Neoadjuvant chemotherapy and the complexity of operative procedure in advanced epithelial ovarian cancer: a retrospective analysis

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Introduction: Complete tumor resection for epithelial ovarian cancer (EOC) generally incorporates complex surgical maneuvers, especially bowel resection. This study retrospectively analyzed the impact of neoadjuvant chemotherapy (NAC) on complexity of surgical procedures for EOC (represented by bowel resection) and postoperative morbidity.

Methods: We retrospectively recruited all patients with Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stages IIIC–IVB EOC who were treated in our center between 2011 and 2016. Patients were divided into those who received primary debulking followed by chemotherapy (group A), and those who received NAC followed by interval debulking (group B). Patient age, tumor stage, grade, dates of commencement and completion of therapy, intraoperative events, completion of surgical resection, and postoperative events were evaluated.

Results: Of 92 patients, 42 were assigned to group A and 50 to group B. Their FIGO stages were group A—stages IIIC: 34 (80.9%), IVA: 6 (14.3%), and IVB: 2 (4.8%); and group B—stages IIIC: 45 (90%), IVA: 5 (10%), and IVB: 0 (0%). The 2 groups did not significantly differ in completeness of surgical cytoreduction or rates of bowel resection, intraoperative complications, or postoperative morbidities.

Conclusion: NAC did not reduce rates of bowel resection, intraoperative complications, and postoperative morbidity in advanced EOC compared with primary surgical cytoreduction. Future prospective studies will be required to corroborate our results.

Keywords: Epithelial ovarian cancer, Intraoperative complications, Neoadjuvant chemotherapy, Postoperative morbidity

Introduction

Epithelial ovarian cancer (EOC) is considered the most deadly female genital tumor in developed countries[1–3]. Ovarian cancer caused an estimated 5600 deaths in Germany in 2010[1] and is expected to cause ~14,000 deaths in the United States in 2017[2]. More than 60% of cases present at advanced stages (stage IIIC and above) on presentation[1]. Primary cytoreductive surgery (CRS) with complete tumor resection, followed by 6 cycles of platinum-based chemotherapy is widely considered to be the standard of care for these patients[4]. An alternative strategy, using neoadjuvant chemotherapy (NAC) to shrink the tumor and optimize outcome from a later surgery, is reportedly noninferior to the standard therapy, as shown by randomized controlled trials[5,6]. This strategy showed survival comparable even to primary cytoreduction in a recent retrospective study[7] where the number of chemotherapy cycles before the CRS should not exceed 4[8]. However, this has not been recommended by many leading bodies[4]. Because of the complexity and extensiveness of the surgical procedures required to attain complete tumor resection, which include multiple bowel resections, liver resections, and peritoneal stripping, many patients suffer from severe postoperative morbidity that may lead to delayed initiation of chemotherapy, which may in turn affect the patient's overall survival[9]. The strategy of beginning with NAC, which aims at decreasing the tumor mass and thus improving chances for a complete tumor resection, using less complex surgical procedures and decreasing chances of postoperative complications. This single-institution study retrospectively evaluated the impact of NAC on the complexity of surgical procedure, represented by bowel resection, and postoperative morbidity.

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Methods

This was a retrospective cohort study, performed at the Oncology Center of Mansoura University (OCMU), Department of Surgical Oncology, in accordance with the Declaration of Helsinki, and approved by the ethics committee of the Faculty of Medicine, University of Mansura (El Gomhoreya Street, Mansura, Egypt), under the approval number R/17.11.21. The results of the study

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are reported in accord with the STROCSS criteria for reporting on retrospective cohort studies[10].

We analyzed medical records of all patients with Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage IIIC–IVB EOC who were treated in our center between January 1, 2011 and June 30, 2016. Patients' records that met the inclusion criteria underwent pseudonymization to mask patients' identities, as per IRB approval. We included patients who either received primary CRS followed by 6 cycles of carboplatin (AUC 5) and paclitaxel (175 mg/m^2) every 3 weeks (group A) or received 3 cycles of carboplatin (AUC 5) and paclitaxel (175 mg/m^2) followed by interval debulking surgery, which in turn was followed by 3 cycles of carboplatin and paclitaxel in the aforementioned doses (group B). Response to NAC was assessed after the 3 cycles according to RECIST criteria[11]. The assignment of patients into either of the treatment groups was based on the decisions of their respective physicians during diagnostic laparoscopy. Patients with suspected advanced EOC each signed an informed consent on receiving either of the treatment modalities.

The first step in the treatment algorithm was a diagnostic laparoscopy. During laparoscopy, tumor stage was documented and a biopsy was obtained, part of which was sent for frozen section. If the diagnosis of ovarian cancer was confirmed and a complete/optimal tumor resection seemed possible, the team proceeded to laparotomy and primary CRS; otherwise, the laparoscopy was concluded and the patient proceeded to NAC. The initial tumor stage obtained during the staging laparoscopy was assigned to the patient throughout the treatment period, even if the stage changed after undergoing NAC. Patient's age, tumor stage, grading, intraoperative events (bowel resection, bleeding, urinary, and intestinal tract injuries), postoperative events (wound healing disorders, including wound infection, thromboembolic events, and anastomosis leakage), and completion of surgical resection, were documented and tabulated. In this study, complete resection was defined as complete macroscopic tumor resection with no detectable gross tumor tissue. Optimal resection was defined as microscopically detectable tumor tissue in the specimen and/or macroscopically nonresectable tumor residue <1 cm in diameter. Suboptimal resection was defined as tumor residue > 1 cm, provided that in all cases, maximal surgical effort from the most experienced gynecologic oncologist was attempted to reach complete resection.

Statistical analyses

The data were analyzed by the aid of SPSS for Windows, version 21.0. Normality of the data were evaluated using the Kolmogorov-Smirnov test. Qualitative data are presented as numbers and percentages. The continuous variables are shown as means ± SDs for parametric data, and as medians and ranges for nonparametric data. The χ^2 test was used to evaluate correlations between categorical variables. The groups were compared using either the Mann-Whitney U test for nonparametric data or the Student t test for parametric data or. Analyses of variance were used to compare the means of more than 2 groups; the Kruskal-Wallis test was used to compare medians of more than 2 groups. For all of the statistical tests, the threshold of significance was set at 5%. Differences were considered significant if the probability of error was <5% ($P < 0.05$).

Results

In the study period, we found 113 patients who met the inclusion criteria in our records. After excluding patients who were diagnosed with tumors other than EOC during the diagnostic laparoscopy and those with missing data, a total of 92 patients were left. Of these, 42 patients were managed through upfront CRS (primary cytoreduction) followed by ACT (group A), and 50 patients received platinum-based ACT of 3–6 cycles before interval debulking (group B). Median ages did not significantly differ between groups A (57 y) and B (56 y; $P = 0.9$). Groups A and B did not significantly differ in distribution of FIGO stage [$P = 0.5$; group A—stages IIIC: 34 (80.9%), IVA: 6 (14.3%), and IVB: 2 (4.8%); and group B—stage IIIC: 45 (90%), IVA: 5 (10%) and IVB: 0 (0%)]. Thirty-seven (88.1%) patients in group A and 46 (92%) patients in group B had papillary serous carcinoma, while 5 (11.9%) patients in group A and 4 (8%) patients in group B had mucinous carcinoma. In group B, 17 (34%) patients showed no response to chemotherapy (ie, NAC), 30 (60%) patients showed partial response, and 3 (6%) patients showed complete remission. **Table 1** compares the 2 groups regarding CRS completeness and bowel resection rates; significant differences were not seen. **Table 2** compares the 2 groups with regard to intraoperative complications and postoperative morbidities, where significant differences were also not seen.

Discussion

The extent of CRS for EOC appeared to be the most influential independent factor on survival, with complete surgical removal of all grossly identifiable tumor residues having the best prognosis, followed by optimal CRS, which leaves behind tumor residues <1 cm. In contrast, those who still harbor gross tumor residues > 1 cm have overall survival approaching that of patients who did not undergo any surgical intervention at any time[12–16]. In many cases, complete, or even optimal, surgical cytoreduction is not feasible due to extensive tumor growth. This has led some authors to advocate against aggressive surgery for ovarian cancer. They suggested that tumor biology is the main factor that affects the extent of tumor spread, the attainability of complete surgical resection, and hence survival; as a logical sequence to this suggestion, they assumed that complete/optimal surgical

Table 1

Comparison between the 2 groups with regard to completeness of surgical resection and the need to perform bowel resection ($P < 0.05$).

	n (%)		
	Primary Surgery (Group A) (N = 42)	Interval Debulking (Group B) (N = 50)	
Completeness of surgical cytoreduction			
Complete resection	11 (26.2)	19 (38.0)	
Optimal resection	25 (59.5)	29 (58.0)	
Suboptimal resection	6 (14.3)	2 (4.0)	$\chi^2 = 0.73$, $P = 0.39$
Bowel resection			
Not performed	13 (31)	17 (34)	$\chi^2 = 2.31$, $P = 0.128$
Performed	29 (69)	33 (66)	

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Table 2

Frequency of intraoperative and postoperative complications in both groups.

	n (%)		
	Primary Surgery (Group A) (N = 42)	Interval Debulking (Group B) (N = 50)	
Intraoperative complications			
Bleeding	21 (50.0)	19 (38.0)	$\chi^2 = 1.46$, $P = 0.22$
Urinary bladder injury	2 (4.8)	1 (2.0)	$\chi^2 = 0.85$, $P = 0.35$
Ureteric injury	1 (2.4)	0	
Inadvertent intestinal injury	0	1 (2.0)	
Postoperative complications			
Anastomosis leakage	2 (4.8)	2 (4.0)	$\chi^2 = 0.09$, $P = 0.76$
Impaired wound healing and infection	11 (26.2)	8 (16.0)	$\chi^2 = 1.42$, $P = 0.23$
Thromboembolic manifestations	1 (2.4)	2 (4.0)	$\chi^2 = 0.09$, $P = 0.75$

cytoreduction is attainable only in cases where the tumor has not spread beyond resection[17,18]. Randomized trials suggested another approach that entailed NAC, followed by interval debulking. These trials suggest that this approach provides non-inferior overall survival compared with primary surgery followed by chemotherapy[5,6]. As a result of this finding, complete CRS was thought to be feasible in more patients, after NAC. This was not confirmed in our cohort or in other published reports, which showed no increase in complete resection rates and no reduction in morbidity rates in these patients in comparison with patients treated with primary debulking[19]. The study by Tozzi and colleagues tested the influence of NAC on the surgical technique of visceral peritoneal debulking, but did not have bowel resection as its primary end point. One retrospective study showed a reduction in bowel resection rate after NAC, but did not include any control group for comparison; as such, their suggestions and conclusions may be liable to claims of design flaws[20]. In contrast, our study examined both treatment modalities in a comparable group of patients, avoiding such claims. Our reported anastomosis leak was comparable to published data, which reported leak rates between 1.7% and 6.8%[21,22].

The limitations of our study include a selection bias due to the fact that patient allocation to either of the treatment modalities was based on the attainability of complete tumor resection, which was determined during the diagnostic laparoscopy performed initially, before starting treatment. This led to the selection of patients with poorer prognosis into group B. However, this point could be disputed by the comparable surgical resection rates in both of our groups.

Published rates of complete, optimal, and suboptimal tumor resection vary greatly in the literature, in both prospective and retrospective reports, which reflects the heterogeneity of this disease and the variability in surgical expertise between treatment centers worldwide. Complete CRS ranges between 15% and 86%, whereas optimal cytoreduction ranges between 10% and 80.6% in reported data[5,6,19,23–26]; our results were in keeping with these published data.

Our findings suggest that neoadjuvant platinum-based chemotherapy did not alter the complexity of the operative procedure in advanced EOC; the incidence of bowel resection, intraoperative complications, and postoperative morbidity in advanced EOC did not show significant reduction compared with primary surgical cytoreduction. Future well-designed prospective randomized larger studies will be required to validate those results.

Ethical approval

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Author contribution

B.R.: contributed to protocol and project development, and data collection. A.E. contributed to data collection, management and analysis. H.N. contributed to project development and data analysis. D.E.-E. contributed to analysis and interpretation of data. K.M.A. contributed to project development and data collection. E.M. contributed to project development and data analysis. A.A.S. contributed to project development and data analysis. All authors contributed to manuscript writing and editing, and approved of the manuscript in its current submitted form and agree to be held accountable for the accuracy and integrity of any part of this work.

Conflict of interest disclosures

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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