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Prognostic Significance of Postoperative Morbidities in Patients With Advanced Epithelial Ovarian Cancer Treated With Neoadjuvant Chemotherapy and Delayed Primary Surgical Debulking

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Background: To examine the prognostic significance of postoperative morbidities in patients with ovarian cancer treated with neoadjuvant chemotherapy and interval surgical debulking.

Methods: Retrospective chart reviews of all patients treated with neoadjuvant chemotherapy and interval debulking were performed from 1999 to 2002. Descriptive statistics were used to summarize the distributions of important clinical variables. Logistic regression was used to identify statistically significant predictors of postoperative morbidities. Cox regression was used to model time to first clinical progression. Survivals were estimated by the Kaplan-Meier method and compared with the log rank test. $P < .05$ was considered to be statistically significant.

Results: Fifty-eight patients were treated with neoadjuvant platinum-taxane combination chemotherapy. Major surgical complications were observed in four patients (6.8%). There were no perioperative deaths. The presence of concurrent medical comorbidities was associated with the development of significant postoperative morbidities ($P = .038$). Cox regression showed any macroscopic residual disease ($P = .04$) and the presence of significant postoperative morbidities (odds ratio, 4.7, 95% confidence interval, 1.8–12.7, $P = .002$) to be predictive of a shorter progression-free interval.

Conclusions: Neoadjuvant chemotherapy followed by interval surgical debulking carried a low risk for postoperative morbidity. The adverse influence of marked postoperative morbidity on progression-free survival needs further study.

Key Words: Postoperative morbidities—Neoadjuvant chemotherapy—Prognosis—Ovarian cancer.

Epithelial ovarian cancer is currently the fifth leading cause of death in Canadian women.[1] Standard treatment in patients with ovarian cancer includes aggressive initial tumor debulking surgery followed by adjuvant platinum-taxane combination chemotherapy. Rationales for aggressive tumor resection were based on a number of retrospective case series that demonstrated that suboptimal tumor residual (frequently defined as being between 1 and 2 cm) after surgery to be a strong prognostic indicator.[2–4] However, it is not uncommon for patients with metastatic disease to present in a markedly malnourished state with a poor performance status that

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results from the advanced stage of their cancer. Aggressive tumor debulking surgery initially may not be well tolerated in this population, with potential for high postoperative morbidity and mortality. Postoperative complications can delay starting adjuvant chemotherapy, allowing for further regrowth of tumors and negating the potential benefits afforded by the debulking procedure. Furthermore, there is a good chance that debulking will be suboptimal because of widespread metastatic disease.[5] In this setting, the benefit of surgery is questionable.

Postoperative morbidities in patients undergoing primary cytoreduction had been reported in a number of retrospective and prospective studies. Commonly encountered complications include: wound infection or dehiscence (2.3%), cardiac failure (2%), deep vein thrombosis (2%), pulmonary embolism (1.8%), gastrointestinal or genitourinary fistula (1.5%), postoperative bleeding (1.5%), small bowel obstruction (1%), and a perioperative mortality rate of approximately 1.8%.[6–11] Possible theoretical advantages of neoadjuvant chemotherapy treatment include: decreasing bulk of the metastatic disease to facilitate the surgical debulking and limiting the number of surgical procedures needed to achieve optimal residual disease, resolution of pleural effusions and ascites to facilitate perioperative anesthetic care, and improving the patients' nutritional and performance status so radical tumor resection can be better tolerated, resulting in decreased postoperative morbidities.

The objectives of this study were to examine in detail the prevalence of postoperative morbidities in all patients eligible for neoadjuvant chemotherapy followed by delayed primary surgical debulking and to investigate its potential prognostic values on progression-free interval after primary treatment.

PATIENTS AND METHODS

Retrospective chart reviews of all patients treated with neoadjuvant platinum-taxane combination chemotherapy followed by delayed primary surgical debulking for advanced-stage ovarian cancer were performed from January 1, 1999, to December 31, 2002, to allow for adequate long-term follow-up. The Ottawa Hospital Research Ethics Board approved the research protocol.

Since 1999, neoadjuvant chemotherapy in combination with delayed primary surgical debulking has been the standard of care in our institution for advanced-stage epithelial ovarian cancer because treatment can be instituted much earlier than in the primary surgical approach used to bring the disease under control. During this time, all patients with clinical presentations consistent with metastatic ovarian or primary peritoneal cancer with radiologic appearance of peritoneal carcinomatosis, bilateral enlarged adnexal masses, and grossly increased Ca-125 underwent ultrasound-guided core biopsy of the most easily accessible tumor mass. Once pathologic confirmations had been obtained that indicated a primary gynecologic origin through histology and immunohistochemistry studies and patients did not show signs of uncontrollable pain or obstructive symptoms requiring urgent exploratory laparotomy, three cycles of carboplatinum (area under the curve = 6) and paclitaxel (175 mg/m^2) were administered intravenously every 3 weeks. A delayed interval surgical debulking procedure was scheduled at approximately 4 weeks after the third cycle of chemotherapy in all patients who received neoadjuvant chemotherapy, irrespective of the degree of response to chemotherapy. The goal of the surgical procedure was to maximally debulk any macroscopic tumors. Radical upper abdominal surgical debulking procedures were not routinely performed. A similar chemotherapy regimen was resumed for three more cycles as soon as patients sufficiently recovered from surgery, with no further anticipated major postoperative complications. All medical and surgical interventions were supervised by members of the division of gynecologic oncology at the University of Ottawa.

Relevant patient demographics, together with disease- and treatment-related variables obtained from chart reviews, included: age, presence of concurrent medical comorbidities, best response to neoadjuvant treatment, tumor grade, histology, residual disease status, and status at last documented follow-up visit. Postsurgical morbidities were assessed by examining the extent of perioperative blood transfusion needs, length of postoperative hospital stay, need for readmission to the hospital within 4 weeks of surgery, and time to resumption of adjuvant chemotherapy. Postoperative morbidity was defined as the presence of any of the following: transfusion of four or more units of packed red blood cell, reoperation and/or readmission to the hospital within 4 weeks of the surgical procedure, need for intensive care unit admission perioperatively, or any major cardiopulmonary and renal complications.

Descriptive statistics were used to summarize demographic variables. χ^2 tests were used to test for statistically significant associations between categorical variables. Backward stepwise logistic regression models were built to identify preoperative factors that

TABLE 1. *Distribution of medical comorbidities and relevant disease-related demographics in 58 patients receiving neoadjuvant chemotherapy and interval debulking*

Finding	n (%)
Medical comorbidities	
Cardiovascular	3 (5.2)
Pulmonary	1 (1.7)
Hypertension	9 (15.5)
Two or more comorbidities	2 (3.4)
None	43 (74.1)
Tumor stage	
II	4 (6.9)
III	52 (89.7)
IV	2 (3.4)
Tumor grade	
1	3 (5.2)
2	8 (13.8)
3	4 (81)
Tumor histology	
Serous	43 (74.3)
Mucinous	2 (3.4)
Endometrioids	4 (6.9)
Clear cells	1 (1.7)
Anaplastic	6 (10.3)
Mixed tumors	2 (3.4)

were associated with postoperative morbidities. Cox proportional hazard models were used to model time to first clinical disease recurrences. Median survivals were estimated by the Kaplan-Meier method. Log rank tests were used to compare survival outcomes. $P < .05$ was considered statistically significant. SPSS software version 13 was used for all statistical analysis.

RESULTS

Seventy-two patients presented with disease clinically consistent with advanced ovarian cancer over the study period. Fifty-eight patients (80.6%) were treated by the neoadjuvant chemotherapy protocol when no indication for acute surgical intervention, such as severe pain or obstructive symptoms, was present. The mean age for the group was 64 years (range, 36–88 years). Forty-seven patients (81%) were postmenopausal at the time of diagnosis. Seventy-four percent of the patients had no concurrent marked medical comorbidities. All other patients had their medical conditions well controlled with oral medications. Table 1 lists the distribution of medical comorbidities and relevant disease-related demographics in the study group. The most commonly encountered medical comorbidity was hypertension. As expected, most patients presented at stage III (89.7%) and had grade 3 tumor (81%). Serous pathology was present in 74% of tumor samples. No unexpected pathology was encountered at the time of surgical exploration.

Bowel resections were required in two patients (3.4%). Microscopic, < 1 cm, and between 1- to 2-cm residual diseases were found in 16 patients (27.6%), 16 patients (27.6%), and 14 patients (24.1%), respectively. The most common reason for suboptimal residual disease was bulky disease located in the upper abdominal regions. The median estimated blood loss was 400 mL. Blood transfusion was given in 29% of patients. The median amount of transfusion need was two units of packed red blood cells, which was most commonly provided on postoperative day 3. Of the 17 patients who received transfusions, six transfusions were given for symptomatic anemia. Eleven patients received transfusions in anticipation of upcoming chemotherapy. The median postoperative hospital stay and time to resumption of chemotherapy was 5 and 14 days, respectively.

Marked postoperative complications were observed in four patients (6.8%). One patient (1.7%) had postoperative bleeding that required more than four units of blood, and two patients needed repeat laparotomy within 4 weeks as a result of wound dehiscence and complete mechanical small bowel obstruction. There was one case (1.7%) of postoperative myocardial infarction, which required admission to the intensive care unit. Eight patients (13.6%) required readmission within 4 weeks of surgery as a result of paralytic ileus (n = 2), partial small bowel obstruction (n = 2), *Clostridium difficile* bowel infection (n = 1), symptomatic atrial fibrillation (n = 1), esophagitis (n = 1), and upper urinary tract infection (n = 1). There was no case of pulmonary embolism, deep vein thrombosis, cerebrovascular accident, or operative mortality in this series. The most commonly performed surgical procedures were total abdominal hysterectomy, bilateral salpingooophorectomy, and complete infracolic omentectomy.

Logistic regression analysis revealed that the presence of preoperative medical comorbidities, despite patients being under good control with medication, was significantly associated with the development of postoperative morbidities ($P = .038$). Age, cancer grade, residual disease after surgery, and percentage of Ca-125 response to neoadjuvant chemotherapy were not associated with statistically significant postoperative complications in the model.

Cox proportional hazard models demonstrated macroscopic residuals ($P = .04$) and the presence of postoperative morbidities (odds ratio, 4.7; 95% confidence interval (95% CI), 1.8–12.7; $P = .002$) to be the most statistically significant predictive variables adversely affecting time to first disease progression. Furthermore, there was a negative trend ($P = .08$) of

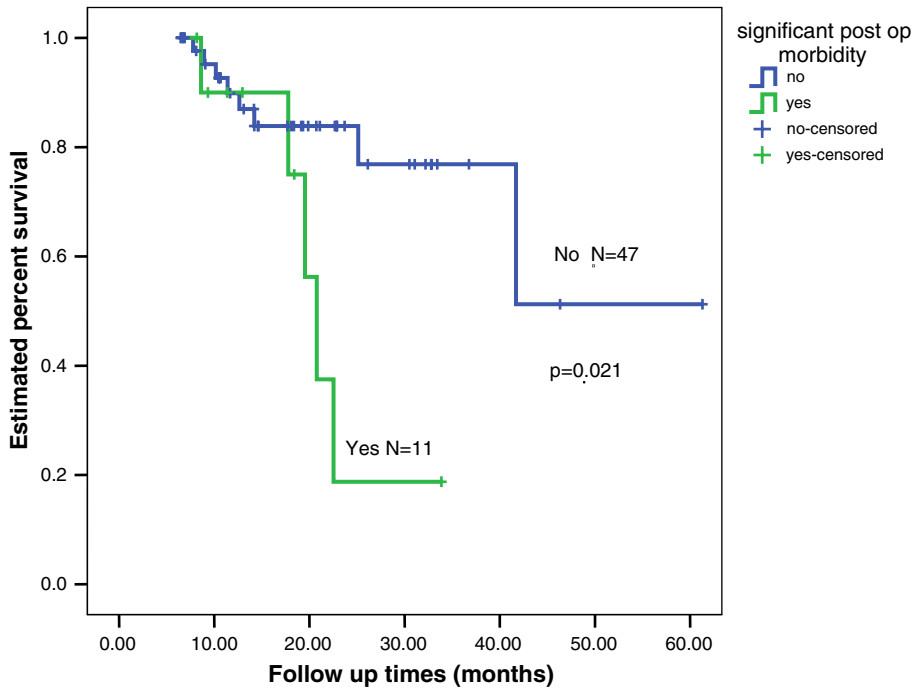

FIG. 1. Estimated survival functions in patients with and without marked postoperative morbidities.

increasing age on the progression-free interval independent of other variables.

At a median follow-up time of 19 months, 13 patients had died from disease. The estimated median survival was 41.5 months (95% CI, 32.2–50.8). In patients with no marked postoperative morbidities, the estimated survival was 45.6 months (95% CI, 35.5–55.8). In contrast, the estimated survival in patients who experienced severe postoperative morbidities was significantly shorter, at 21.7 months (95% CI, 16.4–26.9; $P = .021$). Figure 1 shows the survivals for the two groups stratified for the presence of postoperative morbidities. There was no observed statistically significant difference in overall survival between different residual disease amounts, a finding that is most likely the result of the small number of patient in each residual disease strata. However, there was a trend toward better median survival in patients with <1 cm residual disease. Figure 2 shows the estimated progression-free intervals stratified by residual tumor status and confirms the importance of microscopic residual disease to time to disease recurrence.

DISCUSSION

Despite many recent advancements in surgical techniques and chemotherapy treatments, most patients with advanced ovarian cancer will die of their disease. Treatment strategies should try to balance the need to maximally prolong the progression-free interval and minimize treatment-associated morbidities. Patients with advanced ovarian cancer are at risk for major morbidities from initial aggressive resection to remove tumor masses involving multiple intra-abdominal organs in an effort to achieve optimal residual disease status. This can result in delays of adjuvant chemotherapy and a high chance of receiving suboptimal debulking.

Our study showed that interval surgical debulking after neoadjuvant chemotherapy treatment in patients with advanced-stage ovarian cancer has a low rate of postoperative morbidity, with an optimal debulking rate similar to that commonly reported in other series that used initial surgical debulking. However, the perioperative complication rate seemed to be lower than standard up-front surgery. This could perhaps be explained by the smaller volume of tumor that would need to be resected and the lesser extent of surgical resections required to obtain optimal residual disease status. This would allow for quick resumption of chemotherapy to minimize treatment interruptions and maintain tumor control. Most of our patients was able to restart their chemotherapy within 2 weeks of surgery without impairment in wound healing and without a higher risk of hematologic or infectious complications.

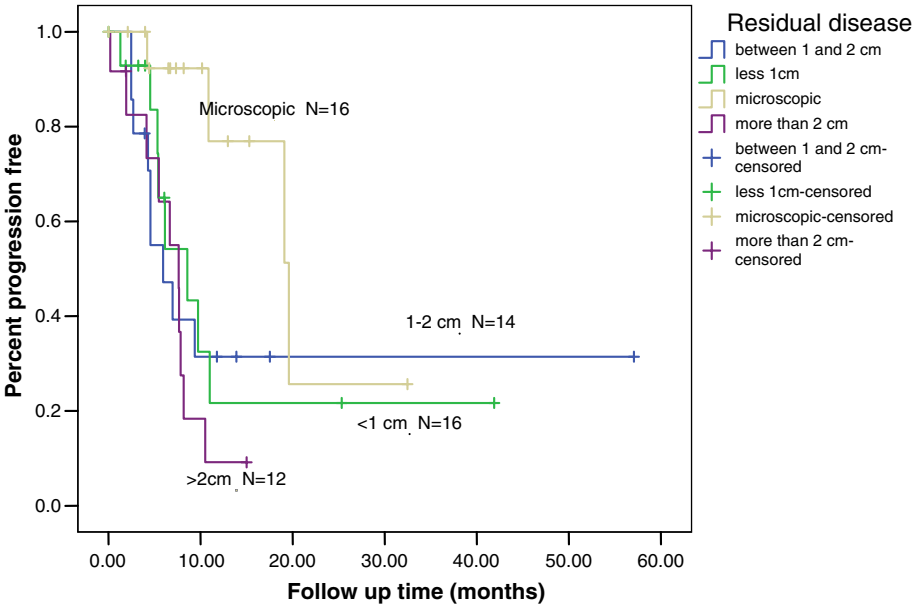

FIG. 2. Progression-free estimate stratified by amount of residual disease.

Similarly, in other tumor sites, the neoadjuvant chemotherapy approach permitted less surgical intervention and better quality of life without compromising oncologic outcomes. In breast cancer, neoadjuvant chemotherapy has been used to downstage primary breast lesions, allowing for breast-conserving techniques while resulting in excellent local control.[12,13] In addition, neoadjuvant chemotherapy has also been shown to be an effective option to downstage advanced rectal cancers, allowing for sphincter-preserving surgical procedures. This markedly reduced the need for terminal colostomy, which allowed for improvement in patients' quality of life.[14–18]

As expected, patients with concurrent medical comorbidities, even if well controlled, were more likely to experience postoperative morbidities independent of age, tumor response, and tumor residuals status. Careful preoperative medical optimization and refinement in operative techniques, together with aggressive postoperative supportive care, should further minimize the potential effect of this factor. It is interesting to note that the presence of postoperative morbidities was an important independent adverse prognostic variable with regard to progression-free interval. It could have reflected the detrimental effects of chemotherapy delays in patients with severe postoperative complications or the possible immunosuppressive effects of blood transfusion and major added physical stress on tumor control, as reported in other tumor types.[19–24] This important observation requires further investigations and analysis in larger studies to confirm its importance and to allow for future optimization strategies.

The limitations of our study were its relatively small sample size and the retrospective nature with probable selection bias, because not all patients were treated with neoadjuvant chemotherapy. The small sample size probably accounted for the nonstatistically significant difference in estimated survival in patients with different residual diseases. However, to our knowledge, this is the largest series of patients with ovarian cancer without major contraindication to initial surgery who were treated with the neoadjuvant approach. The findings of this study will need to be prospectively confirmed in larger studies.

Similar to patients treated with primary surgical debulking and adjuvant chemotherapy, we documented the prognostic importance of tumor residual status after surgery in predicting the progression-free interval in patients treated with neoadjuvant chemotherapy. It was noted that only patients left with microscopic residual diseases experienced a statistically significant improvement in progression-free intervals (Fig. 2). Progression-free intervals were not statistically different between patients left with different amounts of macroscopic residual disease (<1 cm, 1 to 2 cm, or >2 cm). This could be because most chemosensitive tumor bulk would have been removed by presurgical chemotherapy treatment. Tumor cells found at the time of interval surgical debulking, as a whole, can be expected to be relatively more chemoresistant than those found at the time of initial diagnosis. As such, a complete macroscopic tumor

debulking to microscopic residuals would have to be achieved to be of benefit, especially when a similar chemotherapy regimen was to resume postoperatively. This finding, if confirmed in larger studies, might serve as a basis for revision of the definition of optimal residual disease in a neoadjuvant setting as being microscopic rather than <1 to 2 cm as the currently accepted standard in patients treated with primary surgical debulking. The effects of residual disease status on overall survival could not be properly assessed in our study because of the small number of patients in each category, but a trend toward better survival was observed in patients with small residual disease, similar to patients treated with up-front surgical debulking followed by adjuvant chemotherapy.

In view of the universally poor outcomes in patients treated with chemotherapy alone, we would routinely recommend aggressive surgical debulking as an important therapeutic intervention in patients with ovarian cancer treated with neoadjuvant chemotherapy. Furthermore, patients whose disease was debulked to microscopic residuals might also benefit from intraperitoneal chemotherapy regimens that would allow for increase of dose intensity to overcome the acquired drug resistance. We are currently investigating this combined intravenous neoadjuvant chemotherapy and intraperitoneal protocol in patients who were optimally debulked at the time of interval debulking at our center.

In conclusion, aggressive surgical debulking is indicated in patients treated with neoadjuvant chemotherapy with anticipated low postoperative morbidities, as documented in this study. Neoadjuvant chemotherapy remains an attractive treatment option in patients with advanced ovarian cancer. The current ongoing OV13/ EORTC 55971 randomized phase 3 study comparing up-front debulking surgery versus neoadjuvant chemotherapy in patients with stage IIIC or IV epithelial ovarian carcinoma will further clarify the role of neoadjuvant chemotherapy in this patient population.

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