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Value of Diaphragmatic Surgery During Interval Debulking Surgery

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Abstract. *Background/Aim: The aim of this study was to assess the value of diaphragmatic surgery to achieve optimal debulking in patients with advanced ovarian cancer treated by neoadjuvant chemotherapy (NAC). Patients and Methods: This is a retrospective review of the medical records of 182 patients. Diaphragmatic surgery was performed during interval debulking surgery (IDS) in 74 patients between January 2002 and December 2014. The patients were divided in 2 groups: with or without histological residual diaphragmatic disease. The time-course of serum CA125 levels, cytoreductive outcome, overall survival (OS) and relapse-free survival (RFS) were analyzed. Patients without diaphragmatic peritonectomy (DP) during IDS were included in the survival analysis. Results: One hundred thirty-two (72.5%) patients had FIGO stage III disease and 43 (23.6%) patients had stage IV disease. Histological examination of DP was positive in 45 patients and negative in 29 patients. CA125 normalization after the 3rd cycle of NAC was significantly associated with negative DP. OS tended to be higher in the DP-negative group (37.8 months vs 19 months, p=0.1). Median OS was 40.7 months in the case of IDS without DP and 22 months in the case of IDS with DP (p=0.048). Conclusion: Evaluation of residual diaphragmatic disease can be difficult after NAC. The CA125 tumor marker appears to be a useful tool to define the indications for DP. Diaphragmatic surgery after NAC may be of limited value.*

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Ovarian cancer is diagnosed at an advanced stage in about 75% of patients (1). The pathophysiology and intra-abdominal site of ovarian cancer account for the peritoneal dissemination of this disease. Eighteen to 42% of patients with advanced ovarian cancer present with diaphragmatic metastases, especially to the right hemi-diaphragm. Diaphragmatic carcinomatosis is considered to be the second most important obstacle after portal triad involvement that precludes optimal cytoreduction (2). Diaphragmatic peritonectomy is useful and even essential to achieve optimal surgery.

The standard management of ovarian cancer includes cytoreductive surgery followed by platinum-based chemotherapy (3, 4). No residual tumor after cytoreductive surgery is universally considered to be the most important prognostic factor. However, upper abdominal surgical procedures are associated with certain complications that need to be managed. The extent of diaphragmatic resection, liver mobilization and pleural opening are all risk factors for pleural and pulmonary morbidity. The incidence of pulmonary complications ranges between 20% and 70% in various published studies (5-8).

A meta-analysis by Bristow *et al.* demonstrated a significant impact of optimal cytoreduction on survival of patients with advanced ovarian cancer. Each 10% increase in optimal cytoreduction rate was associated with a 5.5% increase in median survival time (3).

For some patients, initially deemed unresectable, chemotherapy is administered prior to surgery. Neoadjuvant chemotherapy (NAC) is used in patients in whom adequate debulking surgery is unlikely to achieve reduction of the tumor burden, or in patients with excessive co-morbidities to undergo an extensive and lengthy operation. Optimal cytoreduction remains the most important prognostic factor even after NAC. However, preoperative and intraoperative evaluation of residual peritoneal carcinomatosis remains difficult.

Table I. *Clinical and pathological characteristics*.

	Overall population (n=182)	No DP (n=108)	Positive DP (n=45)	Negative DP (n=29)	*p*-Value
Age*	63.5 (39-81)	62 (21-83)	64 (39-77)	62 (41-81)	0.90
BMI*	23 (17.6-37.5)	23.7 (16.5-35.4)	23.2 (17.6-37.5)	22.9 (17.8-34.3)	0.37
Menopausal status	159 (87.4%)	96 (88.9%)	38 (84.4%)	25 (86.2%)	0.46
Gravidity*	2 (0-8)	2 (0-10)	2 (0-8)	2 (0-5)	0.42
Parity*	2 (0-8)	2 (0-9)	2 (0-8)	2 (0-4)	0.68
FIGO stage					0.22
IIIC	132 (72.5%)	76 (70.4%)	36 (80%)	20 (69%)	
IV	43 (23.6%)	26 (24.1%)	9 (20%)	8 (31%)	
Type					0.88
Serous	160 (87.9%)	94 (87%)	40 (88.9%)	26 (89.6%)	
Endometrioid	3	5	1	2	
Clear cell	1	4	1	0	
Mixed	1	2	1	0	
Undifferentiated	3	3	2	1	
Grading					0,47
1	13 (7.1%)	7 (6.5%)	4 (8.9%)	2 (7%)	
2	54 (29.7%)	35 (32.4%)	13 (28.9%)	6 (20.7%)	
3	87 (56.8%)	45 (41.7%)	23 (51.1%)	19 (65.5%)	
Diagnostic CA125 level (IU/ml)**	2412 (45-15640)	1952 (15-26220)	2449 (45-11080)	2350 (5-15640)	0.84
Cycles of NAC*	6 (3-9)	6 (1-9)	6 (3-9)	6 (3-7)	0.86

BMI: Body mass index; FIGO: International Federation of Gynecology and Obstetrics; NAC: neoadjuvant chemotherapy. *Median (range); **mean (range).

NAC before surgery can cause fibrosis and adhesions in the peritoneal cavity and may interfere with perioperative evaluation of tumor spread. Although interval surgery appears to be less aggressive and associated with lower morbidity than primary debulking surgery, some procedures may be inappropriate due to inadequate preoperative assessment.

Few data are available concerning the impact of NAC on diaphragmatic peritoneum and the performance of visual inspection of tumor spread. Moreover, the significance of residual disease remains unknown.

The aim of this study was to report histological examination of the diaphragmatic peritoneum after NAC and its significance.

Materials and Methods

After IRB approval, we conducted a multicenter retrospective review of the Curie Institute, René Huguenin Center, Tenon Hospital and Paoli-Calmettes Institute on databases. Between January 2002 and December 2014, 254 patients with advanced epithelial ovarian cancer received platinum- and taxane- based NAC. The medical records of all patients with epithelial ovarian cancer were reviewed. Patients underwent exploratory laparotomy or laparoscopy with minimal surgery, followed by NAC, interval debulking surgery and adjuvant chemotherapy. Diaphragmatic disease was initially present in 182 patients (71.7%). Seventy-four patients (45.7%) underwent diaphragmatic surgery after NAC and consisted the study population. The following clinical, biochemical, radiological and pathological variables were collected for each patient: age, weight, personal and family history, genetic predisposition, characteristics of disease (histology, stage, and surgery) and relapse (treatment-free interval, site, and management). In this retrospective study, two groups were considered depending on the results of histological examination of the diaphragmatic peritonectomy specimen: residual diaphragmatic disease (positive diaphragmatic peritonectomy, positive DP) or no residual diaphragmatic disease (negative DP).

Data analysis was performed with R Version 3.2.2 software. Chi-square test or Fisher's exact test was used for comparison of categorical variables. Student's *t*-test and Kruskal-Wallis test were used for comparison of continuous variables. A $p<0.05$ was considered statistically significant. Survival curves were determined by the Kaplan-Meier method. Relapse-free survival was estimated until the day of first relapse or death according to the guidelines for evaluating the response to treatment using either RECIST or CA125 criteria.

Results

Most patients (63%) had previously undergone open diagnostic laparoscopy to establish the diagnosis and estimate the extent and resectability of the disease in order to achieve no macroscopically visible residual tumor.

Demographic and tumor characteristics of the study population are shown in Table I. The median age was 63.5 years (range=39-81 years). The majority (72.5%) of patients had FIGO stage IIIC (International Federation of Gynecology and Obstetrics) with serous histology tumors

Table II. *Evolution of CA125 level and outcome after therapeutic management.*

	Overall population (n=182)	No DP (n=108)	Positive DP (n=45)	Negative DP (n=29)	*p*-Value
CA125 after 3 cycles*	75 (4-5799)	166 (4-3546)	328.9 (13-5799)	43 (10-322)	<0.00001
CA125 after 3 <35 IU/ml	100 (54.9%)	70 (64.8%)	6 (13.3%)	24 (82.8%)	<0.00001
CA125 before IDS*	84 (1.7-3478)	75 (1.7-1200)	162.8 (6-3478)	19 (6-67)	0.00001
CA125 before IDS <35 IU/ml	136 (74.7%)	89 (82.4%)	12 (26,7%)	25 (86.2%)	<0.00001
CC-0	65 (87.8%)	105 (97.2%)	38 (84.4%)	27 (93.1%)	0.0001
Relapse	118 (64.8)	68 (63%)	32 (71.1%) including 2 progressions	18 (62.1%)	0.06

CC-0: No residual disease after interval debulking surgery. *Mean (range).

(87.9%) and poorly differentiated tumors (56.8%). Forty-five patients had positive DP and 29 had negative DP. Age, BMI, stage, tumor histology, grade, and mean CA125 level at diagnosis were similar between the two groups (Table I). The majority of DP procedures were performed on the right hemidiaphragm, consistent with the known circulation of peritoneal fluid along the right paracolic gutter (9). All patients underwent other simultaneous cytoreductive procedures, including hysterectomy +/- bilateral salpingo-oophorectomy (86.5%) if not previously performed, total omentectomy (93.9%), pelvic (30.4%) and para-aortic lymphadenectomy (31.8%), abdominal or pelvic peritonectomy (37.8%), bowel resection (27%), appendectomy (37.8%) and splenectomy (2.7%). CC0 (no residual macroscopic disease) at the end of surgery was achieved in 88% of cases. Complications following diaphragmatic peritonectomy were pleural effusion, subcapsular hematoma, and pneumothorax. No intra-operative complications were attributed to DP.

Demographic and tumor characteristics were similar for patients with and without DP.

Serum CA125 levels at diagnosis were similar in the two groups (2,449 IU/ml *vs*. 2,350 IU/ml, p=0.89). In contrast, there was a difference for the pre-operative CA125 level (162.8 IU/ml *vs*. 19 IU/ml), with a level <35 IU/ml in the majority of DP-negative patients. All patients received at least 3 cycles of NAC (range=3-7 cycles). The mean CA125 level after the 3rd cycle of NAC was lower for patients with negative DP compared to patients with positive DP (43 IU/ml *vs*. 328.9 IU/ml). Additionally, CA125 normalization after the 3rd NAC was significantly associated with negative DP (Table II). Residual disease status appeared to influence survival with 10 recurrences observed during the first 6 months in the DP-positive group (22.2%) *versus* only 1 recurrence in the DP-negative group (3.5%). Overall survival (OS) tended to be higher in the DP-negative group with a median OS of 37.8 months *versus* 19 months (p=0.1) (Figure 1). No significant difference in terms of relapse-free survival (RFS) was observed between the two groups (9.37 months *vs*. 10.4 months). Moreover, median OS was statistically significantly different between patients with and without diaphragmatic surgery: 22 months and 40.7 months, respectively (p=0.048) (Figure 2).

Discussion

Complete cytoreduction is the main objective in the surgical management of advanced stage ovarian cancer (10). Bristow *et al*. showed that each 10% decrease of residual tumor volume was associated with 5.5% increase in median survival among patients undergoing primary cytoreduction (3).

Similarly, no residual disease after surgery is correlated with a better prognosis in patients undergoing interval debulking surgery (IDS) (11).

Assessment of disease resectability is essential to guide the treatment strategy. Despite tremendous progress in imaging of peritoneal carcinomatosis, visual assessment at the time of laparoscopy and surgery provides the most accurate information regarding the feasibility of disease resection (12, 13). This assessment is based on various scores. The FIGO classification relatively imprecisely reflects tumor spread, particularly in stage III and IV disease. In 2010, Chereau *et al*. analyzed value of various scores as prognostic indicators for resectability and survival probability of patients with ovarian cancer (14). The PCI (Peritoneal Cancer Index) and modified Fagotti score were considered to be more suitable for the prognosis of resectability (13). Upper abdominal tumor spread is usually considered to be the major limitation to complete tumor resection (15, 16). This site refrained 76.3% of surgeons (17). Diaphragmatic peritoneal spread has been reported in 42% of patients with tumor confined exclusively to the pelvic cavity and in 71% of patients with bulky metastases extending beyond the pelvic brim and diaphragmatic involvement occurs in approximately more than half of patients with advanced ovarian cancer, with a higher frequency on the right hemidiaphragm compared to the left hemidiaphragm (16, 18).

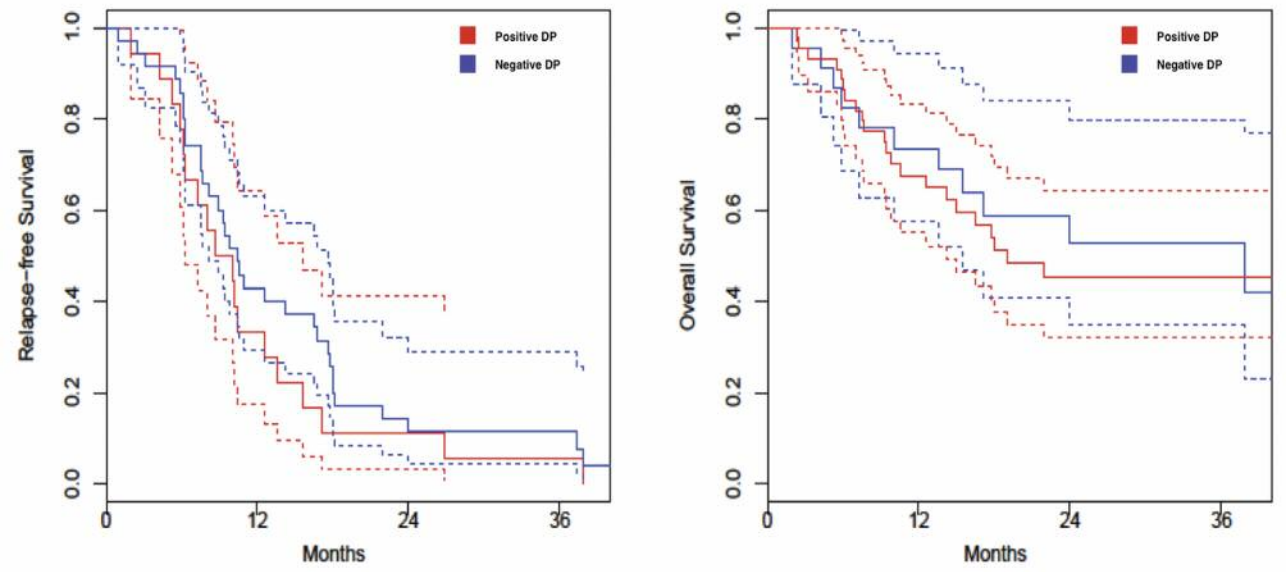

Figure 1. *Comparative outcomes between positive and negative histological diaphragmatic peritonectomy (DP) (Kaplan–Meier method).*

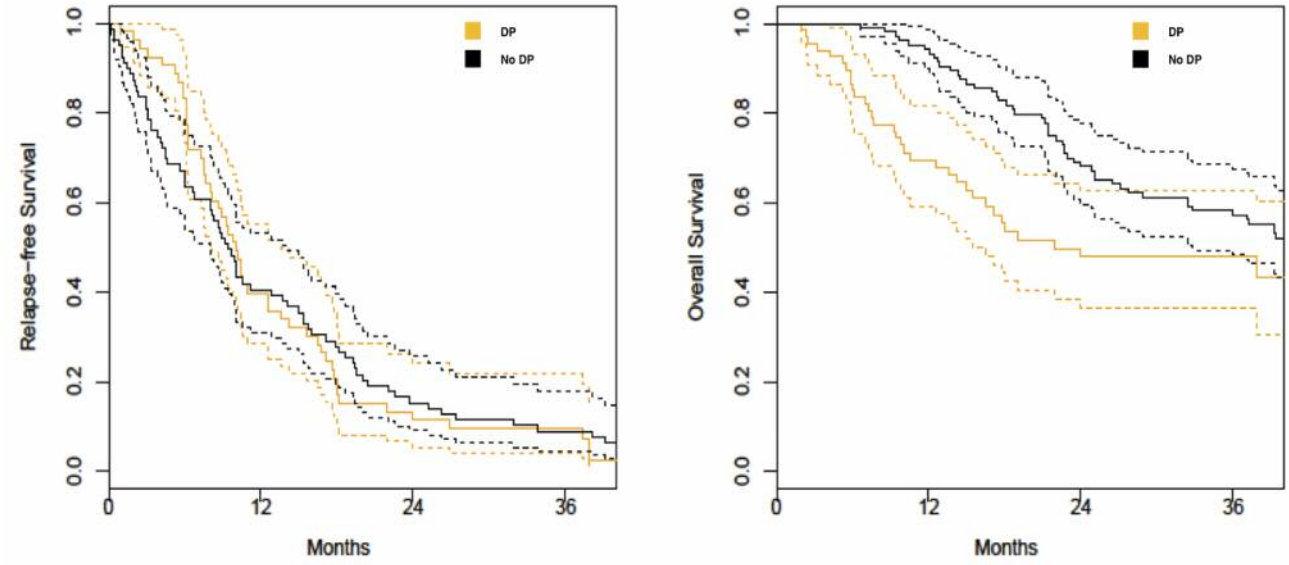

Figure 2. *Comparative outcomes between interval debulking surgery with and without diaphragmatic peritonectomy (DP) (Kaplan–Meier method).*

The results of the study suggest that intraoperative assessment of the diaphragm is difficult after NAC. Chemotherapy changes the macroscopic appearance of the tissues. Only 45 of 74 DP were positive, with residual tumor. Surgery was more extensive than necessary in 39% of patients. In addition to necrosis and fibrosis, elastosis, myxoid degeneration and hyalinization of the stroma with widespread tissue infiltration by inflammatory cells (lymphocytes and plasma cells) were also noted in patients treated by NAC (19). It can, sometimes, be difficult to confirm the presence of residual tumor, and definite confirmation of residual tumor may require examination of multiple histological sections from areas showing pronounced stromal changes, sometimes with multiple levels and immunohistochemistry (20, 21). Systematic biopsies of the diaphragmatic peritoneum combined with intraoperative examination have already been proposed, but the results tended

to be disappointing, with a poor negative predictive value (22).

Since 2000, many authors had reported the prognostic value of CA125, for primary CA125 level has been extensively studied in the context of primary debulking surgery, and has been used to predict complete cytoreduction. The preoperative CA125 cut-off corresponding to optimal sensitivity and specificity was 500 IU/ml (23). A CA125 level after the 3rd cycle of NAC less than 75 IU/ml appears to be an independent predictive factor of complete IDS surgery (24). Our results indicate that a normal CA125 value after the 3rd cycle of NAC accurately identified patients with diaphragmatic peritoneal tumor sterilization (p=0.025). The upper abdominal surgical procedures are at risk for complications (25). The extent of the diaphragmatic resection, liver mobilization and pleural opening are all risk factors for pleural and pulmonary morbidity (6-8). NAC followed by IDS in patients with advanced ovarian carcinoma, achieved similar overall and progression-free survival as primary debulking surgery followed by chemotherapy, with fewer complications, lower post-operative morbidity (19), and better quality of life (26). NAC allows less extensive surgery. In our study, diaphragmatic peritonectomy after NAC was performed in 74 patients. DP should have been performed for 182 patients in the context of primary debulking surgery. NAC simplified the surgical procedure in 54.3% of cases, and with accurate evaluation of diaphragmatic residual disease could have further reduced the number of DPs.

The data of this study also suggest that negative diaphragmatic peritonectomy histology is associated with better survival.

In 2016, the American Society of Clinical Oncology (ASCO) included platinum-based NAC in the reference treatments for advanced ovarian cancer. With an increased rate of interval debulking surgery in the future, surgeons could, therefore, be confronted with post-treatment tissues for which the malignant nature can be difficult to assess.

In conclusion, the decision to perform DP depends on the surgeon's preference, the extent of disease observed at laparotomy, and the patient's condition. DP is only performed after the upper abdomen has been adequately exposed and the liver has been mobilized, which is associated with a longer operating time and an increased the risk of complications. Macroscopic intraoperative evaluation tends to over-estimate residual diaphragmatic disease, and frozen section histological examination is not very contributive. In light of these results, diaphragmatic surgery after NAC may be of limited value. The CA125 tumor marker appears to be a useful tool for evaluation of residual disease. Already used in the evaluation of initial or secondary resectability and platinum sensitivity, CA125 normalization after the 3rd cycle of NAC can help to guide the indication for DP.

Conflicts of Interest

All of the Authors declare that they have no competing interests.

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