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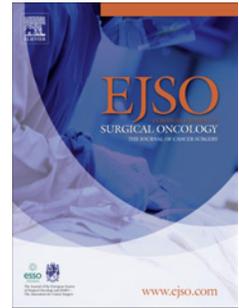
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**Morbidity of diaphragmatic surgery for advanced ovarian cancer:  
retrospective study of 148 cases**

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## Abstract

**Background:** Treatment of Advanced Ovarian Cancer (AOC) includes surgery with complete cytoreduction, one of the strongest prognostic factors. To achieve complete cytoreduction, diaphragmatic surgery is often required. There is currently a lack of information in the literature regarding the morbidity and impact of this type of surgery. The aim of this study is to report specific pulmonary morbidity and overall morbidity associated with diaphragmatic surgery in patients with AOC.

**Materials and Methods:** We conducted a multicentric (6 centres), retrospective study that included 148 patients operated on between 2004 and 2008. Patient characteristics, surgical course and postoperative complications were collected.

**Results:** The complete cytoreduction rate was 84%. The surgery was categorised by timing as initial, interval or recurrence surgery in 38%, 51% and 11% of patients, respectively. In 69% of patients, one or more postoperative complications occurred: pulmonary complication (42%), digestive fistula (7%) or lymphocyst (18%). The pulmonary complications were pleural effusion (37%), pulmonary embolism (5%), pneumothorax (4%) and pulmonary infection (2%). These complications required revision surgery, pleural evacuation, or lymphocyst evacuation in 13%, 14%, and 11% of the cases, respectively. Postoperative mortality was 3%. Risk factors for pulmonary complications were the addition of extensive upper surgery to the diaphragmatic surgery ( $p=0.014$ ) and the size of the diaphragmatic resection ( $p=0.012$ ).

**Conclusions:** Diaphragmatic surgery achieved complete removal of the tumour but resulted in pulmonary complications in addition to complications of radical surgery.

**Key words:** ovarian cancer, diaphragmatic surgery, complete surgery, morbidity, survival

## Introduction

Both retrospective and prospective reports have demonstrated that optimal cytoreduction for advanced epithelial ovarian cancer is the cornerstone of effective treatment<sup>1,2</sup>. In patients with stage IIIC/IV disease (i.e., Advanced Ovarian Cancer, AOC), diaphragm involvement is very common<sup>3</sup>. Because of late diagnosis, the overall five-year survival rate for ovarian cancer is commonly approximately 30%<sup>4</sup>. Bulky diaphragm disease had been reported as one of the most common sites of disease leading to suboptimal cytoreduction and therefore to a lower rate of survival. Surgical procedures already exist to treat diaphragm disease, which typically increase the rate of complete and optimal debulking and yield better survival compared to patients with residual disease found only in the diaphragm<sup>5</sup>. Since 1986, some authors have reported their experience with diaphragmatic surgery in advanced ovarian cancer. The related reports highlighted feasibility, improvement in outcome in cases of optimal cytoreduction and specific pulmonary morbidity<sup>6-16</sup>. Moreover, incorporation of extensive upper abdominal procedures, such as partial liver section, distal pancreatectomy or splenectomy, may lead to improved cytoreduction<sup>17-23</sup>. Extensive surgery could increase postoperative morbidity (digestive fistula, lymphocyst or infection)<sup>13, 24-34</sup>. Therefore, radical surgery for advanced ovarian cancer could improve survival but with an increase in postoperative morbidity. To date, the studies reporting diaphragmatic surgery in AOC have included less than 90 patients, were unicentric studies, and were focused on pulmonary complications only. We conducted a retrospective, multicentric study that included 148 patients who underwent diaphragmatic surgery for AOC to investigate pulmonary and general complications due to extensive surgery.

## Materials and Methods

During the period from 2004 to 2008, 148 patients underwent diaphragmatic surgery for stage IIIC or IV ovarian cancer at six French surgical oncology departments. The individual records of all patients were reviewed and analysed. Patient and tumour characteristics, intra-operative findings, postoperative courses and outcomes were analysed. Diaphragmatic surgeries may have consisted of stripping, muscle resection or electrosurgical ablation. The mean diameter of the diaphragmatic resection was also studied. The indication of chest tube placement followed the surgeon's preference and typical practice at each centre. The chest tube was typically placed at the pleural opening, especially in the case of multiple openings. Extensive upper abdominal surgery included splenectomy, cholecystectomy, distal pancreatectomy, partial liver section and lesser omentum resection. Residual disease was reported as complete (no residual disease, R0) or incomplete<sup>35</sup>. Intra-operative estimated blood loss, operative time, and length of hospitalisation were all recorded. The duration of drainage, secondary pleural puncture requirement and post-operative complications such as digestive fistula, lymphocyst and infection were also recorded.

Because this study was a retrospective study, no Institutional Review Board approval was needed.

## Statistical Analysis

Data were analysed using the chi-square test and Student's t-test. Differences were considered significant at a level of  $p < 0.05$ . Cox proportional hazards regression was used for multivariate analysis.

## Results

The median age of patients was 59 years (Table 1). Most patients were of stage FIGO 3C (91%) and had grade 2 (46%) or 3 (43%) lesions. The mean rate of CA 125 at the time of the diagnosis was 1588 UI/l. Eighty-one patients received neo-adjuvant chemotherapy. Initial surgery was performed in 38% of patients, interval surgery in 51% of cases and surgery for recurrent disease in 11% of cases. The histological type was more often serous (69%) or endometrioid (8%), and the mean size of ovarian tumours was 67 mm. During cytoreduction, 80% of patients had salpingo-oophorectomy, 76% had hysterectomy, 91% had omentectomy, 69% had pelvic lymph node dissection, 72% had para-aortic lymph node dissection, and 55% underwent appendectomy. Intestinal resection was performed in 68% of cases. Extensive upper abdominal surgery included lesser omentum resection (35%), splenectomy (31%), cholecystectomy (18%), distal pancreatectomy (4%), partial liver section (9%) and partial gastrectomy (3%). All patients underwent diaphragmatic surgery. On the right hemi-diaphragm, coagulation was performed in 25% of cases, stripping (resection of the diaphragm peritoneum) was performed in 91% of cases, and muscle resection was performed in 62% of cases, with 51% of pleural openings (procedures may have been combined). Fewer patients underwent left hemi-diaphragm surgery (42%): coagulation was performed in 32% of cases, stripping in 74% of cases and muscle resection in 15% of cases (including 8% with pleural opening). The mean size of diaphragmatic resection was 126 mm for the right side and 74 mm for the left side. Pleural drainage was established during the surgical course for 35% of patients, and the mean duration of drainage was 5.1 days. The mean operative time was 426 minutes, and the estimated blood loss was 1465 ml. One hundred and twenty-four (84%) patients underwent complete cytoreduction (R0), and 24 underwent incomplete resection (16%).

Details about the extent of surgery according to the timing of surgery (i.e., initial, interval or recurrence) are reported in Supplementary file 1.

Postoperative complications occurred in 102 patients (Table 2), and pulmonary complications were diagnosed in 63 patients. The complications included pleural effusions in 37% of patients, pulmonary embolisms in 5%, pneumothorax in 4% and pulmonary infections in 2%. Sixty-two patients had non-pulmonary complications, including digestive fistulas (7%), lymphocysts (18%) and fever or infections (55%). Revision surgery was necessary for 13% of patients, secondary drainages or pleural punctures for 14% of patients and lymphocyst punctures for 11% of patients. Rehospitalisation was required for 20% of patients. Four patients died within 30 days of operation (3%), all from septic complications.

When we calculated the rate of postoperative complications (total, pulmonary or non-pulmonary) according to the number of patients managed during the study period (> or < 20 patients), there was no significant difference between the groups (Supplementary file 2).

We next compared surgical characteristics and postoperative complications between initial surgery and interval surgery. We found significant differences in the mean duration of surgery (467 min for initial surgery vs. 409 for interval surgery,  $p=0.019$ ) and for the occurrence of intestinal resection ( $p=0.011$ ), lymphadenectomy ( $p=0.04$ ) and partial liver section ( $p=0.004$ ). Despite these results, we did not find any significant differences in the occurrence of postoperative complications or the results of the surgery.

Risk factors for pulmonary complications were the addition of extensive upper surgery to the diaphragmatic surgery ( $p=0.014$ ) and the size of the diaphragmatic resection ( $p=0.012$ ). For severe complications (resulting in death or high morbidity), we identified past history of surgery ( $p=0.012$ ) and intestinal resection ( $p=0.013$ ) as risk factors. Time of surgery (initial or interval surgery) was not a risk factor for the occurrence of postoperative complications, regardless of type (pulmonary, non-pulmonary or severe complications).

The median follow-up time for the group was 19.1 months. The two-year disease-free survival was 37%. The five-year overall survival and disease-free survival estimations were 45% and 10%, respectively. There were no differences for disease free survival (DFS) or overall survival (OS) between initial and interval surgeries.

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## Discussion

For AOC, residual disease after surgery is the most relevant determining factor for survival<sup>1,2</sup>. Because more than 75% of patients with advanced ovarian cancer had diaphragmatic disease on at least one side, diaphragmatic surgery is a major step in cytoreductive surgery<sup>3</sup>. However, radical surgery has its own morbidity, including both pulmonary and non-pulmonary (digestive fistula, lymphocyst, fever or infection) complications. In this study of 148 patients with diaphragmatic surgery as part of the radical cytoreductive surgery for stage-3C and stage-4 ovarian cancer, postoperative complications occurred in 69% of cases: 43% of patients had pulmonary complications, and 42% of patients had non-pulmonary complications.

### Extension of radical surgery

Diaphragmatic carcinomatosis is one of the most frequent localisations in AOC. We reported patient and tumour characteristics in accordance with literature findings: the median age was 59 years, and the tumours were most often serous (49%) and grade 2 (46%) or 3 (43%). The rate of complete cytoreduction was 84%. To obtain this high rate of complete cytoreduction, extensive surgery including upper abdominal surgery and digestive resection was often performed. Moreover, this rate can be explained by the high rate of interval surgery. In the literature, during extensive surgery with the aim of optimal resection, authors reported rates of diaphragmatic surgery ranging from 10 to 100%, intestinal resection from 20 to 100%, splenectomy from 1 to 33%, distal pancreatectomy from 0 to 11%, partial liver section from 0 to 16% and cholecystectomy from 2 to 20%<sup>2,5,10,13,22,25,36</sup>. In this study, in addition to systematic diaphragmatic surgery, we performed similar rates of intestinal resection (68%), splenectomy (31%), cholecystectomy (18%), partial liver section (9%) and distal

pancreatectomy (4%). These results suggest that diaphragmatic surgery is only one component of radical surgery. Therefore, postoperative morbidity included, in addition to pulmonary complications, other specific complications such as digestive fistula and lymphocysts.

### **Pulmonary complications**

During diaphragmatic surgery, the pleural space was opened in 51% of cases. Rates found in others studies ranged from 7 to 52% (Table 3)<sup>6-16</sup>. Pulmonary complications occurred in 43% of cases, with the main complication being pleural effusion (37%). Other complications were pneumothorax (4%), pulmonary infections (2%) and pulmonary embolism (5%). Several studies have reported rates of pulmonary complications after diaphragmatic surgery for ovarian cancer (Table 3). In these studies, the rates of diaphragmatic surgery ranged from 14 to 100%, and complete surgery was achieved in 43 to 93% of cases. Pneumothorax was found in 0 to 33% of cases. Pleural effusion occurred in 0 to 59% of cases, depending on the rate of chest drainage established during surgery (from 0 to 65%). In a previous study, we concluded on the relevance of chest drainage in cases of pleural opening<sup>13</sup>. Eisenhauer et al.<sup>10</sup> had previously claimed that systematic placement of chest tubes was not justified because, in their view, the occurrence of postoperative pleural effusion was not a major postoperative complication. However, in their study, only 40% of patients had lymphadenectomies, and 60% had only diaphragmatic surgery. In our experience, the need for secondary drainage or pleural puncture extended the length of hospitalisation and post-operative pain; therefore, placement of a chest tube in cases of pleural opening might be relevant<sup>13</sup>. Rates of secondary pleural puncture or chest tube placement in the literature ranged from 0 to 44%; this variability may be related to the number of chest drains inserted during surgery. The rates of secondary pleural puncture or chest tube placement in our study

were 14%, in agreement with these data. The rate of pleural effusion reported in our study could be explained by the importance of achieving 62% muscle resection and a median size of right hemi-diaphragm resection of 126 mm in diaphragmatic surgery. This rate emphasised the relevance of chest drainage in decreasing postoperative interventions.

Risk factors for the occurrence of pulmonary complications were the addition of other upper abdominal procedures and the size of the diaphragmatic resection<sup>15</sup>. Other studies found liver mobilisation<sup>10</sup> or pleural opening<sup>11</sup> to be risk factors. Because we routinely divide the hepatic ligaments to mobilise the liver, we were unable to test this association in our cohort.

### **Non-pulmonary complications**

The rates of non-pulmonary complications found in our study were similar to those reported in the literature<sup>13,21-34</sup>: digestive fistula from 1.4 to 8.2%, lymphocyst from 0.6 to 32%, and septic complications from 3.7 to 41.4%. The revision surgery rate in our study was in accordance with data in the literature that report rates from 4.1 to 16.5%. Four patients died during the 30 postoperative days, all from septic complications. Rates in the literature ranged from 0.3 to 5.7%. In a recent meta-analysis, Gerestein et al.<sup>30,37</sup> found that the more frequent causes of postoperative mortality were adverse surgical events, pulmonary complications and cardiovascular complications.

The important rate of iterative surgery found among our population was in accordance with the rates reported in the literature for extensive surgery (from 4.1% to 16%)<sup>13,24-26,28,31</sup>.

### **Expert centres**

Another major consideration when debating morbidity for AOC is the management of patients in expert centres. Indeed, publications increasingly highlight the importance of not only

surgical skills and experience but also of high-quality surgical care delivered by a multidisciplinary team that includes oncology nurses, anaesthesiologists, pathologists, dieticians and physiotherapists for the management of advanced ovarian cancer patients<sup>19</sup>. Many retrospective studies have reported that debulking operations performed by gynaecologic oncologists result in the best outcomes (including survival) compared to surgery performed by general gynaecologists or general surgeons<sup>20-22</sup>. Therefore, centralisation of these patients in expert centres is recommended.

In this study, no differences were found between the centres with under or over 20 patients. This outcome was expected because all surgeons were gynaecologic oncologists and all these centres were used to perform radical surgery not only for ovarian cancer but also for advanced cervical, endometrial or vulvar cancer.

### **Conclusion**

One of the strengths of this study is the report of not only specific postoperative complications of diaphragmatic surgery but also other complications of extensive surgery for AOC.

In conclusion, diaphragmatic surgery is an essential step in cytoreductive surgery for AOC and improves survival. When this surgery is used, it causes pulmonary complications in addition to morbidity due to the need for radical surgery.

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**Table 1. Patients, tumor characteristics and surgical procedures performed.**

	n (%)
<b>Median age (range)</b>	59 (18 – 84)
<b>BMI (range)</b>	23.1 (16.4 – 52)
<b>FIGO stage</b>	
III C	135 (91%)
IV	13 (9%)
<b>Tumor grade (n=76)</b>	
1	8 (11%)
2	35 (46%)
3	33 (43%)
<b>Histologic type</b>	
Serous	102 (69%)
Endometrioid	13 (8%)
Mucinous	4 (3%)
Other	29 (20%)
<b>Type of surgery</b>	
Initial	57 (38%)
Interval	75 (51%)
Recurrence	16 (11%)
<b>Pre-operative CA 125 level (range)</b>	1588 (10 – 12500)
<b>Neo-adjuvant chemotherapy</b>	81 (55%)
<b>Standard Surgery</b>	
Hysterectomy	112 (76%)
Unilateral or bilateral salpingo-oophorectomy	119 (80%)
Omentectomy	134 (91%)
Intestinal resection	100 (68%)
Appendectomy	81 (55%)
Pelvic lymphadenectomy	102 (69%)
Para-aortic lymphadenectomy	107 (72%)
<b>Extensive upper abdominal surgery</b>	
Splenectomy	46 (31%)
Cholecystectomy	26 (18%)
Distal pancreatectomy	6 (4%)

Partial liver section	13 (9%)
Partial gastrectomy	4 (3%)
Lesser omentum resection	52 (35%)
<b>Diaphragmatic surgery</b>	
<b>Right</b>	<b>148 (100%)</b>
Coagulation	37 (25%)
Stripping	134 (91%)
Muscle resection	91 (62%)
Pleural opening	75 (51%)
Mean diameter size of diaphragmatic resection (mm)	126 (8 – 400)
<b>Left</b>	<b>62 (42%)</b>
Coagulation	20 (32%)
Stripping	45 (74%)
Muscle resection	9 (15%)
Pleural opening	5 (8%)
Mean diameter size of diaphragmatic resection (mm)	74 (10 – 250)
Pleural drainage	52 (35%)
Mean operative time (min) (range)	426 (150 – 720)
Estimated blood loss (ml) (range)	1465 (200 – 7000)
<b>Resection</b>	
Complete R0	124 (84%)
Incomplete	24 (16%)

**Table 2. Surgical Outcome**

	n (%)
Patients with one or more post-operative complications	102 (69%)
Patients with non-pulmonary complications	62 (42%)
Fever / infection	81 (55%)
Lymphocyst	26 (18%)
Digestive fistula	10 (7%)
Urinary fistula	1 (1%)
Patients with pulmonary complications	63 (43%)
Pleural effusion	55 (37%)
Pulmonary embolism	7 (5%)
Pneumothorax	6 (4%)
Pulmonary infection	3 (2%)
Secondary drainage or pleural puncture	21 (14%)
Length of hospitalization (days) (range)	14.8 (1 – 60)
Re-hospitalization	30 (20%)
Iterative surgery	19 (13%)
Post-operative mortality	4 (3%)

**Table 3: Review of studies on diaphragmatic surgery for ovarian cancer. (RD: Residual disease)**

	Year	Number of patients	Diaphragmatic surgery	Time of surgery	Complete surgery	Pleural opening	Chest drain	Pleural effusion	Pneumothorax	Pleural punctures or chest tube
<b>Deppe (6)</b>	1986	14	100%	Initial	100% RD < 2 cm	-	-	0 %	0 %	0 %
<b>Montz (7)</b>	1989	14	100%	Initial	93%	28 %	28 %	0 %	7 %	0 %
<b>Kapnick (8)</b>	1990	21	100%	Initial (76%) Recurrence (24%)	100% RD <1 cm	52 %	52 %	0 %	33 %	0 %
<b>Cliby (9)</b>	2004	41	100%	Recurrence (85%)	80%	24 %	24 %	9,8%	5%	15%
<b>Eisenhauer (10)</b>	2006	59 / 215	27%	Initial	-	27 %	12%	58 %	2 %	15 %
<b>Dowdy (11)</b>	2008	56 / 382	14%	Initial (66%) Interval (34%)	95% RD < 1 cm	-	-	30 %	0 %	12.5%
<b>Devolder (12)</b>	2008	69 / 137	50%	Initial (55%) Interval (42%) Recurrence (3%)	85 %	7 %	0 %	59 %	6 %	17 %
<b>Chéreau (13)</b>	2009	18 / 37	48%	Initial	89 %	38 %	0 %	38 %	5 %	44 %
<b>Fanfani (14)</b>	2010	87/234	37%	Initial (58%) Interval (18%) Recurrence (24%)	100% RD < 1 cm	13.8%	65%	43%	5%	11%
<b>Tsolakidis (15)</b>	2010	89	100%	Initial	90%	-	-	63%	10%	16%
<b>Gouy (16)</b>	2010	63	100%	Initial (35%) Interval (65%)	95%	47%	14%	2%	3%	5%
<b>Current Study</b>	2010	148	100%	Initial (38%) Interval (51%) Recurrence (11%)	84%	51%	35%	37%	4%	14%

**Figure 1 : Progression-free and Overall Survival**

Figure 1a : Progression-free Survival

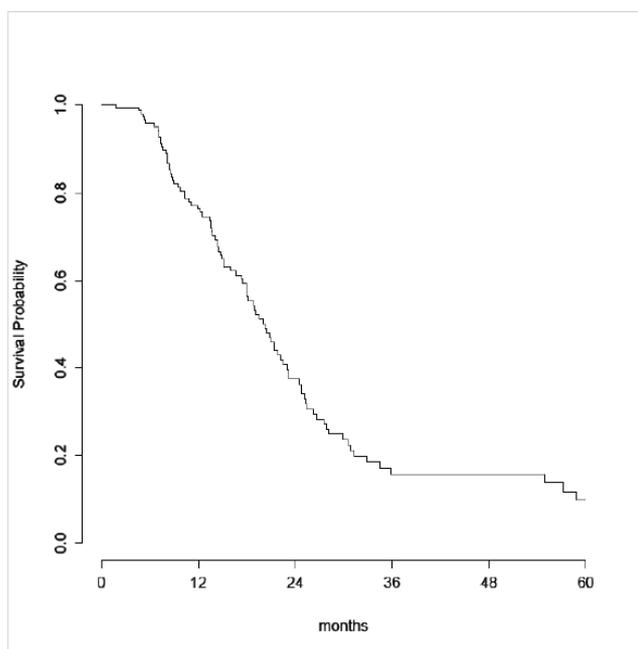


Figure 1b : Overall Survival

