

ORIGINAL ARTICLE

## Secondary Surgical Cytoreduction for Advanced Ovarian Carcinoma

Peter G. Rose, M.D., Stacy Nerenstone, M.D., Mark F. Brady, Ph.D.,  
Daniel Clarke-Pearson, M.D., George Olt, M.D., Stephen C. Rubin, M.D.,  
David H. Moore, M.D., and James M. Small, M.D., Ph.D.,  
for the Gynecologic Oncology Group

### ABSTRACT

#### BACKGROUND

We evaluated the effect of adding secondary cytoreductive surgery to postoperative chemotherapy on progression-free survival and overall survival among patients who had advanced ovarian cancer and residual tumor exceeding 1 cm in diameter after primary surgery.

#### METHODS

Women were enrolled within six weeks after primary surgery. If, after three cycles of postoperative paclitaxel plus cisplatin, a patient had no evidence of progressive disease, she was randomly assigned to undergo secondary cytoreductive surgery followed by three more cycles of chemotherapy or three more cycles of chemotherapy alone.

#### RESULTS

We enrolled 550 women. After completing three cycles of postoperative chemotherapy, 216 eligible patients were randomly assigned to receive secondary surgical cytoreduction followed by chemotherapy and 208 to receive chemotherapy alone. Surgery was declined by or medically contraindicated in 15 patients who were assigned to secondary surgery (7 percent). As of March 2003, 296 patients had died and 82 had progressive disease. The likelihood of progression-free survival in the group assigned to secondary surgery plus chemotherapy, as compared with the chemotherapy-alone group, was 1.07 (95 percent confidence interval, 0.87 to 1.31;  $P=0.54$ ), and the relative risk of death was 0.99 (95 percent confidence interval, 0.79 to 1.24;  $P=0.92$ ).

#### CONCLUSIONS

For patients with advanced ovarian carcinoma in whom primary cytoreductive surgery was considered to be maximal, the addition of secondary cytoreductive surgery to postoperative chemotherapy with paclitaxel plus cisplatin does not improve progression-free survival or overall survival.

From Case Western Reserve University and the Division of Gynecologic Oncology, MetroHealth Medical Center — both in Cleveland (P.G.R.); the Department of Medicine, University of Connecticut, and Hartford Hospital — both in Hartford (S.N.); the Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, N.Y. (M.F.B.); the Division of Gynecologic Oncology, Duke University Medical Center, Durham, N.C. (D.C.-P.); the Division of Gynecologic Oncology, Pennsylvania State University, Hershey Medical Center, Hershey (G.O.); the Division of Gynecologic Oncology, University of Pennsylvania Cancer Center, Philadelphia (S.C.R.); the Division of Gynecologic Oncology, Indiana University School of Medicine, Indianapolis (D.H.M.); and UniPath and Colorado Gynecologic Oncology — both in Denver (J.M.S.). Address reprint requests to Ms. Denise Mackey at the Gynecologic Oncology Group Administrative Office, 4 Penn Center, 1600 JFK Blvd., Suite 1020, Philadelphia, PA 19103.

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**I**N MOST PATIENTS WITH OVARIAN CARCINOMA, the disease is diagnosed at an advanced stage because of the lack of effective screening. Standard treatment of such cases is a combination of maximal resection of primary and metastatic carcinoma and postoperative chemotherapy. Retrospective studies have demonstrated that the amount of residual tumor after primary surgery is a prognostic factor.<sup>1-6</sup> The Gynecologic Oncology Group (GOG) found that when the diameter of residual tumor is no more than 1 cm, survival tends to be longer, and this finding is also considered to indicate optimal debulking.<sup>5</sup> Patients with residual tumor of no more than 1 cm who are treated with a platinum analogue and paclitaxel have a median progression-free survival of approximately 22 months and an overall survival of approximately 52 months, as compared with 14 and 26 months, respectively, among patients with larger residual tumors.<sup>7,8</sup>

Efforts to improve survival among women with advanced ovarian cancer have had only limited success. Two randomized trials reported increased survival when paclitaxel replaced cyclophosphamide in combination with cisplatin.<sup>9,10</sup> In both studies, median progression-free survival and overall survival increased by 35 to 40 percent.

Secondary surgical cytoreduction after chemotherapy is a strategy for reducing tumor burden. Several prospective studies have shown that after two to six cycles of chemotherapy, residual disease can be reduced to 1 cm or less in 50 to 90 percent of patients who had undergone suboptimal debulking during primary surgery.<sup>11-16</sup> The duration of survival in one study was reported to be 42 months among patients who underwent optimal cytoreduction with either primary or secondary surgery.<sup>13</sup> A randomized study conducted by the European Organisation for Research and Treatment of Cancer (EORTC) found significant increases in median progression-free survival (by five months) and overall survival (by six months) among patients who underwent suboptimal primary debulking followed by secondary surgery after three cycles of cisplatin and cyclophosphamide.<sup>17</sup> We sought to determine whether secondary cytoreductive surgery improved progression-free survival and overall survival among patients who had advanced ovarian cancer and residual tumor of more than 1 cm and who received cisplatin and paclitaxel.

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## METHODS

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### STUDY DESIGN AND EVALUATION

Eligible patients had stage III or stage IV ovarian carcinoma with residual intraperitoneal tumor that exceeded 1 cm in diameter after they had undergone surgery with the goal of removing as much tumor as possible. The histologic appearance and stage of the tumor were confirmed by central pathological review. Initially, patients with stage III or stage IV disease (on the basis of the presence of a malignant pleural effusion or a resected anterior abdominal-wall tumor) were eligible, but in March 1996, we began to exclude women with stage IV disease (without having reviewed our results until then), after the EORTC trial reported a greater benefit from secondary surgery after the exclusion of such patients from the analyses.

Pretreatment requirements included a history taking, physical examination, determination of race and Gynecologic Oncology Group (GOG) performance status by the investigator, electrocardiography, a complete blood count, renal- and liver-function tests, urinalysis, evaluation of the tumor by means of computed tomography (CT) of the abdomen and pelvis, chest radiography, and measurement of electrolyte and CA-125 levels in serum. A GOG performance status of 2 or better and a life expectancy of at least eight weeks were required. No history of cancer, chemotherapy, or radiotherapy was permitted. Patients had to have the following laboratory findings: a leukocyte count of at least 3000 per cubic millimeter, a platelet count of at least 100,000 per cubic millimeter, a granulocyte count of at least 1500 per cubic millimeter, a serum creatinine level of no more than 2.0 mg per deciliter (177  $\mu$ mol per liter), a bilirubin level that was no more than 1.5 times the upper limit of the normal range at the institution, and serum alanine aminotransferase, serum aspartate aminotransferase, and serum alkaline phosphatase levels that were no more than 3 times the upper limit of the normal range at the institution. Patients with tumors of low malignant potential, nonepithelial cancers, active infection, hepatitis, gastrointestinal bleeding, or a history of congestive heart failure, myocardial infarction, unstable angina, or abnormal cardiac conduction within the preceding six months were ineligible.

The institutional review board of each participat-

ing institution approved the protocol. Before receiving treatment, all patients provided written informed consent consistent with federal, state, and local requirements. Patients filled out quality-of-life questionnaires at four points in the study.

#### CHEMOTHERAPY

Chemotherapy was consistent with prior GOG protocols.<sup>8,9,18</sup> Paclitaxel (135 mg per square meter of body-surface area) was administered as a 24-hour infusion followed immediately by an intravenous infusion of cisplatin (75 mg per square meter). Appropriate premedications were given to avoid hypersensitivity reactions to paclitaxel and lessen gastrointestinal symptoms. After patients recovered from the hematologic effects of chemotherapy (defined by an absolute granulocyte count of at least 1500 per cubic millimeter and a platelet count of at least 100,000 per cubic millimeter), chemotherapy was to be repeated every 21 days for a maximum of six cycles. The dose of paclitaxel was to be reduced to 110 mg per square meter in the event of neutropenic fever, grade 4 thrombocytopenia, or grade 3 or 4 mucositis or diarrhea and further reduced to 90 mg per square meter in the event of persistent grade 3 or 4 adverse effects. To be consistent with other GOG protocols, in April 1997, paclitaxel doses were reduced to 110 mg per square meter in the event of asymptomatic grade 4 neutropenia, with granulocyte colony-stimulating factor to be administered for recurrent episodes. The dose of cisplatin was reduced to 50 mg per square meter in the event of grade 2 neuropathy, tinnitus, or symptomatic hearing loss and discontinued in the event of grade 3 or 4 neuropathy or persistent elevation of the serum creatinine level above 2.0 mg per deciliter. Patients were removed from the study if treatment was delayed by more than two weeks.

#### EVALUATION AND RANDOMIZATION

Three weeks after the third chemotherapy cycle, patients were evaluated for a response by means of a physical examination and CT of the abdomen and pelvis, unless CT findings had been normal at study entry and a previously elevated serum CA-125 level had returned to normal. Patients whose disease had not progressed and who had residual extraperitoneal tumor that was no more than 1 cm in diameter were randomly assigned to chemotherapy plus secondary surgical cytoreduction or chemotherapy alone.

#### SECONDARY SURGICAL CYTOREDUCTION

Secondary cytoreduction (laparotomy with a maximal effort to resect all gross tumor) was to be performed as soon as possible after hematologic recovery, but within six weeks after the completion of the third chemotherapy cycle. The fourth cycle of chemotherapy was to be administered as soon as possible, but no more than six weeks after secondary surgery.

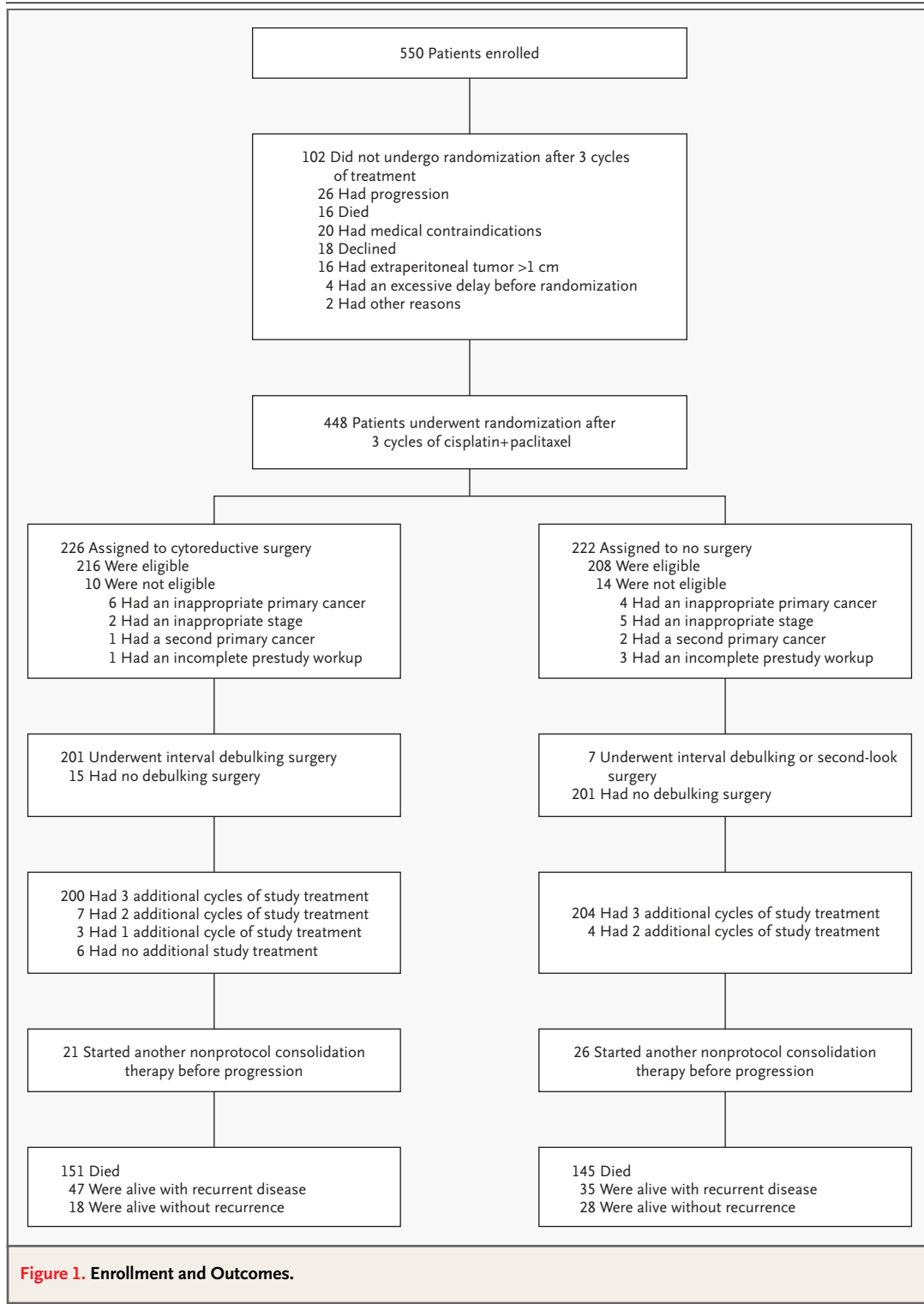
#### FOLLOW-UP

Patients were reassessed six to nine weeks after completing protocol therapy by means of history taking, physical examination, evaluation of GOG performance status, a complete blood count, measurement of electrolytes, renal- and liver-function tests, CT of the abdomen and pelvis, chest radiography, and measurement of serum CA-125 levels. They were to be followed up every three months for two years, then semiannually for three years, and yearly thereafter. Progression was defined as a clinically evident increase in disease or an increase in serum CA-125 values to at least 100 U per milliliter (for patients whose CA-125 levels failed to return to normal, a doubling of the nadir CA-125 levels). Elevated serum CA-125 levels were confirmed by retesting at least two weeks later.

#### STATISTICAL ANALYSIS

The time at risk for disease progression or death was measured from the date of randomization. Progression-free survival was measured to the date of progression or death or to the date of last contact for patients who were alive and progression-free. Only eligible, randomized patients were included in the primary treatment comparisons. Between-group comparisons were based on assigned treatments and included randomized patients regardless of the amount of study treatment they received. The planned analysis was a log-rank test stratified according to the clinical response after three cycles of chemotherapy. In order to compare our results with those of the EORTC study,<sup>17</sup> we also assessed progression-free and overall survival from the date of study enrollment.

The study was designed to ensure the enrollment of at least 400 eligible, randomized patients with data that could be evaluated. The final analysis was scheduled to occur after at least 225 deaths had been reported. It was considered that a 29 percent reduction in the death rate in the secondary-surgery



group would be clinically significant. This effect size is equivalent to an 11 percent increase in the proportion of patients who survived more than 2.8 years (the expected median). Assuming proportional hazards, this study would provide an 81 percent chance of detecting a treatment effect of this size (treatment hazard ratio, 1.40) when the type I error was limited to 0.05 for a one-sided test. In this report, all P values are two-sided.

An interim analysis of survival and adverse events was to be performed when at least 60 deaths had occurred in the chemotherapy-alone group. A spending function for a type I error similar to that of O'Brien and Fleming was specified for the survival analysis. These results were presented in July 1999 to the GOG Data-Monitoring Committee, which decided to continue the study as planned. Adverse events, graded according to GOG Common Toxicity Criteria,<sup>19</sup> were summarized as the maximal reported grade.

Study regimens were sequentially assigned by the GOG Statistical and Data Center in a blinded fashion with the use of randomly permuted blocks. Within each parent institution, separate treatment blocks were maintained for patients who had and those who had not had a response to the first three cycles of chemotherapy and for those with and those without radiographically measurable disease at study entry.

## RESULTS

From June 1994 through January 2001, 550 patients were enrolled. Figure 1 shows that disease progression was the commonest reason for non-randomization; 16 patients died before undergoing randomization, and 24 randomized patients were subsequently deemed ineligible after a central review. Of 424 eligible, randomized patients, 216 were assigned to chemotherapy plus secondary surgery and 208 to chemotherapy alone (Fig. 1).

Most patients were white, were 50 to 59 years of age, had a GOG performance status of 1, and had measurable stage III, grade 3, serous papillary carcinoma (Table 1). The nature of the initial surgery, performed by a fellowship-trained or certified gynecologic oncologist in 95 percent of patients, was similar in both groups. At secondary surgery, the median diameter of the tumor was 2 cm (range, 0 to 20). Protocol compliance was good, with only 7 percent of the patients who were randomly assigned to undergo secondary cytoreduction not receiving sur-

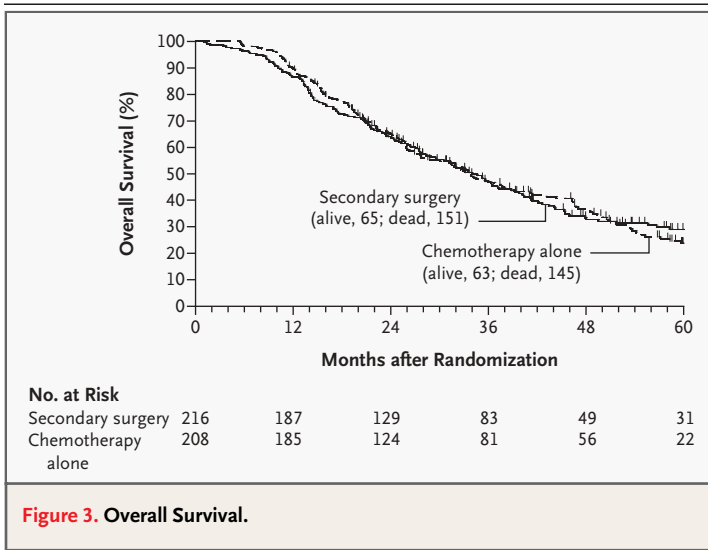
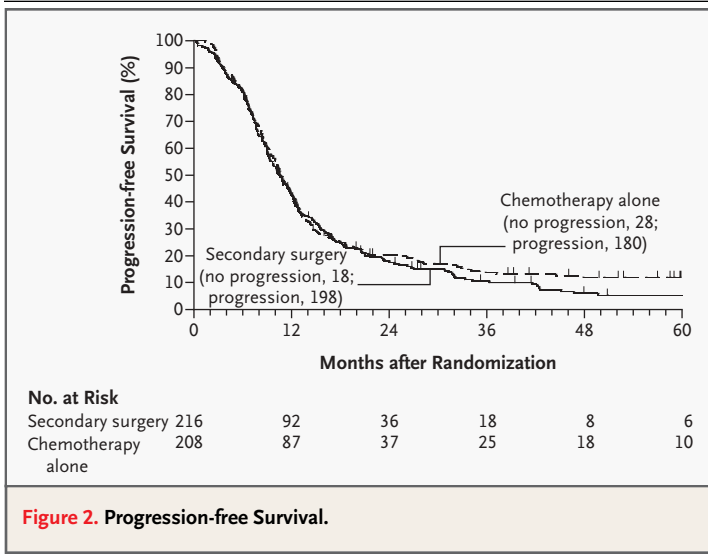
**Table 1. Characteristics of 424 Randomized, Eligible Patients.**

Characteristic	Secondary Surgery (N=216)	Chemotherapy Alone (N=208)
Age — yr		
Median	58.1	57.0
Range	25.4–81.6	27.0–81.6
Race or ethnic group — no. (%)		
Black	10 (5)	14 (7)
White	198 (92)	183 (88)
Hispanic	5 (2)	6 (3)
Other	3 (1)	5 (2)
GOG performance status — no. (%)*		
0	83 (38)	83 (40)
1	119 (55)	108 (52)
2	14 (6)	17 (8)
Cell type — no. (%)		
Serous	165 (76)	159 (76)
Endometrioid	17 (8)	11 (5)
Mucinous	1 (<1)	2 (1)
Clear cell	4 (2)	3 (1)
Mixed epithelial	20 (9)	17 (8)
Adenocarcinoma, unspecified	4 (2)	8 (4)
Undifferentiated or other	5 (2)	8 (4)
Histologic grade — no. (%)		
1	19 (9)	21 (10)
2	85 (39)	82 (39)
3 or clear cell	112 (52)	105 (50)
Stage — no. (%)		
III	200 (93)	200 (96)
IV	16 (7)	8 (4)
Measurable disease — no. (%)	152 (70)	145 (70)
Size of residual tumor — no. (%)		
1.0–2.0 cm	27 (12)	26 (12)
2.1–5.0 cm	92 (43)	91 (44)
5.1–10.0 cm	72 (33)	78 (38)
>10.0 cm	25 (12)	13 (6)

\* GOG denotes Gynecologic Oncology Group.

gery. Among patients who were randomly assigned to receive chemotherapy alone, 3 percent had secondary surgery in violation of the protocol.

Ninety-three percent of patients randomly assigned to chemotherapy plus secondary surgery and 98 percent of those randomly assigned to chemotherapy alone received three additional cycles of chemotherapy. The median time from the comple-



tion of the third cycle of chemotherapy to the initiation of the fourth cycle was 45 days (90th percentile, 63) in the secondary-surgery group, as compared with 21 days (90th percentile, 28) in the chemotherapy-alone group ( $P < 0.001$ ). Nonprotocol “consolidation” therapy was given before clinical progression in 21 patients in the secondary-surgery group (10 percent) and 26 patients in the chemotherapy-alone group (12 percent,  $P = 0.45$ ) (Fig. 1).

As of March 2003, 296 patients had died. Among surviving patients, the median duration of follow-up was 46.6 months in the secondary-surgery group

and 47.6 months in the chemotherapy-alone group. The median time to progression or death was 10.5 months in the secondary-surgery group and 10.7 months in the chemotherapy-alone group (Fig. 2). After adjustment for measurable-disease status and response after the first three cycles of chemotherapy, a proportional-hazards model estimated that the risk of progression or death was 7 percent higher in the secondary-surgery group than in the chemotherapy-alone group (hazard ratio, 1.07; 95 percent confidence interval, 0.869 to 1.31;  $P = 0.54$ ). Approximately 8 percent of patients in each group had rising serum CA-125 levels as their only indication of progression.

The median duration of survival was 33.9 months in the secondary-surgery group and 33.7 months in the chemotherapy-alone group (Fig. 3). The adjusted estimate of the relative risk of death for the secondary-surgery group as compared with the chemotherapy-alone group was 0.989 (95 percent confidence interval, 0.786 to 1.24;  $P = 0.92$ ), indicating that secondary surgery did not appreciably increase overall survival after initial maximal surgical cytoreduction.

The effect of secondary surgery on overall survival was assessed on the basis of the maximal diameter of residual tumor (2.0 cm or less, 2.1 to 5.0 cm, or 5.0 cm or more) after initial surgery, the patient’s age, performance status, and the presence or absence of measurable disease before chemotherapy. A consistent lack of effect of secondary surgery was seen. The tumor diameter before secondary surgery was associated with survival: the death rate among patients with at least one mass that exceeded 1 cm in diameter was 71 percent higher than the rate among patients with tumors of 1 cm or less (hazard ratio, 1.71; 95 percent confidence interval, 1.21 to 2.42;  $P = 0.003$ ). Of 112 patients whose tumor exceeded 1 cm in diameter before they underwent secondary surgery, 79 (approximately 70 percent) had a residual mass of less than 1 cm and 33 (approximately 30 percent) had a residual mass of at least 1 cm after secondary surgery. The death rates in these two groups did not differ significantly (hazard ratio, 1.25; 95 percent confidence interval, 0.785 to 2.00;  $P = 0.34$ ).

Adverse effects were similar in frequency and severity in the two groups. There were 35 patients with peripheral neuropathy of grade 2 or higher in the secondary-surgery group (16 percent) and 54 in the chemotherapy-alone group (26 percent,  $P = 0.01$ ), suggesting that the brief respite from chemotherapy

in the former group may have ameliorated the neurologic adverse effects. The rates of expected hematologic adverse effects were very similar between groups. The secondary-surgery group had a higher rate of grade 3 or grade 4 gastrointestinal adverse effects than the chemotherapy-alone group (7 percent vs. 4 percent). Among patients who were randomly assigned to secondary surgery, two had a grade 4 pulmonary adverse event and three had a grade 4 cardiovascular adverse event, as compared with zero patients and one patient, respectively, in the chemotherapy-alone group. In two patients, study treatment after randomization may have contributed to the cause of death (renal insufficiency developed in one and pneumonia and respiratory failure developed in the other).

#### DISCUSSION

In this randomized trial of the treatment of advanced ovarian cancer after a maximal attempt to debulk the tumor during primary surgery, we found that chemotherapy plus aggressive secondary surgery did not improve progression-free or overall survival as compared with chemotherapy alone. This finding contrasts with a previous EORTC trial of similar design.<sup>17</sup> Both studies involved patients of similar age with advanced ovarian cancer and ascites (Table 2), and both had acceptable rates of protocol compliance. The dissimilar results could reflect differences in efforts to maximize primary surgical debulking, the amount of residual disease after primary surgery, or the chemotherapy regimens. Our study required a maximal surgical effort that included a laparotomy, with the removal of as much gross disease as possible, whereas the extent of surgery was not specified in the EORTC study. The amount of residual tumor after primary surgery measured 5 cm or less in 55 percent of our patients, as compared with less than one third of the patients in the EORTC study, perhaps reflecting more aggressive primary cytoreductive surgery in our study.

The more efficacious combination of cisplatin and paclitaxel (as compared with cisplatin plus cyclophosphamide, used in the EORTC study) may have blunted any sign of improvement from secondary surgery in our trial. The EORTC trial, which completed enrollment in May 1993, predated the use of paclitaxel for ovarian cancer in Europe. However, even among patients treated with a combination of paclitaxel and a platinum, the amount of

**Table 2. Comparison of the Current and the European Organisation for Research and Treatment of Cancer (EORTC) Studies.**

Feature	Current Study	EORTC Study*
No. of eligible patients	424	319
Eligible patients included in analysis (%)	100	87
Age (yr)		
Median	57	59
Range	25–81	32–74
Papillary serous carcinoma (%)	76	57
Stage IV disease (%)	6	22
Primary surgery performed by gynecologic oncologist (%)	95	Not indicated
Ascites at primary surgery (%)	79	75
Median size of residual tumor after primary surgery (%)		
≤2.0 cm	12	5
2.1–5.0 cm	43	23
>5.0 cm	44	72
Chemotherapy regimen	Paclitaxel and cisplatin	Cyclophosphamide and cisplatin
Secondary surgery performed by gynecologic oncologist (%)	99	Not indicated
Patients completing 6 cycles of chemotherapy (%)	95	84
Median progression-free survival from study entry (mo)†		
Secondary surgery	12.5	18
Chemotherapy alone	12.7	13
Median survival from study entry (mo)†		
Secondary surgery	36.2	26
Chemotherapy alone	35.7	20

\* Data are from van der Burg et al.<sup>17</sup>

† To facilitate comparisons between trials, survival was assessed from the time of entry into the study.

residual disease is an important predictor of survival.<sup>20</sup> The frequency and timing of clinical evaluations during surveillance may also have contributed to differences in survival.<sup>21</sup>

There are hurdles specific to studies evaluating surgical (as opposed to medical) interventions.<sup>22</sup> In our trial, the surgeons' training was known and specific surgical procedures were required. This fact notwithstanding, there are most likely differences in surgical aggressiveness that are difficult to quantify. Although the association between residual disease and survival is well known, the clinical significance of the number and size of tumor deposits and

the definition of optimal residual disease are matters of controversy. Tumor measurements have a high degree of interobserver variability,<sup>23</sup> but in our study, the same surgeon usually performed both operations.

Patients with ovarian cancer are often examined by a surgeon or obstetrician-gynecologist who is not prepared to perform an aggressive cytoreductive surgery.<sup>24</sup> Perhaps secondary surgery plus chemotherapy could benefit patients in whom the primary surgery was inadequate, as suggested by results of phase 2 trials and the EORTC trial.<sup>13,14,17</sup>

Although surgery is currently considered the initial standard treatment for patients with a good performance status who have apparent, advanced

disease, the value of neoadjuvant (preoperative) chemotherapy is being investigated.<sup>25-29</sup> The benefit of this approach is uncertain, since the progression-free interval for patients who have a complete response to chemotherapy is much shorter for those who begin with bulky disease.<sup>30</sup> A randomized European trial comparing primary surgery plus postoperative chemotherapy with neoadjuvant chemotherapy plus surgery is ongoing.

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#### APPENDIX

The following GOG member institutions participated in this study: University of Alabama at Birmingham, Duke University Medical Center, Abington Memorial Hospital, Walter Reed Medical Center, Wayne State University, University of Minnesota Medical School, University of Mississippi Medical Center, Colorado Gynecologic Oncology Group, University of California at Los Angeles, University of Washington, University of Pennsylvania Cancer Center, Milton S. Hershey Medical Center, University of Cincinnati, University of North Carolina School of Medicine, University of Iowa Hospitals and Clinics, University of Texas Southwestern Medical Center at Dallas, Indiana University Medical Center, Wake Forest University School of Medicine, Albany Medical Center, University of California Medical Center at Irvine, Tufts–New England Medical Center, Rush–Presbyterian–St. Luke’s Medical Center, SUNY Downstate Medical Center, University of Kentucky, Community Clinical Oncology Program, the Cleveland Clinic Foundation, State University of New York at Stony Brook, Washington University School of Medicine, Cooper Hospital/University Medical Center, Columbus Cancer Council, M.D. Anderson Cancer Center, University of Massachusetts Medical School, Fox Chase Cancer Center, Medical University of South Carolina, Women’s Cancer Center, University of Oklahoma, University of Virginia, Tacoma General Hospital, Thomas Jefferson University Hospital, Mayo Clinic, Tampa Bay Cancer Consortium, Brookview Research, and Ellis Fischel Cancer Center.

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