Surgical Procedures and Morbidities of Diaphragmatic Surgery in Patients Undergoing Initial or Interval Debulking Surgery for Advanced-Stage Ovarian Cancer

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BACKGROUND: Surgical management of advanced-stage ovarian cancer (ASOC) can require diaphragmatic surgery (DS) to achieve complete cytoreduction. The aim of this study was to evaluate modalities and morbidities of DS at the time of initial surgery (INS) and interval debulking surgery (IDS; performed after neoadjuvant chemotherapy).

STUDY DESIGN: Retrospective review of patients undergoing (unilateral or bilateral) DS at the time of INS or IDS for ASOC.

RESULTS: Between 2005 and 2008, 63 patients were studied. Treatment of the diaphragm was unilateral in 31 patients and bilateral in 32 patients. DS was performed respectively at the time of INS in 22 patients (35%) and IDS in 41 (65%) patients. Complete cytoreductive surgery was achieved in 95% (21 of 22 in the INS group and 39 of 41 in the IDS group). Surgical procedures used during DS were (in the INS and IDS groups, respectively) stripping in 14 (64%) and 16 (39%), coagulation in 2 (9%) and 10 (24%), and both procedures in 6 (27%) and 15 (37%). An intraoperative chest tube was placed in 14% of patients in each group. Postoperative chest complications requiring treatment occurred in 6 cases: pulmonary embolism (3 cases), symptomatic pleural effusion requiring chest drainage (1 case), and pneumothorax necessitating chest drainage (2 cases).

CONCLUSIONS: Rate of overall morbidity related to DS was not statistically different in patients undergoing INS and IDS. Surgical treatment of this upper part of the abdomen is key to achieving complete cytoreductive surgery in ASOC. (J Am Coll Surg 2010;210:509–514. © 2010 by the American College of Surgeons)

Survival is enhanced in patients with advanced-stage ovarian cancer (ASOC) when all visible disease is removed.[1-3] Overall and disease-free survival are clearly improved in patients with macroscopic complete resection of peritoneal spread (compared with patients with macroscopic residual disease, even if the size of this residuum is small).[1-3] The goal of debulking surgery is to obtain total clearance of the peritoneal cavity; such surgery should now, in 2010, be considered as the "real" optimal debulking surgery.[1] Among the established prognostic factors in ovarian cancer (ie, age, stage, grade, and residual disease), only residual disease status can be influenced by surgeon's experience. A recent review seems to suggest that the surgeon is a prognostic factor in ovarian cancer.[4] The upper abdomen is a key area where complete surgical cytoreduction is mandatory in patients with advanced cancer. The surgeon's skill is reflected in the quality of the dissection of this site. It is also the seat of residual disease in cases of incomplete cytoreductive surgery.

In this context (debulking), the morbidity of surgery is controversial. Because the objective of complete cytoreduction is to achieve long-term survival with the best quality of life, justification of diaphragmatic surgery (DS) during a cytoreductive operation continues to be challenged.[5,6] The aim of this study was to evaluate modalities and morbidities of DS at the time of initial surgery (INS) and interval debulking surgery (IDS; performed after neoadjuvant chemotherapy).

Disclosure Information: Nothing to disclose.

Received November 25, 2009; Revised January 5, 2010; Accepted January 7, 2010.

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ISSN 1072-7515/10/$36.00
doi:10.1016/j.jamcollsurg.2010.01.011

Abbreviations and Acronyms

ASOC = advanced-stage ovarian cancer
DS = diaphragmatic surgery
IDS = interval debulking surgery
INS = initial surgery

METHODS

Between 2005 and 2008, one-hundred and sixteen patients underwent cytoreductive surgery (INS or IDS) for ASOC at the Institut Gustave Roussy. Among them, 63 patients underwent unilateral or bilateral DS during debulking. This study population was divided into 2 groups; 22 patients had DS at the time of INS (INS group) and 41 at the time of IDS (IDS group).

All cytoreductive operations were carried out with the intent of maximally removing all visible tumor. DS was performed and combined with extensive radical procedures if they were likely to result in macroscopically complete cytoreduction.

DS was performed in 3 steps: first, we mobilized the liver to explore the diaphragmatic peritoneum; second, we performed unilateral or bilateral resection and/or coagulation; third, if we made a pleural opening, we repaired it after evacuation of pneumothorax with or without the need for a chest tube. If diaphragmatic lesions were ≤1 mm (without involvement of the muscle), coagulation was performed. If lesions measured >1 mm (or <1 mm but with involvement of the muscle), resection of the peritoneum was preferred to remove the disease. A chest tube was routinely placed if a large resection (>5 cm) of the diaphragm (including muscle) was needed.

Patient medical records were retrospectively reviewed to extract demographic data and perioperative information. Age, histology, and grade were extracted from patient charts. The stage of the disease, based on spread during initial management, was determined using the 1987 International Federation of Gynecology and Obstetrics classification. Surgical data included information on preoperative diagnosis and evaluation (in particular, the need for neoadjuvant chemotherapy to perform complete surgery) and operative variables, including extent of disease; surgical procedure; pleural opening; and chest tube (use of a per- or postoperative chest tube). Postoperative complications included events up to 6 weeks after surgery. Data were analyzed using Student's *t*-test and chi-square analysis as appropriate. A p value <0.05 was considered significant.

RESULTS

From 2005 and 2008, si63 patients underwent DS during the surgical treatment of ovarian cancer. Twenty-two patients underwent this procedure during cytoreduction of the initial tumor (INS group). Forty-one DS were performed after neoadjuvant chemotherapy (IDS group).

Table 1. General Characteristics of Patients during Initial Management According to the Different Groups

Variable	Group 1: initial surgery (n = 22)	Group 2: interval surgery (n = 41)	p Value
Total n	22	41	
Age, y, median (range)	53 (24−74)	53 (20−70)	NS
Postmenopausal, n (%)	14 (64)	26 (63)	NS
History of gynecological disease,* n (%)	7 (32)	11(27)	NS
Initial cancer antigen−125 level, n (%)			0.03
≤500	10 (45)	11 (27)	
>500	7 (32)	28 (68)	
Unknown	5	2	
Histological subtype of ovarian tumor, n (%)			
Serous	14 (64)	30 (73)	
Clear cell	2	2	
Endometrioid	0	3	
Transitional cell	1		NS†
Mucinous	3	1	
Other	2	5	
Tumor grade, n (%)			NS
1	3 (14)	5 (12)	
2	8 (36)	7 (17)	
3	11 (50)	18 (44)	
Unknown	0	11 (27)	
FIGO stage, n (%)			NS
IIIC	21 (95)	39 (95)	
IV	1	2	
Courses of neoadjuvant chemotherapy, n (%)			
1 or 2		3	
3 or 4		29 (71)	
>5		9	

*History of benign gynecological disease (hysterectomy or adnexectomy) or personal or familial cancer.
†Serous versus nonserous histological subtypes.
FIGO, International Federation of Gynecology and Obstetrics.

Patient characteristics are shown in Table 1. Median age, menopausal status, tumor grade, tumor histology, and International Federation of Gynecology and Obstetrics stage were not significantly different between the 2 groups. Most patients had serous histology (64% and 73% in the INS and IDS groups, respectively) and stage IIIC disease (95% in both groups). Patients in the IDS group were more likely to have higher initial cancer antigen−125 levels than patients in the INS group (p = 0.03). The

Table 2. Characteristics of Patients Undergoing Cytoreductive Surgery According to the Different Groups

Variable	Group 1: initial surgery (n = 22)	Group 2: interval debulking surgery (n = 41)	p Value
Standard procedures, n (%)			
Lymphadenectomy			NS
Pelvic and para-aortic	18 (82)	30 (73)	
Pelvic alone	0	1	
Not done	4	10	
Supracolic omentectomy	22 (100)	41 (100)	NS
Extensive procedures, n (%)			
Splenectomy	7 (32)	14 (34)	NS
Diaphragmatic surgery	22 (100)	41 (100)	NS
Bowel resection	15 (68)	28 (68)	NS
Small bowel resection	3	10	
Hemicolectomy	2	9	
Total colectomy	0	1	
Low anterior resection	15	24	
No. of intestinal anastomoses			NS
1	11	21	
2	4	7	
Permanent stomia	0	1	
Macroscopic residual tumor, cm			
None	21 (95)	39 (95)	NS
<1	0	1	
>1	1	1	

majority of IDS patients received 3 or 4 courses of neoadjuvant chemotherapy (71%).

The majority of patients required extensive surgery, such as bowel resection (68% in both groups). There was no significant difference between INS and IDS groups in the frequency of standard and extensive procedures (Table 2). There was no residual macroscopic tumor after cytoreductive surgery in 95% of patients in both groups (21 of 22 and 39 of 41 patients in the INS and IDS groups, respectively).[1] We discovered liver metastasis during surgery in 2 patients (1 in each group). Macroscopic extensive unresectable disease was discovered on the small bowel in the second patient in the IDS group.

Characteristics of DS are shown in Table 3. There was no statistically significant difference between the rate of uni- or bilateral treatment of the diaphragm during INS and IDS surgery (NS). There was no statistical difference between the modalities used for DS and pleural opening during initial and interval surgery.

When we examined the use of chest tubes during surgery, we found 3 (14%) and 6 (14%) procedures, respectively, in the INS and IDS groups (NS). Postoperative complications and variables directly related to DS are listed in Table 4. There were 2 pulmonary embolisms in the INS group and 1 in the IDS group. Secondary drainage with a chest tube was necessary in 3 patients in the IDS group: 1 for pleural effusion and 2 for pneumothorax. Postoperative complications and variables not directly related to DS are listed in Table 4. Additional surgery was necessary in 5 patients for 2 digestive fistulas (1 in each group), 2 abdominal abscesses (1 in each group), and 1 vaginal cuff hematoma. No deaths were reported. Median number of days in hospital was 16 (range 9 to 35 days) in the INS group and 14 (range 9 to 40 days) in the IDS group (NS).

Table 3. Characteristics of Patients Undergoing Diaphragmatic Surgery According to the Different Groups

Variable	Group 1: initial surgery (n= 22)	Group 2: interval debulking surgery (n = 41)	p Value
Unilateral, n (%)	13 (59)	18 (44)	NS
Stripping alone	10	10	
Coagulation alone	1	5	NS
Stripping and coagulation	2	3	
Pleural opening	2 (54)	7 (38)	
Bilateral, n (%)	9 (41)	23 (56)	NS
Stripping alone	4	6	
Coagulation alone	1	5	
Stripping and coagulation	4	12	
Pleural opening	5 (55)	11 (47)	
Unilateral	5	9	
Bilateral	0	2	NS
Total pleural opening	12 (54)	18 (44)	NS
Thoracostomy tube during surgery	3 (14)	6 (14)	NS

DISCUSSION

DS might be required as part of the management of bulky upper abdominal disease in order to achieve complete resection, the goal of ovarian surgery. Few articles are specifically devoted to this procedure in this context (Table 5). This is a retrospective study, but it concerns a continuous analysis in which none of the patients requiring DS for ovarian malignancies were excluded. In addition, this series included a large number of patients undergoing DS (the second largest series published to date) and treated during a short study period (4 years) with the same team of surgeons. The largest series previously published involved 69 patients treated during a study period of 9 years.[12]

The first goal of the debulking surgery in ASOC is to obtain a macroscopic complete resection of the peritoneal spread.[1-3] The first step of the procedure is to explore the

Table 4. Postoperative Morbidity after Cytoreductive Surgery in Both Groups

Variable	Group 1: initial surgery (n = 22)	Group 2: interval debulking surgery (n = 41)	p Value
Hospital stay, d, median (range)	16 (9−35)	14 (9−40)	NS
Major morbidity,*n (%)			
Anastomotic leakage	1 (5)	1 (2)	
Vaginal cuff hematoma	0	1 (2)	
Abdominal abscess	1 (5)	1 (2)	
Pulmonary complications, n (%)			
Pulmonary embolism	2 (9)	1 (2)	
Thoracostomy tube after surgery	0	3 (7)	
For pneumothorax		2 (5)	
For pleural effusion		1 (2)	

*Morbidity requiring additional operation.

diaphragmatic areas to try to ensure that all peritoneal spread could be removed. At our institution, if this goal could not be achieved, we do not use DS to achieve a suboptimal debulking surgery. This point explains why a very small number of patients in the present study had residual disease at the end of debulking surgery.

In recent studies on DS in ASOC[6-14], the authors reported bowel resection rates ranging from 29% to 89%, with a majority of large bowel resections; splenectomy rates ranging from 9% to 21%; and pelvic and para-aortic lymphadenectomy rates ranging from 25% to 94%. With this extensive surgery, rates of complete cytoreduction reported in the literature ranged from 16% to 89%.[6-14] In this study, we achieved similar rates: 68% of intestinal resections, 33% of splenectomies, 76% of pelvic and para-aortic lymphadenectomies, and 95% of complete cytoreduction.

Diaphragmatic carcinomatosis is one of the most frequent secondary lesions in ASOC, and DS is a major step in cytoreductive surgery. The right hemidiaphragm was more frequently involved in all studies.[7-14] However, a higher rate of bilateral DS was reported in the studies with a higher rate of complete cytoreduction. In our institution, we performed bilateral DS in 50% of the cases to obtain a 95% rate of complete cytoreduction.[6] This point is very important and indicates the need to include techniques for treating upper abdominal carcinomatosis in surgical oncology training programs.

The first complication of DS was hydrothorax. In the literature, the rate of postoperative pleural effusion after cytoreductive surgery with DS ranged from 10% to 59%.[7-14] Dowdy and colleagues[11] reported a strong association between pleural opening and postoperative pleural effusion. In addition, data in the literature suggest that the rate of chest-tube placement during and after surgery was correlated with the rate of pleural opening (Table 5). However, there is no consensus about use of a chest tube, and there are 2 points of view. Einenkel and colleagues[14] reported a high rate of chest-tube use (36% during surgery and 18% after surgery) and recommended generous use of chest tubes when the pleural space is opened. In contrast, Devolder and colleagues[12] did not place a chest tube during surgery in their study and mentioned a low rate of postoperative chest drains (7%). Devolder and colleagues did not recommend prophylactic use of a chest tube during DS, even though pleural opening was

Table 5. Review of Studies on Diaphragmatic Surgery for Advanced-Stage Ovarian Cancer

First author	Year	n*	n*/nt, %	Study period, y	Time of surgery	Complete resection, %	Bilateral diaphragm involvement, %	Pleural opening, %	Chest tube during surgery, %	Chest tube after surgery, %
Deppe[7]	1986	14	—	2	Primary	—	—	—	—	0
Montz[8]	1989	14	—	4	Primary	—	—	28	28	0
Kapnick[9]	1990	21	—	2	Primary (n = 16) Recurrent (n = 5)	—	—	52	52	0
Eisenhauer[10]	2006	59	27	4	Primary	—	—	—	12	14
Dowdy[11]	2008	56	<20	17	Primary (n = 37) Secondary (n = 19)	43	—	—	—	12,5
Devolder[12]	2008	69	50	9	Primary (n = 38) Interval (n = 29) Secondary (n = 2)	85	7	7	0	7
Chereau[13]	2009	18	48	3	Primary (n = 14) Interval (n = 4)	89	38	38	0	27
Einenkel[14]	2009	33	—	3	Primary	61	80	>66	36	18
Our study		63	54	4	Primary (n = 22) Interval (n = 41)	95	48	48	17	5

nt, total of patients during the study period.
*n indicates number of patients undergoing diaphragmatic surgery.

performed. In our institution, we placed a chest drain as soon as the diaphragm defect was large (>5 cm), or if several defects are carried out on the same hemidiaphragm. In our study, we used a chest drain during surgery in 17% of cases and a postoperative chest tube was necessary in only 5% of cases.

On the technical point of view, if complete liver mobilization is done at the beginning of the surgical procedure, it is possible to close the defect of the diaphragm using direct sutures. The initial complete liver mobilization allows getting "sufficient diaphragmatic stuff" at the end of the removal (even if a part of diaphragmatic muscle is removed), to make this closure without tension. If a large part of the diaphragm (with muscle) needs to be removed, a permanent mesh could be used to close the defect. This procedure is rarely needed in this context (and was never done in our series).

IDS after neoadjuvant chemotherapy has been investigated in several studies. Two studies concluded that the rate of morbidity was lower in the IDS group.[15,16] More recently, Vergote and colleagues[17] presented the results of a European Organization for Research and Treatment of Cancer randomized trial comparing INS in 329 patients with neoadjuvant chemotherapy followed by IDS in 339 patients with stage IIIC and IV ovarian, fallopian tube, and peritoneal cancer. Mortality in the INS group was considerably higher than in the IDS group (2.7% versus 0.6%). Vergote and colleagues obtained a similar result for morbidity with a higher digestive fistula rate in the INS group (1.2% versus 0.3%). However, the higher rate of incomplete cytoreduction (79% in the INS group and 47% in the IDS group) could be a possible explanation for the difference found in mortality and morbidity. In contrast, no statistically significant differences were found in complications rates in Colombo and colleagues' work[18] comparing 142 patients submitted to INS and 61 patients who underwent IDS. Our study achieved similar results with no notable difference between INS and IDS, particularly in terms of digestive fistula and reoperation. Selection of patients requiring INS or neoadjuvant chemotherapy followed by IDS is a key point to obtaining a high rate of complete cytoreduction and avoiding unnecessary laparotomy. Laparoscopy seems to be the most appropriate procedure for evaluating the resectability of ASOC and for decision making about whether to perform INS or IDS.

The primary objective of this study was to evaluate and compare morbidity of DS at the time of INS and IDS. We compared pulmonary complications in 2 groups of patients at the time of surgery: 22 patients underwent INS and 41 patients IDS. To our knowledge, this is the first study to compare modalities and morbidities of DS in INS and IDS. Use of neoadjuvant chemotherapy reduces peritoneal spread of the disease. Theoretically, in this series, the need for surgical removal of both hemidiaphragms and for resection or stripping (compared with coagulation) would have been reduced in the IDS group (compared with INS group). Our 2 groups were comparable in terms of patient, tumor, and surgery characteristics. There was no significant difference between INS and IDS groups for rates of bilateral DS (41% versus 56%), surgical procedures, pleural opening (54% versus 44%), and use of chest tubes during surgery (14% in each group). Surgical procedures (eg, stripping, coagulation, both procedures) were chosen according to the case-specific invasion of the diaphragm by carcinomatosis. We used coagulation alone in 10 cases in the IDS group and in only 2 cases in the INS group (NS). These 10 cases were the most complex because differentiating fibrosis from residual lesions can be difficult after chemotherapy. Most of the time after chemotherapy, when lesions were smaller (<1 mm) and did not involve the muscle, we decided to use coagulation. Diaphragmatic stripping was the surgical procedure chosen in the other cases. Devolder and colleagues[12] found that survival was better in the diaphragm stripping group than in the coagulation group, but the authors did not specify in which cases they chose coagulation, nor did they mention the timing of surgery in those patients. There was no significant difference between INS and IDS groups in the rates of pulmonary complications: 2 pulmonary embolisms in the INS group and 1 pulmonary embolism, 2 pneumothoraces, and 1 pleural effusion requiring a chest tube in the IDS group. These results are in agreement with previous studies that reported a pneumothorax rate ranging from 0% to 33% and a rate of secondary chest-tube drainage ranging from 7% to 27%.[7-14] Our findings suggest 3 important points. First, when DS is feasible, we can obtain complete cytoreduction at the time of INS or IDS in the majority of cases (95%).[6] The importance of DS was also reported by Aletti and colleagues,[19] who showed that DS and residual disease were predictive factors of survival in the multivariate analysis. Second, we recommend use of a chest tube during surgery when pleural opening is large (>5 cm) or in case of several defects on the same hemidiaphragm. With this attitude, we reported a low rate of pleural effusion and pneumothorax requiring drainage (5%). Third, rate of overall morbidity related to DS is relatively low, but such morbidities depend on the skill of the surgeons and on the team providing care for the patients during the perioperative period (ie, anesthesiologist, ICU, nurse). Previous studies showed an association between a high nurse-to-bed ratio and low surgical mortality.[20,21] The precise rate of morbidity of DS in ASOC should be explored using pro-

spective studies. One of the most important issues in this context is to evaluate carefully pulmonary functions before and after DS.

Author Contributions

Study conception and design: Gouy, Morice
Acquisition of data: Gouy, Chereau, Custodio
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Acknowledgment: The authors thank Lorna Saint Ange for editing.

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