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Is time to chemotherapy a determinant of prognosis in advanced-stage ovarian cancer?

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Abstract

Objectives. Clinicians often question when to start chemotherapy after patients undergo surgery for ovarian cancer. A major unproven concern is whether a long postoperative delay reduces the benefits of an extensive procedure and leads to disease progression. Our objectives were to evaluate the correlation between clinical and pathologic variables and to evaluate the effect of the "time to chemotherapy" (TTC) interval on survival.

Methods. We retrospectively studied data from 218 patients with International Federation of Gynecology and Obstetrics stage IIIC or IV ovarian cancer (TNM stage T3c or T4) who were consecutively treated between January 1, 1994, and December 31, 1998.

Results. Mean age at diagnosis was 64 years (range, 24–87 years; median, 65 years), and 206 patients received postoperative platinum-based chemotherapy. Mean TTC interval was 26 days (range, 7–79 days; median, 25 days). No correlation was found between operative time and TTC interval length ($P=0.99$). Age and performance of rectosigmoidectomy were correlated with longer TTC interval ($P=0.009$ and $P=0.005$, respectively), but TTC was not a predictor of overall survival (odds ratio, 1.00; 95% confidence interval, 0.98–1.01; $P=0.85$). Differences in TTC interval length (≤ 17 days, 18–26 days, 27–33 days, or ≥ 34 days) did not affect survival ($P=0.93$). Even after categorizing patients by residual disease (<1 cm or ≥ 1 cm), no statistically significant effect of TTC on prognosis was identified.

Conclusions. Concerns about the TTC interval should not be used to justify spending less time in the operative arena or using a more conservative approach for patients with advanced ovarian cancer.

Keywords: Chemotherapy timing; Ovarian cancer; Residual disease; Surgery

Introduction

Ovarian cancer is the most severe gynecologic malignancy in terms of aggressiveness and survival, with approximately 16,000 deaths and 22,000 new cases estimated to occur in the United States during 2005 [1]. Griffiths [2] was the first to show in 1975 that the diameter of the remaining tumor after cytoreductive surgery is the principal determinant of prognosis in patients affected by ovarian cancer. Other prospective and retrospective studies have confirmed this observation [3–5]. In patients with advanced ovarian cancer, the goal of cytoreductive surgery is to minimize the amount of residual disease (RD). This aim can be achieved with different techniques that are used more frequently as gynecologic oncologists gain experience with advanced cytoreductive procedures (e.g., diaphragm stripping or resection, bowel resection, splenectomy, and liver resection) [6–11].

Radical surgical procedures used to treat patients with advanced ovarian cancer have resulted in acceptable morbidity rates [12]. We recently reported that patients with advanced ovarian cancer benefit from radical procedures such as diaphragm stripping, resection, or ablation, bowel resection, intensive peritoneal ablation, or splenectomy [13]. A major unproven concern about these radical procedures is that waiting too long after surgery to initiate chemotherapy may reduce the

Abbreviations: DFS, disease-free survival; RD, residual disease; TTC, time to chemotherapy.

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benefits of surgery, thereby leading to disease progression. Furthermore, complications often occur after such intensive procedures and may prolong the recovery period.

In the present study, we sought to evaluate the impact of the "time to chemotherapy" (TTC) interval, defined as the length of time between surgery and initiation of chemotherapy, on the survival of patients who underwent primary cytoreductive surgery and subsequent chemotherapy. We found that concerns about the TTC interval should not be used to justify spending less time in the operative arena or using a more conservative approach for patients with advanced ovarian cancer.

Materials and methods

Relevant clinical data were abstracted from operative reports, hospital and outpatient clinical notes, the Mayo Clinic Cancer Center Registry database, and correspondence from referral institutions. Patients with a diagnosis of primary epithelial ovarian cancer who had undergone primary surgery at Mayo Clinic between January 1, 1994 and December 31, 1998 were identified from surgical and hospital records. Disease status before surgery was recorded in the operative notes for statistical analysis. The study was approved by the Mayo Foundation Institutional Review Board.

All study patients were assessed and classified according to the American Society of Anesthesiology physical status grades before surgery. Surgical stage and cancer grade were defined using criteria from the International Federation of Gynecology and Obstetrics [14]. Patients with stage IIIC or IV ovarian cancer (TNM stage T3c or T4) were included in the study if they underwent primary surgical exploration at our institution and received a postoperative diagnosis of epithelial ovarian cancer. Patients who underwent surgical exploration at another institution or received chemotherapy before surgery and their referral to Mayo Clinic were excluded.

After surgery, all patients received first-line platinum-based chemotherapy, either alone or in combination with paclitaxel or cyclophosphamide, for 6 to 8 courses, every 3 to 4 weeks, according to the different treatment protocols in effect during the years of the study. We did not restrict our analysis only to patients who received paclitaxel nor did we stratify patients according to chemotherapy regimen; we did not find a significant survival difference between the paclitaxel-combination group and all other patients in our cohort. Patients were excluded from the study if data from the first chemotherapy course were not reported. No patient received consolidation therapy at the time of the study. Only 1 patient had intraperitoneal chemotherapy, and the patient's data were included in the analysis.

For statistical analysis, patient characteristics were categorized as follows: American Society of Anesthesiology grades 1 and 2 versus 3 and 4; histologic grade 3 versus 1 and 2; and histologic subtype serous versus all other subtypes. Operative time was categorized as less than 200 min or 200 min and longer (median value). For TTC, patients were categorized by quartiles: $\leq$17 days, 18–26 days, 27–33 days, or $\geq$34 days after surgery. RD was divided into 4 categories: RD of 0 (no gross tumor), macroscopic RD less than 1 cm, RD 1 cm or greater but less than or equal to 2 cm, and RD greater than 2 cm.

Statistical analysis was performed by using the Student's t test, logistic regression analysis, and the log-rank test. We measured overall survival in all cases. Disease-free survival (DFS), defined as the time from diagnosis to the first progression of disease, was measured when data were available. Survival curves were plotted using the Kaplan–Meier method. Differences were considered statistically significant at $P<0.05$. JMP statistical software (version 5.1, SAS Institute Inc, Cary, North Carolina) was used for the analysis.

Results

Data were examined from 218 patients with a diagnosis of International Federation of Gynecology and Obstetrics stage IIIC or IV ovarian cancer (TNM stage T3c or T4). Patient characteristics and tumor features are summarized in Table 1.

Table 1
Patient characteristics and tumor features (n=218)

Variable	Patients	
	No.	%
Patient characteristics		
Age, years		
Mean (range)	63.3 (24–87)	
Median	64	
ASA grade		
1	7	3.2
2	95	43.6
3	102	46.8
4	9	4.1
Unknown	5	2.3
Tumor features		
FIGO stage		
IIIC	174	79.8
IV	44	20.2
FIGO grade		
1	1	0.5
2	13	6.0
3	204	93.6
Histologic findings		
Serous	143	65.6
Mucinous	2	0.9
Endometrioid	20	9.2
Clear cell	8	3.7
Transitional cell	3	1.4
Mixed	21	9.6
Seroanaplastic	19	8.7
Müllerian origin	2	0.9
Cytologic findings		
Positive	201	92.2
Negative	17	7.8
RD, cm		
None detectable	44	20.2
<1	97	44.5
1–2	27	12.4
>2	50	22.9

ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; RD, residual disease.

Primary surgery was performed with the intent to diagnose, stage, and surgically reduce tumor volume. Mean operative time was 215 min (median, 200 min; range, 40–480 min). Mean TTC was 26 days (median, 26 days). The upper and lower quartiles for TTC were 17 and 33 days, respectively. Five patients (2%) died less than 30 days after surgery. Thirteen patients (6%) did not receive chemotherapy because of rapid disease progression, patient refusal, inadequate performance status, or perioperative death; all 13 died less than 3.5 months after surgery and were not included in subsequent analyses.

Aggressive surgical procedures such as diaphragm stripping, resection, or ablation, rectosigmoidectomy, intensive peritoneal ablation, splenectomy, and hepatectomy were correlated with a longer operative time and less RD (data not shown). Nevertheless, of all the surgical procedures, only rectosigmoidectomy was correlated with the TTC interval (Table 2), which suggests that, after most surgical procedures, a standard recovery period is sufficient unless postoperative complications occur. The TTC