
Results of Interval Debulking Surgery Compared with Primary Debulking Surgery in Advanced Stage Ovarian Cancer

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- BACKGROUND:** Results of IDS (after three to four courses of induction chemotherapy) were compared with PDS followed by chemotherapy in patients treated for advanced stage ovarian cancer (stage IIIC or IV).
- STUDY DESIGN:** A retrospective study was done on a group of 57 patients who underwent IDS (because of an unresectable tumor) compared with a group of 28 patients treated with PDS (for resectable disease) followed by chemotherapy. All patients were treated between 1996 and 2001 by the same team of surgeons and received the same regimen of chemotherapy (platinum based plus paclitaxel).
- RESULTS:** Optimal cytoreductive surgery (residual disease ≤ 2 cm) was achieved in IDS and PDS groups in 84% (48 of 57) and 100% (28 of 28) of patients, respectively. Complete resection was observed in 51% (29 of 57) of patients in the IDS group and 54% (15 of 28) of patients in the PDS group. The rates of bowel resection, large peritoneal resection, and postoperative morbidity were significantly reduced in the IDS group. After adjusting for the size of residual disease (≤ 2 cm and absence of residual tumor), overall and event-free survival were not different in the two groups.
- CONCLUSIONS:** Survival rates were similar in patients with advanced stage ovarian cancer who underwent IDS or PDS. The rates of surgical resection and morbidity were reduced after IDS. IDS can be safely used in unresectable advanced stage ovarian cancer. (J Am Coll Surg 2003;197:955–963. © 2003 by the American College of Surgeons)
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Unfortunately, invasive epithelial ovarian cancer remains undiscovered in most patients until it has reached an advanced stage. Currently accepted management is initial debulking surgery to achieve optimal cytoreduction (defined as residual tumor < 2 cm), followed by adjuvant therapy.^{1,2} This aggressive operation is associated with a high risk of morbidity.^{3–5}

The literature reveals several articles discussing the possibility of primary chemotherapy in patients with advanced stage (unresectable, bulky, or both) ovarian

cancer to decrease morbidity or to increase the incidence of resectable tumors.^{6–18} In 1995, Van der Burgh and colleagues¹⁹ demonstrated, in a randomized study, that debulking operations after neoadjuvant chemotherapy (interval debulking surgery) offer good results in patients nonoptimally debulked during initial surgery compared with patients treated with chemotherapy only. Few series have been published that explored results of patients undergoing interval debulking surgery compared with patients treated with initial debulking followed by adjuvant chemotherapy.^{7,12,13} In this article we report the results of a comparative study on a series of 57 patients treated with induction chemotherapy followed by interval debulking surgery.

METHODS

From 1996 to 2001, data from patients with ovarian epithelial cancer treated in or referred to our institution were reviewed and analyzed. Patients excluded from this

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analysis were those with stages I, II, IIIA, IIIB, and IIIC disease (according to the 1987 International Federation of Gynecology and Obstetrics [FIGO] classification), those with minor intraperitoneal spread (only on the omentum in the upper abdomen and for whom complete cytoreductive surgery could be achieved using hysterectomy, bilateral salpingo-oophorectomy, and omentectomy), or stage IIIC disease related to isolated nodal spread without massive involvement of the peritoneum. During this period, data from 86 women treated for an advanced stage (stages IIIC or IV with pleural effusion) ovarian cancer with massive intraabdominal spread were analyzed according to the type of the surgical treatment. These patients had bulky tumors in the pelvis and abdomen.

Patients were classified as having resectable or unresectable advanced stage tumors. Tumors were considered resectable if an optimal cytoreductive operation (intraabdominal residual disease ≤ 2 cm) could be achieved using a standard procedure (including total hysterectomy with bilateral salpingo-oophorectomy plus total omentectomy, with or without lymphadenectomies, isolated resection of the spleen if necessary, and resection of the rectosigmoid if necessary). A pelvic and paraaortic lymphadenectomy was included in the standard operation for patients with good medical status at the end of the debulking surgery and in those with a complete macroscopic resection (absence of residual disease) or very small residual disease (< 1 cm). In patients with a larger amount of residual disease or poor medical condition at the end of the debulking operation, lymphadenectomies were omitted at the time of the debulking operation. Patients who underwent a primary debulking surgery (PDS) received postoperative by adjuvant chemotherapy.

Patients were classified as having unresectable disease if 1) optimal cytoreduction was not possible using a standard procedure (involvement of hepatic pedicle, mesentery, paraaortic involvement above the level of the left renal vessels, involvement of the diaphragmatic muscle) or 2) feasible but with resection of at least two segments of the digestive tract or splenopancreatectomy associated with bowel resection. Most of these patients (54 of 58) underwent an initial surgical procedure to evaluate the spread of disease in the abdominopelvic cavity. In these patients biopsies were performed at several sites at the end of the initial operation, but none had a cytoreductive operation during the initial surgical pro-

cedure. At the end of this initial surgical exploration, residual disease was greater than 2 cm. In some exceptional cases (patients with stage IV disease [pleural effusion], massive intraabdominal spread on initial CT scan, and poor general status), primary chemotherapy was delivered without an initial surgical procedure to evaluate the resectability of the tumor.

A few patients underwent neoadjuvant chemotherapy (initial chemotherapy without initial surgical evaluation of the spread of the disease) or induction chemotherapy (in patients who underwent an initial surgical procedure) in order to reduce the size of the intraabdominal tumor before performing an interval debulking operation (IDS). Patients were followed during each course of chemotherapy by clinical examination, CA125 level determination, and CT scan just before the debulking operation. Debulking surgery was attempted after three or four courses of chemotherapy and was followed by chemotherapy. Indications for lymphadenectomies were similar to those in the group of patients who underwent initial debulking surgery. Only patients with a followup greater than 1 year were included (if they had not died from the disease or had recurrent disease observed within the 12 months after the end of treatment).

All patients were treated by the same team of surgeons (gynecologic oncologists) and received the same regimen of chemotherapy: a platinum-based plus paclitaxel regimen. Characteristics of debulking surgery (residual disease), surgical procedures (bowel resection, peritonectomy, splenectomy, and enterostomy), blood transfusion rates, and postoperative morbidity rates were analyzed. The chi-square test was used to compare proportions and $p < 0.05$ was considered significant. Survival rates were compared for the two groups according to size of residual tumor at the end of debulking surgery. Survival curves were compared using a log-rank test.

RESULTS

Characteristics of the two groups are detailed in Table 1.

Interval debulking surgery group

In 58 patients, 4 patients with stage IV disease (with pleural effusion) with poor medical status and massive intraabdominal spread on CT scan underwent neoadjuvant chemotherapy without an initial surgical procedure (but after radio-guided percutaneous biopsy for histologic diagnosis). Fifty-four patients underwent an initial surgical procedure and their tumors were considered un-

Table 1. Patient Characteristics in Both Groups

Characteristics	Interval debulking surgery (n = 58)	Primary debulking surgery (n = 28)
Age, y (median)	57 (35–74)	56 (33–76)
Stage		
IIIC	48 (83%)	23 (82%)
IV	10 (17%)	5 (18%)
Tumor grade		
1	6 (10%)	1 (4%)
2	17 (30%)	13 (46%)
3	32 (55%)	14 (50%)
Unknown	3 (5%)	0 (0%)
Histologic subtypes		
Serous	46 (79%)	25 (89%)
Mucinous	0 (0%)	0 (0%)
Endometrioid	4 (7%)	3 (11%)
Clear cells	3 (5%)	0 (0%)
Undifferentiated	4 (7%)	0 (0%)
Mixed	1 (2%)	0 (0%)
Median courses of chemotherapy (range)		
Preoperative chemotherapy	3 (2–5)	0
Postoperative chemotherapy	5 (3–7)	6 (5–9)

resectable. This initial surgical procedure was performed by laparoscopy or laparotomy in 12 and 42 patients, respectively. Location of the tumor is detailed in Figure 1. During this initial surgery, procedures performed included ovarian biopsies or unilateral or bilateral salpingo-oophorectomy (35 patients); partial or complete omentectomy (26 patients); hysterectomy with bilateral salpingo-oophorectomy (16 patients); and appendectomy (5 patients). Perioperative blood transfusion was performed in 11 patients (39%). The median length of hospitalization after initial operation was 8 days (range 3 to 29 days). One patient treated initially by laparotomy had major postoperative morbidity (peritonitis from a perforation of the sigmoid). This patient was excluded from further analysis because interval debulking surgery was not attempted. None of the other patients treated with initial laparotomy or laparoscopic approach had morbidities worthy of note. The median delay between initial operation and the first course of chemotherapy was 17 days (range 2 to 45 days).

Interval debulking surgery (IDS) was performed in 57 patients using a midline incision in all cases. The effect of chemotherapy, compared with the initial spread, on

intraabdominal tumors is detailed in Figure 1. The surgical procedures performed are given in Table 2. The extent of the surgical procedure at the time of IDS was similar with laparoscopy and laparotomy. In 12 patients who underwent an initial laparoscopic evaluation, 4 (33%) had at least one major surgical procedure (bowel resection in 3 patients and resection of the peritoneum of the diaphragm in 1 patient), and 11 of 42 patients (26%) who underwent an initial laparotomy had at least 1 major surgical procedure (bowel resection in 7 patients, resection of the peritoneum of the diaphragm in 2 patients, and splenectomy in 2 patients). Optimal cytoreductive surgery (residual tumor ≤ 2 cm) was achieved in 48 patients (84%). In 9 patients residual tumor was larger than 2 cm. At the end of interval debulking surgery, 29 patients (51%) had no macroscopic residual disease. Histologic examination of the surgical specimens revealed the persistence of large areas of residual disease in 24 patients (42%). Twenty-three patients (40%) had persistent disease but with large areas of tumor necrosis after initial chemotherapy. In six patients (who underwent an optimal cytoreductive operation including pelvic and paraaortic lymphadenectomy), an absence of histologic residual tumor was observed. In one patient who underwent complete lymphadenectomy, there was no peritoneal disease but there was nodal involvement in the paraaortic area. Fourteen of the 31 patients (45%) who underwent lymphadenectomy had positive paraaortic nodes (with positive pelvic nodes in 14 patients). Complications are detailed in Table 3. Major postoperative complications (needing surgical treatment or radiologic procedures) were observed in 4 patients (7%). The median duration of hospitalization was 12 days (range 4 to 23 days). The median delay between IDS and the next course of chemotherapy was 24 days (range, 7 to 66 days).

Primary debulking surgery group

Comparison of the spread of the disease in PDS patients with that in patients who underwent debulking surgery after initial chemotherapy (IDS group) is shown in Figure 2. Hysterectomy, bilateral salpingo-oophorectomy, and omentectomy were performed in all cases. Additional surgical procedures carried out in this group of patients who underwent PDS are detailed in Table 2. Resection of the large bowel was performed in 17 patients (with resection of the small intestine in 7). Perioperative blood transfusion was performed in 11

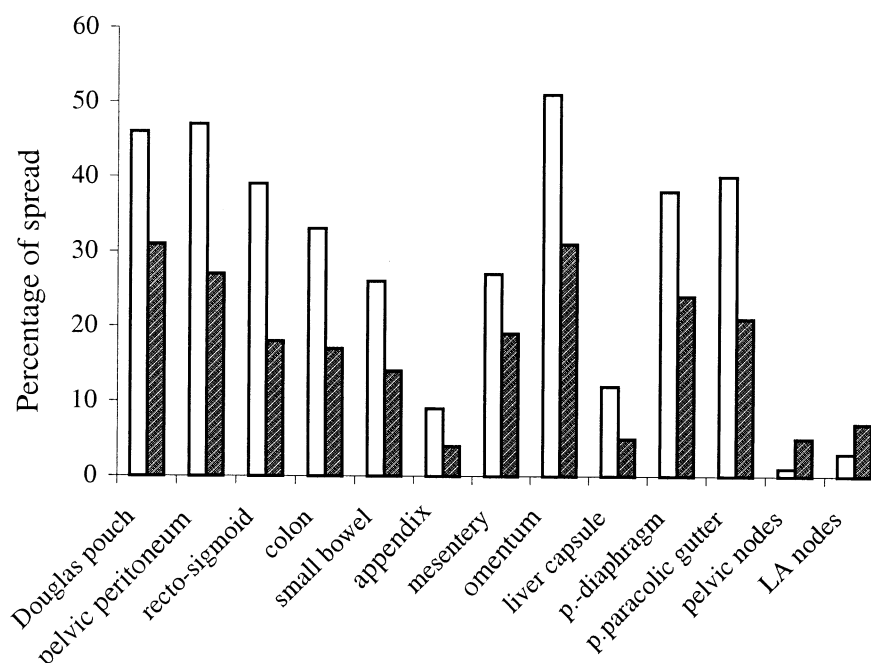


Figure 1. Location of tumor spread before (white column) and after three or four courses of chemotherapy (black column) in the interval debulking group. p, peritoneum.

patients (39%). Ten patients developed major postoperative complications (Table 3); permanent enterostomy was carried out in three patients (10%). Optimal cytoreductive surgery (residual disease ≤ 2 cm) was achieved in all patients, with absence of macroscopic residual disease in 15 (54%). The median duration of hospitalization after debulking surgery was 12 days (range 7 to 30 days). Twelve of the 20 patients (60%) who underwent lymphadenectomy had positive paraaortic nodes (with positive pelvic nodes in 10 patients). The median delay between the PDS and the first course of chemotherapy was 20 days (range 11 to 63 days). The median number of courses of first line chemotherapy is given in Table 1.

The median time of followup for all patients was 20 months (range 6 to 64 months): 17 months (range 6 to 64 months) in the PDS group, and 23 months (range 12 to 61 months) in the IDS group. When we compare the two groups, the rates of bowel resection, large resection of the peritoneum, and major postoperative complications are significantly lower in the IDS group (Tables 2 and 3). After adjustment of the tumor size at the end of debulking surgery, overall survival and disease-free survival in the IDS and PDS groups were compared. In patients with residual tumor ≤ 2 cm, there is a trend

Table 2. Characteristics of Debulking Surgery

	Interval debulking surgery (n = 57)		Primary debulking surgery (n = 28)		
Characteristics	n	%	n	%	p Value
Size of residual tumor					
Optimal cytoreduction (≤2cm)	48	84	28	100	<0.05
No residual disease	29	51	15	54	0.81
Surgical procedures					
Bowel resection	11	19	17	61	0.01
Pelvic lymphadenectomy	36	63	21	75	0.27
Paraaortic lymphadenectomy	31	54	20	71	0.13
Omentectomy	36	63	28	100	<0.001
Large resection of the peritoneum	5	9	14	50	<0.0001
Resection of the peritoneum/diaphragm	9	16	11	40	0.02
Splenectomy	3	5	2	7	0.72
Permanent enterostomy	3	5	3	10	0.35
Blood transfusion	12	21	11	39	0.07

toward a significant difference on the curves, but using the log-rank test, overall and event-free survivals were not statistically different in either group (Figs. 3 and 4). In the subgroup of patients with complete resection and absence of residual disease at the end of surgery, the overall survival was similar in both groups (Fig. 5).

DISCUSSION

This study reflects the evolution of opinions on surgical management of advanced stage ovarian cancer. For the last 20 years, the recommended management for treating such a patient is a cytoreductive operation followed by adjuvant chemotherapy. The strongest prognostic factor is the presence and size of residual tumor at the end of cytoreductive surgery.^{2,3,20-22} The aim of the surgical procedure is to obtain the most complete tumor resection possible. The quality of the surgery depends on the training of the surgeon performing it.²³ Even when performed by experienced surgeons, cytoreductive surgery has a major complication rate of 15% to 45%.^{3,4,5,24} The mortality rate varies between 1% and 7%.^{3,4,12} The high morbidity rate is accompanied by relatively poor survival results, suggesting that this surgical strategy should be reconsidered, particularly in patients with extensive tumor masses. In 1995, Van der Burgh and colleagues¹⁹ published a prospective randomized study on debulking surgery after neoadjuvant chemotherapy. Recently, during an American Society of Clinical Oncology (ASCO) meeting, Rose and associates²⁵ presented an interesting randomized study on secondary debulking surgery (in patients who underwent a suboptimal cytoreductive operation including hysterectomy, bilateral adnexectomy, and omentectomy during the initial operation) after chemotherapy (paclitaxel regimen) with different results from those reported by Van der Burgh and colleagues. After the data published by Van der Burgh's group, we developed a strategy of interval debulking surgery for patients with advanced stage (unresectable) ovarian cancer.¹⁸

Several other studies previously discussed the benefit of initial chemotherapy to reduce the size of the tumor. Some authors reported results without any comparison to a control group of patients with initial debulking surgery, demonstrating that the treatment was feasible.^{6,8,11,16,17} Other studies were comparative but without any matching.¹²⁻¹⁵ In some of these studies, debulking surgery was not systematically attempted at the end of neoadjuvant chemotherapy.^{12,13} Two case-control stud-

Table 3. Postoperative Morbidity after Debulking Surgery in Both Groups

Morbidity	Interval debulking surgery (n = 57)		Primary debulking surgery (n = 28)		p Value
	n	%	n	%	
Major morbidity*	4	7	10	36	0.01
Anastomotic leakage†	1	9	6	35	
Peritonitis	0	0	1	4	
Bleeding	2	3	0	0	
Vaginal abscess	1	2	1	4	
Urinary fistulae	0	0	2	7	
Other morbidity					
Lymphocyst	3	5	1	4	0.43
Infection of ascitis	1	2	0	0	
Phlebitis	1	2	1	4	

*Morbidity requiring a new procedure (surgical or radiologic).

†Percentage determined in the subgroup of patients who underwent a bowel resection.

ies suggested that survival was similar in both groups, but with a reduced morbidity in patients who underwent interval surgery.^{7,18} After the series reported by Vergote and associates,¹² our study is, to our knowledge, the second largest series reported. Our report is not a prospective randomized trial, but it has two important advantages over previous series: all patients were treated by the same team of surgeons and received the same regimen of chemotherapy. Nevertheless, there is potential bias in our series: the spread of the tumor was less extensive in patients who underwent initial debulking surgery compared with those who underwent interval surgery. The difference theoretically favors the primary debulking surgery group. But after adjustment of the size of the residual tumor at the end of debulking surgery, the survival of patients was similar in both groups. These important data seem to demonstrate that the prognostic value of the size of the residual tumor is similar no matter when the debulking surgery takes place.

Our study is the only one that discusses characteristics of the surgicopathologic response on the peritoneum and lymph nodes. In the series of Ansquer and associates¹⁶ and Jacob and colleagues,⁷ details are provided about the response on the peritoneum, but correlation with histologic status of the lymph nodes is not reported. In six of our patients (who underwent pelvic and paraaortic lymphadenectomy), no residual disease was

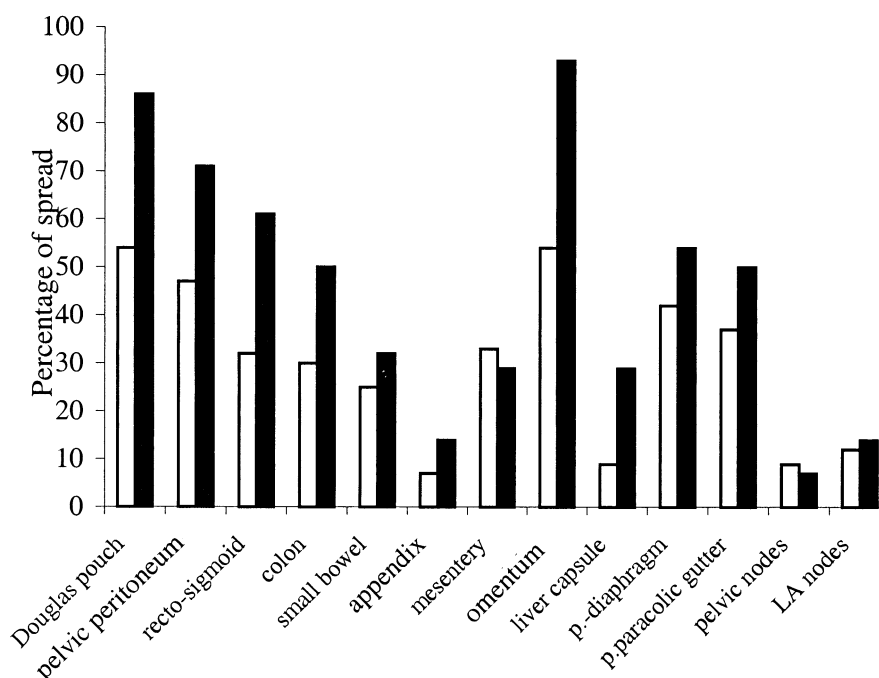


Figure 2. Location of the tumor at the time of the interval debulking surgery group (white column) and primary surgery group (black column). p, peritoneum.

found on the peritoneum or lymph nodes after three courses of chemotherapy. These results testify to the efficacy of chemotherapy on peritoneal spread. When we compared the initial spread of disease to that observed after induction chemotherapy, we observed a regression in the peritoneum in 60% of lesions observed on the bowel or rectum, in 38% on the small bowel, in 35% on the pelvic peritoneum, and 30% on the peritoneum of paracolic gutters and of the diaphragm (Fig. 1). The rates of bowel resections, large peritonectomies, and resections of the peritoneum of the diaphragm, are significantly different in the two groups (Table 3). The differences explain that morbidity is reduced in patients who undergo interval surgery with a better quality of life (reduced rates of enterostomy). We observed that morbidity rate in patients who underwent primary debulking surgery is quite high (36%) but does correlate with data on major complications reported in the literature.^{3-5,24} Our rate of anastomotic leakage is also high (6 of 17 anastomoses: 35%) in this group of patients, but it was observed in patients with ascitis (which can influence the appraisal of the latter) or in patients who underwent additional major procedures. This rate was reduced and acceptable (1 of 11 anastomosis; 9%) in the group of patients who underwent interval surgery. Another ad-

vantage of interval surgery management in patients with advanced stage disease is to select chemosensitive patients. In case of patients with progression of their disease undergoing first line chemotherapy (based on plat-

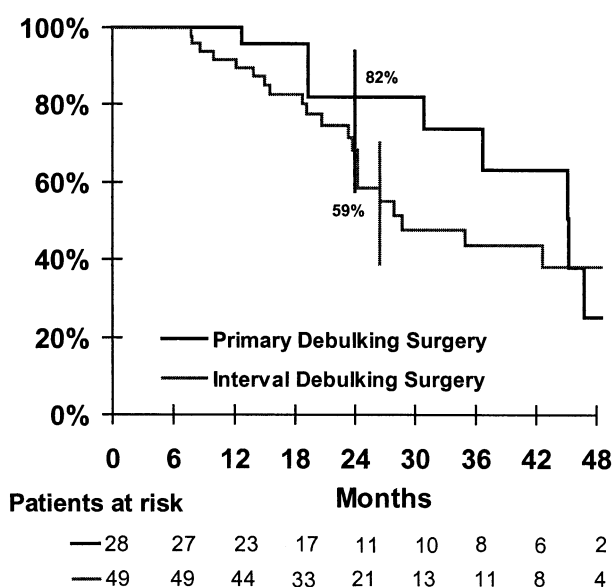


Figure 3. Overall survival in the interval debulking surgery and primary debulking groups in patients with residual disease ≤ 2 cm.

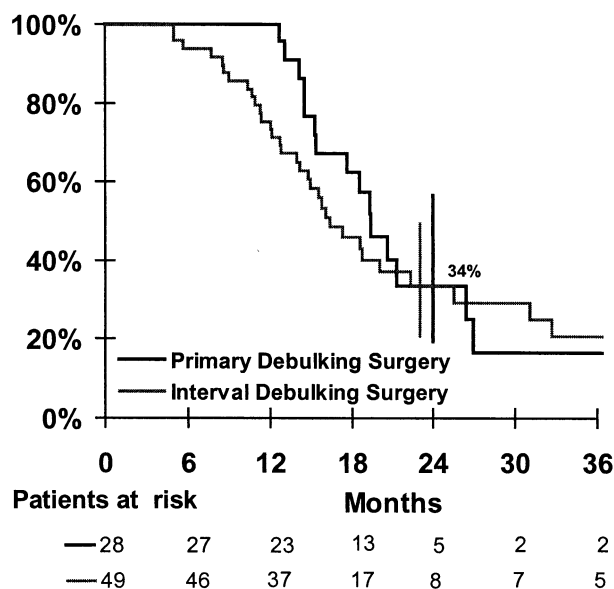


Figure 4. Event-free survival in the interval debulking surgery and primary debulking surgery groups in patients with residual disease ≤ 2 cm.

inum plus paclitaxel regimen), debulking surgery should be discussed but, a priori, should not be performed.

The rate of lymph node involvement reported in our study is high (14 of 31; 45%) but agrees with the literature's data on lymph node involvement in stages III and IV ovarian cancer.²⁶ Lymph node metastases from epi-

thelial ovarian cancer do not seem to be chemosensitive lesions.²⁶ Because of this high rate of involvement, optimal debulking surgery (with minimal or absence of residual disease on the peritoneum) should include pelvic and paraaortic lymphadenectomy. This procedure is probably not applicable for patients with a larger residual tumor because in such cases, the presence of a residual tumor in the abdominal cavity is the most important prognostic factor. One patient without peritoneal disease had isolated nodal involvement. Figure 1 shows that the rates of lymph node metastases are similar in patients before and after chemotherapy. These results suggest that nodal metastases are chemoresistant lesions, so they question the therapeutic value of lymphadenectomy in ovarian cancer. Even if metastatic lymph nodes do not seem to be chemosensitive lesions, the therapeutic value of nodal debulking is not yet confirmed. Actually, a multicentric randomized study has been conducted to clarify the therapeutic value of lymph node resection for patients with advanced stage disease.

These results raise several questions and remarks. The first one concerns the criteria used to select patients for IDS and patients for initial debulking surgery. Our data do not imply that all patients with peritoneal carcinomatosis should have neoadjuvant chemotherapy. In fact, when an initial debulking operation is feasible and achieves a minimal residual tumor with an acceptable morbidity, it should be performed (patients with stages II, IIIA, IIIB, and IIIC with minor carcinomatosis). In our series, this operation was used in patients with less advanced peritoneal spread whose tumors could be optimally debulked during initial surgery. All patients in the primary debulking surgery group were adequately selected and had residual tumors ≤ 2 cm. Initial chemotherapy before debulking surgery should be performed only in patients with massive peritoneal involvement for whom optimal surgery is not possible (eg, involvement of the hepatic pedicle, mesentery, paraaortic involvement above the level of the left renal vessels, or diaphragmatic muscle) or is possible only with multiple bowel resections or extensive operations (splenopancreatectomy, bowel resection of two or more intestinal segments), carrying a high risk of postoperative morbidity. In some surgical teams, the selection of unresectable tumor is performed using preoperative abdominopelvic CT.^{11,13} We agree with Vergote and associates¹² that a surgical procedure is better than CT scan for confirmation of diagnosis and evaluation of operability. With

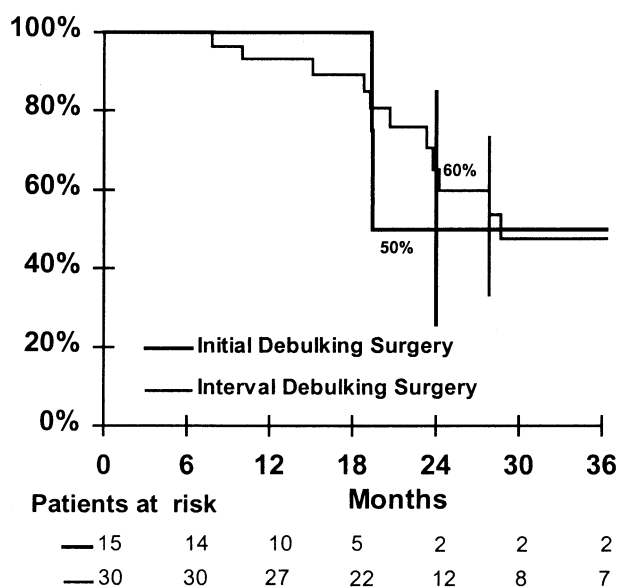


Figure 5. Overall survival in the interval debulking surgery and primary debulking surgery groups in patients with absence of macroscopic residual disease at the time of debulking surgery.

surgical exploration, a more accurate evaluation of the initial extension of the disease is possible. Oophorectomy, if technically easily feasible, or peritoneal or omental biopsies can be performed to confirm the diagnosis. Such initial surgery is also helpful for evaluating the effect of chemotherapy by comparing the tumor mass at the interval debulking with that of the initial surgery.

In this series, the initial operation is performed using laparotomy, but for the last 4 years, we have used laparoscopy to evaluate the resectability of the tumor. Using a laparoscopic procedure, the delay between the initial operation and the first course of chemotherapy is substantially reduced, between 4 and 10 days. A recent study suggested that the laparoscopic approach is an accurate procedure to evaluate the resectability of ovarian cancer.²⁷ The main risk of this approach is the occurrence of metastatic seeding on the trocar site. We have reported several cases of trocar metastasis after laparoscopy for ovarian cancer. Most of these patients had advanced stage disease.²⁸ This complication was reported by Vergote's team in 19% of patients who underwent this procedure.²⁹ This risk could be reduced when the peritoneum is closed after laparoscopy.³⁰ But confirming the findings of Vergote and associates,³¹ we believe that the risk of trocar-site metastasis in patients with such advanced disease is clinically unimportant in terms of patient outcomes.

In conclusion, interval debulking surgery (after primary chemotherapy) in patients with advanced stage ovarian cancer seems to offer the same chance of survival as does initial debulking surgery, but with a reduction in morbidity. These preliminary results should be confirmed by a randomized trial being conducted by the European Organization for Research on the Treatment of Cancer group, but results of this study are not expected for several years. While waiting for such important data, collecting results of interval surgery is important to precisely evaluate such management. This management (primary chemotherapy followed by interval debulking surgery) may also benefit patients who are diagnosed and undergo an incomplete nonoptimal primary debulking operation before transfer to a tertiary care center.

Author Contributions

Study conception and design: Morice, Dubernard, Castaigne

Acquisition of data: Dubernard

Analysis and interpretation of data: Morice, Dubernard

Drafting of manuscript: Morice, Atallah

Critical revision: Pautier, Pomel, Lhomme

Statistical expertise: Rey

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