Surgical Second Look in Ovarian Cancer: A Randomized Study in Patients With Laparoscopic Complete Remission—A Northeastern Oncology Cooperative Group-Ovarian Cancer Cooperative Group Study

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Purpose: **The usefulness of extensive and repetitive surgery for patients with ovarian cancer still remains unproven (at least for some conditions). We planned an accurate prospective test of the hypothesis that patients with advanced-stage disease, after they had reached a clinical complete remission (CR), may benefit from surgical second look (SSL).**

Patients and Methods: **One hundred two patients in CR (as assessed by clinical findings, markers, and visualization by computed tomographic [CT] scan and laparoscopy), after initial debulking and first-line chemotherapy, were randomized to two arms, which were well balanced for predictive criteria such as age, stage at presentation, histology, grading, date of randomization, and residua after first surgery. Forty-eight patients were randomly assigned to receive follow-up evaluation only, while 54 were assigned to receive second surgery (eight of them refused). Of 46 surgical patients, 35 had negative and 11 positive surgical findings (24% clinically false-negative).**

Results: **Despite the microscopic residua found at open surgery, and the fact that the patients were then treated with second-line chemotherapy, SSL did not increase the probability of survival in this setting. In an analysis of the results according to the intention-to-treat criteria, after a 60-month follow-up period, the overall survival rates in the two groups of patients (SSL *v* no SSL) were 65% and 78%, respectively ($P = .14$). Multivariate analysis according to predictive criteria confirmed there was no significant difference between the two groups ($P = .39$).**

Conclusion: **Our study shows the following: (1) our second-line treatment is scarcely effective; (2) SSL accurately defines complete responders to first-line chemotherapy; (3) SSL per se does not prolong survival; and (4) if confirmed, a less invasive procedure could replace SSL as a valuable method in new first-line regimens in ovarian cancer patients with clinical CR confirmed by laparoscopy.**

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THE SECOND-LOOK LAPAROTOMY or surgical second look (SSL), initially proposed by Wangensteen et al[1,2] in the setting of gastrointestinal neoplasias, was subsequently introduced as a diagnostic tool in the chemotherapy of ovarian cancer.[3-5] Conversely, surgical second effort (SSE) may define operations specifically aimed at debulking or eradicating known persistent ovarian cancer. It is now commonly held that no therapeutic advantages are gained from SSL,[6-15] but data are scanty.

Since 1979, computed tomographic (CT) scans and SSL findings have been compared in terms of diagnostic performance.[16-20] According to a review by Reuter et al,[21] the false-negative rate in these studies varies between 8% and 64%; however, the diagnostic value of CT scans may have been underestimated, since patients with palpable disease and a high CA 125 serum level were usually excluded from these studies.

However, many anatomic sites of interest, such as the mesentery, omentum, surface of intestinal loops, and parietal peritoneum, possess structural features that are not amenable to exhaustive CT scan examination, especially for just visible or microscopic deposits. Nonetheless, despite this apparent inaccuracy, CT scans have a reasonably good specificity that ranges from 88% to 99%.[16-21]

Exact laparoscopic staging is not always possible, but laparoscopic detection of residual tumor has now become common practice. An accurate comparison of SSL with laparoscopic findings has seldom if ever been reported. False-negative laparoscopy findings range from 29.1% to 55%,[22-27] but the interpretation of these reports is ham-

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pered by the small number of patient series reported (between 14 and 24).To date, only a few and limited studies have shown beneficial effects from second-line chemotherapy.[28,29]

Considering these data and our previous experience with a combination of fluorouracil and cisplatin (with a 32% overall response rate in patients who received first-line therapy either with or without cisplatin),[29] our Ovarian Cancer Cooperative Group, within the framework of the Northeastern Oncology Cooperative Group (Gruppo Oncologico Clinico Cooperativo del Nord-Est [GOCCNE]), decided to initiate a randomized study to evaluate the benefits of SSL in advanced ovarian cancer.

PATIENTS AND METHODS

Patients considered eligible for the study had histologically confirmed ovarian carcinoma[30] with any degree of differentiation, had reached a complete clinical remission (CR) after first-line chemotherapy according to clinical findings, serum marker studies, and CT scan, and did not have evidence of residual disease as confirmed by a laparoscopic procedure. Informed consent was required. Women with surgical stages IA, IB, or IIA[31] at presentation were excluded.

Following initial surgery with debulking and staging, patients received first-line chemotherapy according to a randomized trial to evaluate cisplatin (75 mg/m^2) and cyclophosphamide (1,300 mg/m^2) (PCy) versus doxorubicin (70 mg/m^2) and cyclophosphamide (1,300 mg/m^2) (ACy) every 21 days for five cycles. After reaching CR as assessed by clinical findings, CT scan, laparoscopy, and serum markers, all patients were randomized to one of two arms: arm A was assigned to a watch-and-wait policy, and arm B received SSL. For patients with a negative laparoscopy but a positive SSL, second-line chemotherapy was administered as described later (salvage treatment). All 10 participating centers randomized patients through telephone contact with the GOCCNE-Ovarian Cancer Operation Center in Padua.

Laparoscopy, as a rule, was performed after negative CT scans, which were assessed individually by each center.

The CT scan was performed using a third-generation facility (Siemens Somaton DRH [Erlangen, Germany]; or Toshiba X-PEED [Tokyo, Japan]), and each examination required approximately 30 minutes. Patients received an oral dose of approximately 750 mL of 2% Gastrographin (to all patients) plus intravenous administration of approximately 200 mL of a nonionic contrast medium, such as iomexol 350 or iopamidol 370 (to all non–iodine-allergic patients). Multiple sections, at 8-mm intervals from the diaphragmatic dome to the lower pubic symphysis, were examined. In selected cases, a double-contrast visualization for the sigmoid colon was performed.

Laparoscopy[32] was performed in Padua using an operative laparoscope with horizontal vision, equipped with a 3-mm channel for the introduction of probes, scissors, and instruments for the biopsy and cytology of peritoneum. An echo scanner was also available, which allowed panoramic observation preceding endoscopy (prelaparoscopy study) and a detailed analysis of the abdominal organs during the laparoscopic examination (perlaparoscopic study). A systematic survey of all the explorable abdominal areas was performed by changing the patient's position as needed.

During the examination, several biopsies were taken, especially of abnormal-appearing or dubious areas. When no suspicious areas were seen, multiple biopsies of omental residua and colonic fat tissue were performed. In all patients, samples of abdominal fluid (either normal or abnormal in appearance) were obtained and examined cytologically. If no fluid was visible, a peritoneal washing was performed by introducing through the laparoscope 500 mL of prewarmed (37°C) saline, which was mixed by repeatedly changing the patient's recumbency in a 1-minute period. Between 250 to 300 mL of the saline solution was recovered for microscopic examination through a special cannula. Following the procedure, patients were requested to observe an 8-hour period of bed rest and were then usually discharged after 12 to 24 hours.

SSL included biopsy of (1) sites of apparent disease; (2) sites of previous disease, even if normal in appearance; (3) sites with a suspicious appearance; and (4) elective sites where tumor implants from ovarian cancer are known to be common (ie, pelvic peritoneum, colonic gutters, falciform ligament of the liver, inferior aspects of the left and right diaphragm, and retroperitoneal nodes).

As for salvage treatment, all of the SSL-positive patients received second-line treatment that consisted of fluorouracil (500 mg/m^2 on days 1 to 5) and cisplatin (100 mg/m^2 on day 7).[29]

Survival was computed from the date of laparoscopy or laparotomy until death or January 1995.

Survival curves were defined according to the product-limit method.[33] Differences between subgroups were first assessed by means of the log-rank test[34] and then by the Cox model,[35] including all of the variables that were significantly associated with prognosis in the univariate analysis.

Table 1. Distribution of 102 Patients With Advanced Ovarian Cancer According to Treatment Group and Various Characteristics

	Treatment Group			
	Laparotomy		Laparoscopy	
Characteristics	No.	%	No.	%
Age, years				
< 50	20	37.0	17	35.4
≥ 50	34	63.0	31	64.6
Histologic type				
Serous and mixed	33	61.1	35	72.9
Endometrioid	13	24.1	7	14.6
Other	8	14.8	6	12.5
Grade				
I	10	18.5	9	18.8
II	15	27.8	18	37.5
III	29	53.7	20	41.7
Unknown	—		1	2.0
Stage				
IC + IIB, C	22	40.7	25	52.1
IIIA, B, C	31	57.4	22	45.8
IV	1	1.9	1	2.1
Residual tumor				
Microscopic	37	68.5	38	79.1
< 2 cm	11	20.4	7	14.6
≥ 2 cm	6	11.1	3	6.3
First chemotherapy				
Doxorubicin + cyclophosphamide	25	46.3	25	52.1
Cisplatin + cyclophosphamide	29	53.7	23	47.9
Total	54	100	48	100

RESULTS

Baseline characteristics of the patients in each treatment arm are listed in Table 1. No significant difference was noted by age, histologic type and grade, stage, and residual tumor after primary surgery.

The randomization process assigned 48 patients to arm A (no SSL) and 54 to arm B (SSL), but eight of the latter patients (15%) refused any further surgery. Of the remaining 46 patients in arm B, 35 (65%) had a completely negative SSL, while 11 (24%) had some positive tumor findings. Laparoscopy had been grossly negative in all of the cases, as both cytology and histology were negative; in two cases, washing and biopsies were not performed because of technical difficulties.

Evaluation and life-table analysis were calculated according to the intention-to-treat criteria.[36]

As listed in Table 2, the probability of survival at 48 months for laparotomy and laparoscopy was 68% and 83%, respectively; the follow-up time was 70 months. Knowing that the total number of patients randomized was 102 (54 in the laparotomy group and 48 in the laparoscopy group), and that $\alpha = 0.05$, the power found is 0.70.

The multivariate analysis showed no significant influence on survival for the majority of characteristics studied (Table 2). With regard to laparotomy versus laparoscopy, the hazards ratio (HR) was 0.68 (95% confidence interval [CI], 0.28 to 1.64; χ^2 test $P = .39$). The only influential variable was stage; it emerged that stages IIIA, IIIB, and IIIC have an HR of 3.08 (95%CI, 1.12 to 8.43) when compared with the lower stage group, including IC, IIB, and IIC. Conversely, variables such as age (>/< 50 years), histology (endometrioid *v* serous papillary), and grade (II or III *v* I) did not significantly affect survival. The eight patients who were randomized to arm B and refused SSL are all disease-free at present.

Table 2. Multivariate Analysis of Survival in 102 Patients With Advanced Ovarian Cancer

Variable	No.	HR*	95% CI	% Probability of Survival at 48 Months
Treatment				
Laparotomy	54	1†		68
Laparoscopy	48	0.68	0.28-1.64	83
χ^2 ($df = 1$)		0.74	$P = .39$	
Age, years				
< 50	37	1†		81
≥ 50	65	1.21	0.49-2.94	72
χ^2 ($df = 1$)		0.17	$P = .68$	
Histologic type				
Serous and mixed	68	1†		76
Endometrioid	20	2.03	0.79-5.19	70
Other	14	0.70	0.20-2.40	75
Grade				
I	19	1†		100
II	33	4.36	0.53-35.64	74
III	49	5.51	0.70-42.23	66
Unknown	1	—		
χ^2 ($df = 1$)		3.13	$P = .08$	
Stage				
IC + IIB, C	47	1†		89
IIIA, B, C	53	3.08	1.12-8.43	63
IV	2			
χ^2 ($df = 1$)		5.23	$P = .02$	
Residual tumor				
Microscopic	75	1†		80
< 2 cm	18	0.94	0.33-2.68	64
≥ 2 cm	9	1.23	0.39-3.87	56
χ^2 ($df = 1$)		0.72	$P = .79$	
First chemotherapy				
Doxorubicin + cyclophosphamide	50	1†		73
Cisplatin + cyclophosphamide	52	0.84	0.37-1.93	76
χ^2 ($df = 1$)		0.17	$P = .68$	

*Cox model, including terms for treatment, age, histologic type, grade, stage, residual tumor, and first chemotherapy.
†Reference category.

DISCUSSION

The majority of trials so far have investigated the role of combination regimens and different polychemotherapies. Often, the internal coherence and development of randomized trials in advanced ovarian cancer and their methodologic soundness are poor.[36] Randomized studies to address the issue of diagnostic SSL are not currently available, and consequently no conclusion on a possible effect of this procedure on survival can be draw.[8] In the last 40 years, surgery has undergone a gradually changing role and range in the control of ovarian cancer. Although surgical inspection and reinspection initially represented the only reliable means to assess the condition reached with treatment, less invasive procedures have subsequently become available.

In our study, no differences in survival were observed between patients who had a negative SSL and those in the laparoscopy group; furthermore, in patients with microscopic disease detected by SSL, subsequent treatment with cisplatin did not alter survival.

We evaluated survival according to the intention to treat[36] (Fig 1); despite the effective second-line treatment given to the SSL-positive patients, no survival benefit was noted. Our data showed a nonprognostic difference for the majority of characteristics evaluated (ie, residuals, stage, histology, grade, type of first-line chemotherapy, and age). It is therefore possible that small and microscopic residuals have limited significance, or that the tumor detected by SSL is totally chemoresistant, confirming some previous data in the literature.[8]

When the two different treatments administered (ACy in 50 patients and PCy in 52) are considered, in theory there may be some probabilities of a salvage effect from second-line treatment that contains cisplatin in ACy-treated patients, since this population had never been exposed to it previously; however, no statistically significant difference in survival was noted in the study population, in particular in those patients with microscopic residual disease, in accordance with the literature.[37-39]

In most cases, ovarian cancer is confined to the abdominal cavity,[40] and it has been shown to be highly sensitive to chemotherapy; yet, patients who received chemotherapy after positive SSL did not obtain an improvement in survival. It seems that the patients attained no benefit from SSL performed after CR (as assessed by CT scan plus laparoscopy), even though the positive SSL cases underwent further and potentially non–cross-resistant chemotherapy.

These results are probably due to the lack of efficacy of second-line treatments usually reported in the literature.[41] The implication is that even laparoscopy will most probably become obsolete in the near future, and clinical examination, CT scan, and CA 125 dosage will suffice for patient evaluation.

In conclusion, our findings corroborate reports in the literature on the uselessness of SSL in patients with clini-

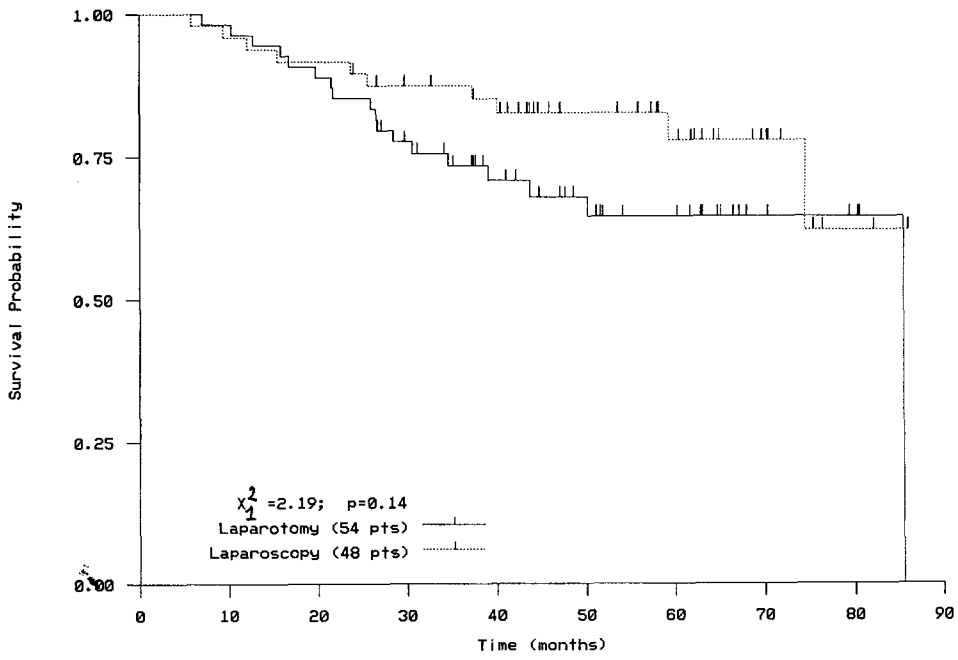

Fig 1. Survival probability according to treatment arm.

cal, biochemical, and laparoscopic CR,[6-15] which could be substituted by less invasive procedures. The results of this trial will also be useful for the evaluation of the new first-line experimental regimens in ovarian cancer, if confirmed by other controlled studies, in this subset of patients.

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