovo diagnosis of epithelial ovarian carcinoma International Federation of Gynecology and Obstetrics (FIGO) stage III-IV. A written informed consent had been obtained from every patient included in the study. The study was approved by ethical committee (No: 33013).

Patient selection

Inclusion criteria

The patients included in the study had a denovo FIGO stage III-IV epithelial ovarian carcinoma (EOC), received a neoadjuvant chemotherapy with good performance status $PS \leq 1$ and followed by interval debulking surgery where complete or optimal cytoreductive surgery was achievable and thereafter completed the adjuvant chemotherapy regimen.

Exclusion criteria

Patient with early ovarian carcinoma, recurrent disease, patients with large residual tumor >1 cm (suboptimal debulking surgery), patients with poor performance status and patients who did not show response to neoadjuvant chemotherapy were excluded from the study.

Preoperative work up

Every patient was subjected to careful history taking, general and local abdominal examination and investigations; laboratory investigations (including tumor marker CA125), abdomino-pelvic ultrasonography, Computed Tomography (CT) scan abdomen and pelvis with oral and intravenous contrast, chest CT scan, Magnetic Resonance Imaging (MRI) and guided core biopsy of primary tumor and/or metastases.

Outcome measures

Patients' data were reported including age, performance status, tumor size and grade, histological type, CA-125 level, neoadjuvant and adjuvant chemotherapy, operative time and length of hospital stay. The main outcome data during the follow up period included early (30-days) and late post-operative complications, progression-free survival or distant metastasis, re-operations and overall survival.

Complete debulking was defined as complete surgical debulking to no macroscopic residual disease (R0). Optimal debulking was defined as surgical debulking to < 1 cm.

residual disease (R1). Complete pathological response (CPR) means no gross visible disease seen at the start of IDS and no pathologic residual disease on pathological examination, Microscopic pathologic response (microPR) means no gross visible disease seen at the start of IDS but with presence of pathologic residual

disease on pathological examination, and Macroscopic pathologic response (macroPR) means gross visible disease seen at the start of IDS and pathologic residual disease on pathological examination. Progressions free survival (PFS) was identified as the time from date of diagnosis to physical, biological, or radiological evidence of disease progression. Overall survival (OS) was identified as the time from date of diagnosis to date of death, or date of last follow-up. The primary end point of the study was OS while the secondary end points were adverse effects and PFS.

Neoadjuvant chemotherapy (NACT)

Chemotherapy regimens received were paclitaxel (175 mg/m² IV) followed by carboplatin (Area Under the Curve [AUC] 5-6 IV) day 1 repeated every 3 weeks for 3 cycles. The response to NACT was evaluated by clinical examination, serum CA 125 level, abdomino-pelvic CT scan and CT chest.

Interval debulking surgery

The patients subjected to a midline exploratory laparotomy. A sample of the ascitic fluid, if any or peritoneal washings was taken for cytological analysis. The goal was to achieve a complete surgical debulking to no macroscopic residual disease or optimal debulking to < 1 cm residual disease. The standard surgery consists of a total ysterectomy and bilateral salpingo-oophorectomy, inspection of all abdominal organs and peritoneal surfaces, sampling of suspicious areas for biopsy, total omentectomy, appendectomy and para-aortic lymphadenectomy if detected intraoperative or by radiological imaging. While the non-standard surgery, means a single organ resection (e.g., small intestine, colon, spleen) to achieve optimal cytoreduction. Resected specimens sent for histopathological examination (Figure 1).

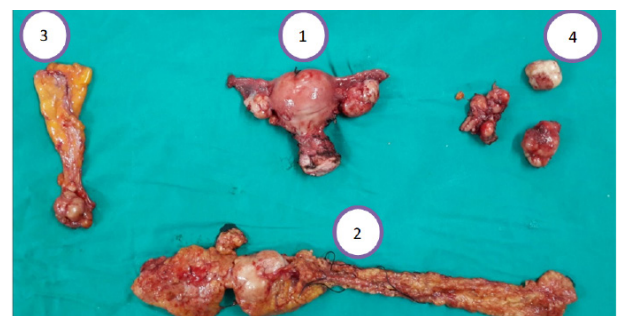


Fig 1: An operative photography shows a total hysterectomy with bilateral salpingo-oophorectomy (1), total omentectomy (2), resected falciform ligament (3) and resected metastatic nodules from the Douglas pouch (4).

Adjuvant chemotherapy

The patients received postoperative another 3 cycles of chemotherapy in form of paclitaxel (175 mg/m² IV) followed by carboplatin (AUC 5-6 IV) day 1 repeated every 3 weeks and the response was evaluated by clinical

examination, serum CA 125 level and abdomino-pelvic CT scan.

Statistical analysis

Data were analyzed using IBM SPSS (Statistical package for the social sciences) software version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. Chi-square test was applied to investigate the association between the categorical variables. Alternatively, Fisher's exact correction test was applied when the expected cell counts were less than 5. For continuous data, they were tested for normality by the Kolmogorov- Smirnov. Distributed data were expressed as range (Minimum and maximum), mean, standard deviation and median Student t-test was used to compare two groups for normally distributed quantitative variables. On the other hand, Mann Whitney test was used to compare two groups for not normally distributed quantitative variables and Kaplan-Meier Survival curve was used for the significant relation with progression free survival and overall survival. Significance of the obtained results was judged at the 5% level.

Follow-up

Postoperative follow-up visits were performed every three months in the first 2 years and every six months thereafter. During the follow-up visits, the patients had been examined clinically and serum CA125 was measured. abdomino-pelvic CT scan was performed routinely every 6 months. Whenever an increase in CA125 level was observed, abdominal-pelvic CT scan with oral and intravenous contrast, chest CT scan and MRI was performed.

RESULTS

Patients demographic and tumor characteristics (Table 1).

The patients' age ranged between 37 to 75 years with a mean age 60.50 ± 7.02 years. Thirty-six patients (50%) had performance status ≤ 1 . As regard tumor staging, 42 patients (58.3%) had stage III disease while grade III was reported in 52 patients (72.2%) and serous pathology in 47 patients (65.3%). After 3 cycles of NACT, CA125 level returned to normal in 31 patients (43.1%). IDS was performed and at time of entry to abdomen, gross tumor was found in 50 patients (69.4%) and complete surgical excision was achieved in 39 patients (54.2%) while, optimal resection leaving less than 1 cm tumor residual was performed in 33 patients (45.8%). Only 8 patients (11.1%) showed complete pathological response (CPR), 14 patients (19.4%) showed micropathological response and 50 patients (69.4%) showed macropathological response. Regression of ovarian mass after NACT is demonstrated in (Figure 2).



Fig 2: MRI of abdomen and pelvis before NACT (a), after NACT (b), CT abdomen and pelvis after NACT, showing regression of ovarian mass.

Operative and post-operative results

The IDS surgery had achieved complete debulking (no macroscopic residual disease) in 39 out of 72 patients (54.2%) and optimal debulking (< 1 cm residual disease) in 33 Patients (45.8%). The duration of surgery ranged between 165.0 – 260.0 minutes with a mean of 219 minutes. The length of hospital stay ranged between 3 -12 days with a median of 6 days.

Complications (Table 2)

Operative complications were reported in 10 patients (13.8%) and the management was shown in (Table 2).

Correlation between clinical variables, pathological response and surgical resection.

On performing univariate analysis, there was no statistically significant correlation between studied clinical variables and pathological response as reported in (Table 3).

While on correlating the studied clinical variables with the type of surgical resection performed, it was found that age of the patients, PS and tumor stage were statistically significant (p values = 0.002, 0.001, 0.003 respectively) (Table 4) as better cytoreduction was feasible in younger patients, better PS and stage III disease.

Follow up

The median follow-up period was 35.5 months (ranged between 14 and 48 months) Disease progression was reported in 37 patients (51.4%), while mortality was reported in 21 patients (29.2%). The OS and the DFS were significantly affected by the degree of surgical debulking. The mean OS was 45.09 months for patients undergone complete cytoreduction versus 35.97 months for patients undergone optimal cytoreduction, $P = 0.004$. The mean PFS was 39.02 months for patients undergone complete cytoreduction versus 31.47 months for patients undergone optimal cytoreduction, $P = 0.01$, (Figures 3,4). As regard pathological response, patients with CPR had better PFS outcome (Mean 44.54 months) than patients with micro/macroPR (Mean 33.39 months) with a statistically significant difference (p value = 0.018). In patients with CPR, improved OS rate was observed than patients with micro/macroPR but with a statistically insignificant difference (Mean 46.33 months versus 39.03 months, (P value = 0.190), (Figures. 3,4).

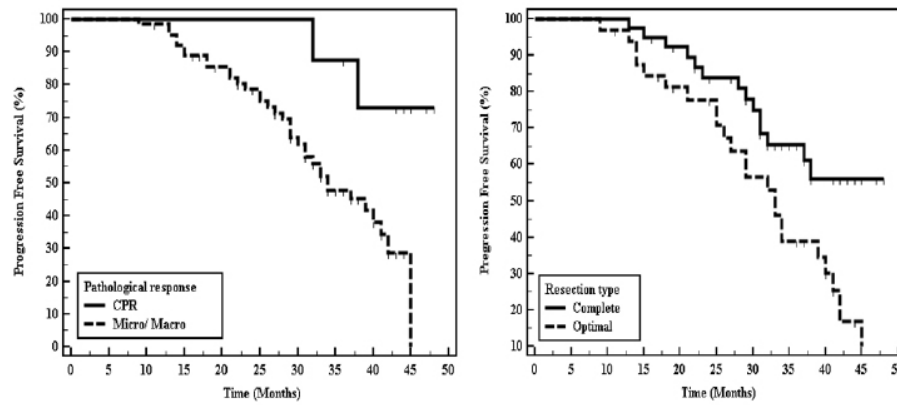


Fig 3: Kaplan-Meier survival curve for progression free survival with pathological response and resection type.

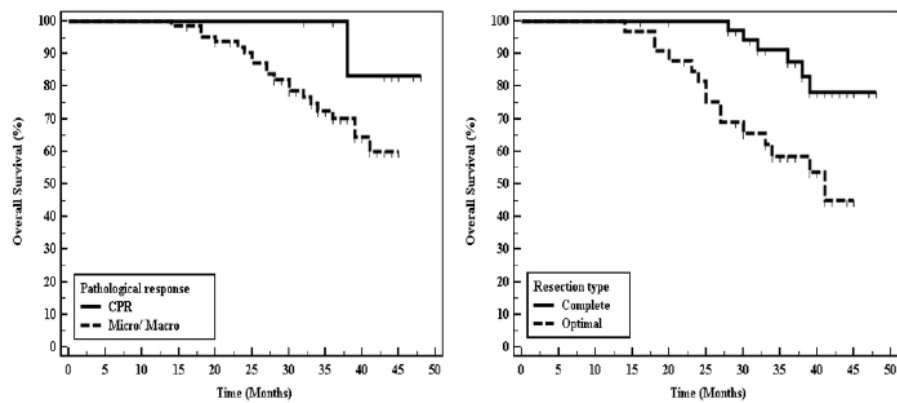


Fig 4: Kaplan-Meier survival curve for overall survival with pathological response and resection type.

Table 1: Patients demographic data and tumor characteristics

Variable	No. (%)
Age (years)	
Mean \pm .	60.50 \pm 7.02
Performance status 0	36 (50.0%)
Stage	
III	42 (58.3%)
IV	30 (41.7%)
Grade	
II	20 (27.8%)
III	52 (72.2%)
Pathology (Serous)	47 (65.3%)
CA125 Normalization	31 (43.1%)
Gross tumor at IDS	50 (69.4%)
Pathological response	
CPR	8 (11.1%)
Micro PR	14 (19.4%)
Macro PR	50 (69.4%)
Resection type	
Complete	39 (54.2%)
Optimal	33 (45.8%)

Table 2: Operative complications and management

Variables	Number	%	Management
Pelvic abscess	3	(4.2%)	Ultrasound guided drainage
DVT	3	(4.2%)	Therapeutic dose of anticoagulants
Wound infection	3	(4.2%)	Daily dressing and antibiotics.
Burst abdomen	1	(1.4%)	Closure over tension sutures

DVT= Deep Venous Thrombosis.

Table 3

Variable	Pathological response		P value
	CPR (n = 8)	Micro/ Macro (n = 64)	
Age (years)			
Mean \pm .	56.63 \pm 9.33	60.98 \pm 6.61	0.098
Performance status			
0	4 (50.0%)	32 (50.0%)	1.000
1	4 (50.0%)	32 (50.0%)	
Stage			
III	6 (75.0%)	36 (56.3%)	0.455
IV	2 (25.0%)	28 (43.8%)	
Grade			
II	2 (25.0%)	18 (28.1%)	1.000
III	6 (75.0%)	46 (71.9%)	
Pathology Serous	7 (87.5%)	40 (62.5%)	0.248
CA125 Normalization	6 (75.0%)	25 (39.1%)	0.068

CPR: Complete Pathological Response.

Table 4

Variable	Resection type		P value
	Complete (N = 39)	Optimal (N = 33)	
Age (years)			
Mean \pm .	58.15 \pm 6.88	63.27 \pm 6.20	0.002*
Performance status			
0	27 (69.2%)	9 (27.3%)	0.001*
1	12 (30.8%)	24 (72.7%)	
Stage			
III	29 (74.4%)	13 (39.4%)	0.003*
IV	10 (25.6%)	20 (60.6%)	
Grade			
II	13 (33.3%)	7 (21.2%)	0.253
III	26 (66.7%)	26 (78.8%)	
Pathology Serous	27 (69.2%)	20 (60.6%)	0.444
CA125 Normalization	17 (43.6%)	14 (42.4%)	0.921

DISCUSSION

The radical surgical resection is the cornerstone of treatment in ovarian carcinoma as better survival outcome is obtained in complete rather than optimal cytoreductive surgery.¹³ Survival rates in patients with ovarian cancer are also affected by existence of residual disease as it is one of the most unfavorable prognostic factors. These data are strongly supporting the concept of achieving complete resection whenever possible.¹⁴

The control of disease in such advanced cases is also very difficult with the initial chemotherapy alone as large poorly vascularized tumor burden is challenging with very high possibility for toxicity and chemoresistance as it is assumed that the larger tumor size, the more likelihood for development of cancer cells mutation responsible for resistance for chemotherapy.¹⁵ This why the combination of interval debulking surgery proceeded and followed by chemotherapy was investigated by many authors. NACT can improve local disease control allowing complete resection of tumor with lower operative morbidity.¹⁶ This was also advised by the FIGO recommendation as it favors the use of NACT before IDS for subgroups of patients with stage III and IV.¹⁷

In this study, the optimal cytoreduction was achieved in 39 Patients (54.2%). This correlates with study of Surwit et al,¹⁸ who reported 55% of cytoreduction less than 1 cm. While Lee et al,¹⁹ reported optimal cytoreduction in 77.8 % of patients who received NAC before IDS.

In this study, complications were reported in 10 patients (13.8%); 3 patients (4.2%) developed pelvic abscess, 3 patients (4.2%) DVT, 3 patients (4.2%) wound infection, and one patient (1.4%) burst abdomen. These results agree with Mourton SM et al,²⁰ who found 3 patients (5%) developed a pelvic abscess and 1 patient (1.7%) with anastomotic leak, also Hegazy MA et al,²¹ found 3.4% of the patients developed DVT and 5% developed wound infection.

The length of hospital stay in the current study ranged between 3- 12 days with a mean of 6.46 days. While Hegazy MA et al,²¹ reported a mean of 10.5 days of hospital stay, also Schwartz et al,²² who reported shorter postoperative hospitalization most probably because of NACT that helped to decrease the tumor burden as on exploration no gross tumor was observed in 22 patients (30.6%) which highlights the value of NACT prior to debulking surgery.

In the current study, 42 patients (58.3%) had stage III while, 30 patients (41.7%) had stage IV. So, they were candidates for NACT (platinum- taxanes combination) followed by IDS to allow control of disseminated disease which goes in agreement with the reported data about high response rate for NACT in stage IV ovarian cancer prior to surgery.²³

Michaan et al,²⁴ reported that complete pathological response (CPR) was achieved in relatively small percentage of patients (5 to 12%) and associated with better prognosis, and this was similar to our results as CPR was reported in 8 patients (11.1%) and they had the best survival rates and longer follow up periods among the studied group (44.54 month for CPR group versus 33.39 months for micro/macro PR group, P = 0.018).

The SCORPION (Surgical complications related to Primary or Interval debulking in Ovarian Neoplasm) study reported that the rate of complete residual disease was 45.5% in PDS vs. 57.7% in NAC-IDS. With better perioperative morbidity and QOL scores in the NACT-IDS arm.²⁵

In this study, the OS and the PFS were significantly affected by the degree of surgical debulking. The overall survival time was 45.09 months for patients undergone complete cytoreduction versus 35.97 months for patients undergone optimal cytoreduction, P=0.004. The disease-free survival was 39.02 months for patients undergone complete cytoreduction versus 31.47 months in patients undergone optimal cytoreduction, P=0.010. This correlates with the studies of Vergote I et al,¹⁰ Rutten MJ et al,²⁶ who reported that; complete resection at primary debulking surgery is the most important independent prognostic factor in advanced ovarian carcinoma.

Also, Zivanovic O et al,²⁷ reported that patients who underwent optimal debulking had significantly improved progression-free and overall survival compared with the patients who underwent suboptimal debulking. Similarly, du Bois et al,²⁸ reported that no gross residual disease was associated with the longest progression-free and overall survival, compared with residual disease ≤ 1 cm and residual disease >1 cm.

The European prospective randomized trials.²⁹ also showed better results in patients with complete cytoreduction (99.1 months in R0 resection vs. 36.2 months for patients with under 1 cm residual disease).

Similarly Rose et al,¹⁶ reported prolonged survival times and significantly better median survival in neoadjuvant chemotherapy followed by interval debulking surgery.

Patients who achieved CPR had significantly better PFS (44.54 months in CPR group and 33.39 in micro/macroPR group, P value = 0.018) but no significantly better OS rates were reported in those patients. While Gao et al demonstrated that PFS and OS were not improved and only the rate of complete cytoreductive surgery was higher in patients who received NACT.³⁰

Study limitation

The most important limitations of the present study are a relatively low number of cases and short follow-up period.

CONCLUSION

Integration of NACT with IDS can offer a valuable treatment strategy for patients with advanced ovarian carcinoma. NACT resulted in better (even complete) pathological response making complete surgical resection achievable with minimal residual disease and low morbidity. Complete resection at debulking surgery and complete pathological response to chemotherapy are very important prognostic factor in advanced ovarian carcinoma, as they were associated with better progression-free and overall survival rates.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Abbreviations

AUC: Area Under the Curve.

CPR: Complete Pathological Response.

CT: Computed Tomography.

DFS: Disease free survival.

DVT: Deep Vein Thrombosis.

EOC: Epithelial ovarian carcinoma.

FIGO: International Federation of Gynecology and Obstetrics.

GOG: The Gynecologic Oncology Group.

IDS: Interval debulking surgery.

MRI: Magnetic Resonance Imaging.

NACT: Neoadjuvant chemotherapy.

OS: Overall survival.

PS: Performance Status.

PDS: Primary debulking surgery.

SPSS: Statistical package for the social sciences.

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