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Upper abdominal surgery in advanced epithelial ovarian cancer diaphragm surgery in Focus

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Vorwort

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Definitions and list of abbreviations:

Progression free survival (PFS): was defined as the length of time between the end of the last chemotherapy cycle to the occurrence of the relapse.

Overall survival (OS): OS was determined as the length of time between the date of first diagnosis and the date of death or end of follow-up.

Optimal cytoreductive surgery: If the complete resection of macroscopic tumor is achieved.

Suboptimal cytoreductive surgery: if the largest dimension of the largest residual tumor measured 1- 10 mm.

ABC: Argon beam coagulation

AGO: Arbeitsgemeinschaft Gynäkologische Onkologie

AOC: Advanced ovarian cancer

AP: Anus Praeter (colostomy)

BSO: bilateral salpingo-oophorectomy

CI: Confidence interval

CTR: Complete Tumor resection

ECOG: Eastern Cooperative Oncology Group Performance Status

EOC: Epithelial Ovarian Cancer

EORTC: European Organization for Research and Treatment of Cancer

FIGO : Fédération Internationale de Gynécologie et Obstétrique

HGSOC: High grade serous ovarian cancer

LGSOC: Low grade serous ovarian cancer

OP: Operation

OR: Odds Ratio

OS: Overall Survival

PCS: primary cytoreductive surgery

PFS: Progression free survival

CTR: complete tumor resection.

Abstract Deutsch:

Hintergrund und Zielsetzung:

Das Ziel dieser Studie ist die Untersuchung des Einflusses der radikalen Oberbauch-Chirurgie auf die Behandlung der Zwerchfellinfiltration im Rahmen eines primären epithelialen Ovarialkarzinoms (EOC), sowie die Auswirkung auf die komplette Tumor-Resektion, Intra-, und postoperative Komplikationen und die Überlebensrate.

Materialien und Methoden:

Es wurden insgesamt 536 Patientinnen mit EOC, FIGO III – IV zwischen 2007 und 2013 eingeschlossen. Alle Patientinnen erhielten eine primäre zytoreduktive Operation am Europäischen Kompetenzzentrum für Eierstockkrebs der Charité. 268 Patientinnen bekamen eine Zwerchfell-Intervention im Rahmen der Behandlung (Deperitonealisierung, Teilresektion oder nur Infrarot-Koagulation) und 268 Patientinnen erhielten keine Zwerchfellinterventionen.

Ergebnisse:

Wir indizierten einen Eingriff am Zwerchfell in 50% der fortgeschrittenen Ovarialkarzinomen-Fälle. Folgende Eingriffe wurden durchgeführt Teilresektion 44,8%, Deperitonealisierung 53% und Koagulation mit Infrarot 2,2%.

Die postoperative Komplikationsrate war in der Zwerchfellinterventionsgruppe erhöht im Vergleich zu der Gruppe ohne Zwerchfelleingriff (49,6% vs. 38,8%) (P=0.04). Interessanterweise bezogen sich die meisten Komplikationen nicht nur auf die Zwerchfellintervention, sondern auch auf die anderen notwendigen abdominellen Eingriffe, die in dieser Gruppe indiziert wurden. Ein Multivariate Analyse zeigte, dass die Infektion (12,7%) und Pleuraerguss

(19,8%) die häufigsten Komplikationen in dieser Gruppe waren. Ein logistik Regressionsanalyse zeigte 2-fach erhöhtes Infektionsrisiko nach PCS wenn die folgende Eingriffe durchgeführt wurden: Darmresektion(p=0.022), Cholecystectomie (p=0.05) und bei postoperativem Tumorrest (OR=1,9, 95% CI=1.1-3.33, p=0.02). Die Zwerchfelleingriffe Waren auch einen Risikofaktor für postoperative Infektion aber diese Ergebnisse waren nicht signifikant.

Das postoperative Pleuraerguss Risiko war 2 –Fach erhöht nach alle aggressive Oberbaucheingriffe im Rahmen der PCS: Zwerchfelleingriffe(p=0.002), Darmresektion (P< 0.001), Cholecystectomie (P=0.019), und Splenektomie (P<0.001).

Die Zwerchfelleingriffe waren in 50% der Patientin indiziert worden um eine CTR zu erreichen.

Wir beobachteten signifikant erhöhte Raten von Darmresektionen (71,3% versus 47,4%), Leberteilresektionen (18,4% versus 5,2%), Cholezystektomien (10,1% versus 4,9%), Splenektomien (24,3% versus 7,8%) und Magenteilresektionen (2,6% versus 0,4%) in der Zwerchfellinterventionsgruppe im Vergleich zu der Gruppe ohne Zwerchfellintervention.

Die einzige mit dem Zwerchfelleingriff verbundene postoperative Komplikation war der Pleuraerguss, welche fast doppelt so häufig beobachtet wurde (von 14,2% auf 25,4%), wenn ein Zwerchfelleingriff erfolgte.

Eine komplette Tumor-Resektion konnte in den beiden Gruppen bei circa 66% der Patientinnen erreicht werden. Trotz des massiven Tumor-Ausbreitungsmusters in der Zwerchfellinterventionsgruppe konnte eine akzeptable Komplikationsrate erzielt werden. Das Gesamt- und progressionsfreie Überleben zeigten keinen signifikanten Unterschied zwischen beiden Gruppen.

Schlussfolgerung:

Das Ziel der chirurgischen Behandlung beim fortgeschrittenen Ovarialkarzinom bleibt die Erreichung der kompletten Tumor-Resektion. Dafür sind komplexe chirurgische Eingriffe im Oberbauch unumgänglich. Darunter fallen die Zwerchfelleingriffe, die mit akzeptabler Komplikationsrate durchführbar sind und in vielen Fällen als wesentliche Intervention gelten, um die Tumorfreiheit zu erreichen.

English Abstract:

The purpose of this study is to evaluate the diaphragm surgery in context of surgical treatment of primary advanced epithelial ovarian cancer (AOC) and its effect on the postoperative complication rate, tumor residual and overall survival.

Methods:

We included 536 patients with first diagnosis of advanced epithelial ovarian cancer. These patients underwent a primary cytoreductive surgery (PCS) as an initial treatment at the Charite Medical University between 2007 and 2013. Half of the patients had a diaphragm surgery as a part of PCS, while the other half did not have any diaphragm surgery.

Results:

The performed surgical interventions were in (44.8%) a diaphragm partial resection, in (53%) a diaphragm stripping and in only (2.2%) infrared coagulation. Most important findings were

1- The high rate of CTR in 66% of all patients.

2- The high postoperative complication rate in the diaphragm surgery group (49.6%) compared with (38.8%) in the other group without a diaphragm surgery.

This higher rate was not directly related to the diaphragm surgery but rather to the increased rate of radical surgical procedures in this group of patients. In multivariate analysis, we found that the most frequent complications in our cohort were the postoperative infection/sepsis (12.7%) and plural effusion (19.8%). A logistic regression analysis showed 2-fold increased risk of infection after an intestinal resection (p=0.022), cholecystectomy (p=0.05), and by tumor residual after surgery (p=0.02). Diaphragm surgery was a risk factor for infection but these results were not statistically significant (OR=1.674).

The risk of postoperative pleura effusion rose about two- fold in the most of aggressive procedures of PCS: diaphragm surgery (p=0.002), intestinal resection (p=0.001), cholecystectomy (p=0.01) and splenectomy (p<0.001).

The diaphragm surgery was necessary in 50% of patients to achieve a complete tumor resection (CTR).

We were able to achieve a CTR in both groups by 66% with acceptable complication rate. Progression-free and overall survival showed no significant difference in both groups.

Conclusion: This study considers the diaphragm surgery as a feasible and essential procedure to achieve a CTR with an acceptable complication rate.

Introduction:

Ovarian neoplasms consist of several histopathological characters; treatment depends on the type of tumor. Epithelial ovarian cancer encircles most malignant ovarian neoplasms (about 80%) (1).

Epithelial Ovarian cancer (EOC) is the seventh most common cancer in women and the 18th most common cancer worldwide with 239,000 new cases diagnosed in 2012 (2). Currently, 29% of the cases were diagnosed in females aged 5 years and over, and about (75%) were diagnosed in women aged 55 and over. The incidence rates related to age rise sharply around age 35-39 (3).

The standard treatment for women with advanced stage epithelial ovarian cancer (EOC) includes surgical procedures followed by adjuvant platinum-based combination chemotherapy. The target of the surgery is to remove and resect all the macroscopic tumor and to stage the patient (4).

Clinical research demonstrates that the amount of residual disease remaining after the primary surgical procedure was the strongest clinical factor related to survival outcome. This has been proved by a large retrospective study including six different Gynecologic Oncology Group (GOG) studies (5). Despite the development in primary therapy of ovarian cancer, about (67.5%) of patients experience the recurrence of tumor within the first five years. If the disease in these women is no longer curable, the aim of therapy would be to enhance the quality of life by abating symptoms and prolonging life if possible (6).

The impact of surgery in primary treatment of EOC:

The role of surgery in newly diagnosed ovarian cancer is broadly approved, even if there is no level I evidence for its role, and the lack of prospectively randomized phase III studies comparing cytoreductive surgery with no surgery. The evidence (level II and III), nevertheless, shows a benefit for primary cytoreductive surgery (PCS). (7), (8).

Meigs (9) was the first to advocate cytoreductive surgery in advanced ovarian cancer to improve the effects of postoperative radiation therapy. Thirty-two years later Munnell (10) reported about the advantage of surgical cytoreduction of tumor volume in patients with ovarian cancer. He recognized that patients who had a greater volume of their tumor removed had an improved survival rate. Subsequently, in 1969, Elclos and Quinlan reported an improved survival in patients with advanced stage ovarian cancer who had their disease reduced to non-palpable implants compared to those left with palpable disease at the completion of surgery (11).

Griffiths (12) reported that the volume residual disease has an inverse correlation with survival. Griffith studied 102 patients with Stage II and III ovarian cancer. He observed an increase in median survival times of 18, 29, and 39 months for patients cytoreduced to 6–15, <5, and 0 mm of residual disease, respectively.

In a series of attempts, which helped in defining the current concept of cytoreductive surgery, there were two reports by Hoskins (13), In the first Study he retrospectively analyzed and reviewed 294 patients who had undergone suboptimal tumor resection as a part of an advanced ovarian cancer debulking operation followed by chemotherapy with cisplatin and cyclophosphamide. At the end of operation, all patients presented with residual tumor larger than 10 mm.

The important results were:

1) patients who had a residual disease diameter measuring between 1 and 2 cm had a higher survival rate compared to patients left with tumors measuring larger than 2 cm) when the residual tumor measured more than 2 cm, the extensive surgical cytoreductive attempts brought no survival benefit. Survival analysis clearly shows a better outcome for patients with 1 to 2 cm of residual tumor, while the survival curves for patients with residual disease measuring 2 to 4 cm, 4 to 6 cm, 6 to 10 cm, and larger than 10 cm are virtually overlie one another.

The second important study by Hoskins & coworkers was also a retrospective review by the Gynecological Oncology Group. This time, they examined 294 patients with optimal residual disease who were subsequently treated with chemotherapy consisting of cisplatin and cyclophosphamide, with or without Adriamycin. In this study, all patients underwent surgical resection to residual disease to less than or equal to 1cm. There were two important findings from this study. First, patients who began surgery with small disease volume had a survival outcome superior to patients who started with larger volume disease, even though all patients were optimally resected. Second, factors other than surgery, such as patient age, tumor grade, and the number of residual lesions, were also important determinants of survival (14).

Du Bois et al.(15), reported a median overall survival of 99.1 months in patients with complete resection compared to 29.6 months for patients with residuals of more than 1 cm.

Furthermore, Bristow et al.(16) showed that each decrease of 10% in residual tumor volume is followed by an increase of 5.5% in median survival in advanced ovarian cancer patients undergoing primary cytoreduction. As a result, the surgical targets of residual disease (optimal debulking) decreased over the years from < 2 cm to be currently defined as no residual tumor (16, 17, 18). Reports of optimal cytoreduction rates greater than 50% in literature generally include a substantial number of patients who underwent extensive upper abdominal procedures to attain optimal residual status (19, 20). This makes the extensive upper abdominal surgery inevitable to achieve CTR. The concept of radical cytoreductive surgery involves the resection of the rectosigmoid colon, splenectomy, diaphragm peritonectomy or resection, and extensive nodal debulking. These procedures are associated with an increase in blood loss, operating time, hospital stay, and risk of complications; however, in most patients these risks can be mitigated by careful pre-operative evaluation and preparation, meticulous surgical technique, sound clinical judgment, and a watchful eye. Since removal the entire clearly visible tumor is considered crucial for long-term survival, surgery should be extended to achieve this goal (21).

Other centers, including our department have shown that the implementation of complex surgical procedures like complete deperitonealization, en bloc resection of the pelvis and upper abdominal surgery in primary cytoreductive surgery is necessary to achieve higher rates of complete resection. Although for technical reasons and lack of surgeons' experience, this objective is not always achievable (22, 23). Most of the time, complete cytoreduction requires extensive and complicated procedures in the upper abdomen, such as diaphragm surgery and, less frequently, liver or pancreatic resection (24, 25). According to a questionnaire from 2001 to the membership of the Society of Gynecologic Oncologists (SGO), diaphragm disease was reported as the second biggest cause of sub-optimal debulking, and this was attributed to lack of training, limited experience and lack of published evidence on survival (26). Furthermore, it has been reported that surgical procedures to remove diaphragm tumor spread increase not only the rate of complete (optimal) and sub-optimal (<10 mm) debulking but also correlate with improved survival too, even compared to sub-optimally debulked patients without diaphragm surgery (27, 28, 29).

The commonly applied diaphragm interventions are:

1. Diaphragm resection, i.e. complete full thickness resection of diaphragm or any kind of partly diaphragm resections.
2. Diaphragm stripping: i.e. diaphragm peritonectomy without resection of diaphragm muscles.

3. Infrared coagulation of peritoneal carcinomatosis on the surface of the diaphragm.

Materials and methods:

To identify patients with advanced ovarian, tubal and peritoneal cancer, we checked our database from the Tumor Bank Ovarian Cancer (www.toc-network.de). This database is a prospective documentation tool which includes clinical data, disease history, tumor spread, presence of ascites, and presence and location of residual tumor mass intra-operatively. These parameters are obtained through an interview with the surgeon immediately after the surgical procedure. The localizations and the causes of the residual tumor were recorded on our ovarian cancer questionnaire and graded according to the Intraoperative Mapping of Ovarian Cancer (IMO) (30). This staging and documentation system was developed at the Charite University. All patients undergoing surgery at our institution due to suspected ovarian malignancy between 2007 and 2013 were reviewed. Log-rank test statistics for analysis of the equality of survival distribution were performed. Statistical significance was defined by $p < 0.05$ and two-sided tests were applied.

Inclusion and exclusion criteria:

We identified 536 eligible patients with first diagnosis of ovarian, tubal or peritoneal cancer, who underwent a primary cytoreductive surgery at the Charite university medical Center between 2007 and 2013, who were retrospectively evaluated. This entire collection involves 268 patients with diaphragm interventions and 268 patients without diaphragm surgery who underwent debulking procedures as a part of primary treatment of ovarian cancer. Patients with non-epithelial ovarian cancer or borderline tumors, patients who underwent only a second-look operation or diagnostic procedure, and those with early stages of epithelial ovarian cancer, and who underwent interval debulking (cytoreductive surgery after neoadjuvant chemotherapy) were excluded. All operations were performed by one of the experienced gynecological oncology surgeons in the institution of gynecology and center of oncological surgery of Charite, Berlin. Cytoreductive surgery for primary ovarian cancers included in this study, included midline laparotomy, aspiration of ascites for cytology (or cytological washings of the abdominal cavity), total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, systematic para aortic lymphadenectomy up to the renal vessels [as a standard staging before publishing the results of LION-study (31)], and bilateral pelvic lymphadenectomy.

The goal of a successful debulking surgery was always, the removal of all visible tumor tissue. To achieve this goal, aggressive surgical procedures were utilized, including extensive intestinal resection, splenectomy and peritonectomy, diaphragm stripping or resection (The preferred surgical method was resection rather than the use of an argon beam coagulator with only one exception, namely when tumor showed diffuse spreading to bowel mesentery and diaphragm surface), abdominal wall resection and low anterior resection or urinary tract excision, distal pancreatectomy, partial liver resection, cholecystectomy, and resection of tumor from the porta hepatis in cases where the head surgeon deemed them necessary to achieve optimal cytoreduction.

We have performed 3 types of surgical techniques in cases of tumor invasion of diaphragms depending on the depth of tumor infiltration and their extent.

Stripping of the peritoneal surfaces of the diaphragm is performed when superficial extension of the disease is found, whereas diaphragm resection is carried out if full or partial muscle thickness is affected. Infrared coagulation was performed by the patients with low performance status who cannot tolerate a complete liver mobilization and the following hypotension and bradycardia. In these Patients, diaphragm stripping or resection is a more time-consuming procedure than coagulation.

The optimal tumor resection was defined as complete tumor resection with no residual macroscopic lesions. Suboptimal resection means debulking the tumor nodules to less than or equal 10 mm in maximal dimension at the end of the surgical procedure. Any tumor residual of more than 10 mm will mean an inoperable situation. As mentioned before the localizations and the reasons of the residual tumor were recorded and graded according to the Intraoperative Mapping of Ovarian Cancer (IMO) (30). Which include the following staging levels:

1. Lower abdomen:

   Level 1: A1, B1, C1 small pelvis (Douglas, Vaginalapex, Uterus, Bladder/Ureter, rectum, Sigma)

2. Upper abdomen:

   Level 2: A2, B2, C2 Intestine/Mesenterium (large intestine, small intestine)

   Level 3: A3, B3, C3 Upper abdomen (Omentum majus, Bursa omentalis, Diaphragma, Liverparenchym, Spleen, stomach)

3. Retroperitoneum:

   Level 4: Lymph nodes (pelvin and para aortal) ± plus diffused peritoneal carcinosis (Abdominal wall und pelvic wall).

All patients provided their written informed consent before clinical data were collected. Approval from Charité local Ethics Committee was provided for this study (EK207/2003). The International Federation of Gynecology and Obstetrics (FIGO) classification stages mentioned in this study depended on the old classification before the modification of 2014 (32). All patients included in the study had FIGO stage III or IV.

Perioperative morbidity was defined as any adverse event occurring within 30 days of surgery. Most postoperative complications were graded according to Chassagne's glossary for complications of treatment in gynecological cancers (33) and the National Cancer Institute Common Toxicity Criteria version 2.0 (NCI-CTC v2) classification system (34). Which contains the following:

1. General grading system section

G0: Absence of complications or acute reversible symptoms or signs which do not modify the planned course of treatment.

G1: Mild complications. These complications are mildly disabling and may cause some functional impairment.

G2: Moderate complications. Both obvious symptoms and signs are present resulting in intermittent or persistent interference with normal activity.

G3: Severe complications. Structural and functional damage are the two criteria which have been adopted to define severe complications: either one or both may apply. Permanent tissue and/or organ damage may or may not be associated with severe disability.

G3.1. Any acute or chronic symptoms or signs which are life-threatening either per se or because of the treatment required.

G3.2. Any permanent or severe tissue and/or organ damage.

G4: Documented evidence that death is due to the primary treatment, or to the complication of treatment, or to the treatment of complication(s). In summary, any death which is considered (even partially) to be due to a complication of treatment of cancer.

Mortality rate is defined as any postoperative occurring death happened in first 30-day of observation period postoperatively.

Statistical methods:

The statistical analysis was performed at the Charité Medical University Berlin. All analyses were performed by IBM SPSS Statistics 21.0 (SPSS, Chicago, IL, USA). Data were analyzed by descriptive statistics. Frequency counts and percentages were used to describe categorical variables, and continuous variables were summarized by the median and range. Groups were compared using Chi-square test, Fisher's exact test, Kendall's tau b, and Mann–Whitney U-test where appropriate. Medians, and 95% confidence intervals (CI) of PFS and OS were estimated according to the Kaplan–Meier method.

Results:

I. Patients characteristics:

536 patients with first diagnosis of ovarian cancer, who underwent a cytoreductive surgery at the Charite university medical Center between 2007 and 2013 were retrospectively evaluated. This entire collection consists of 268 patients with and 268 patients without diaphragm surgery who underwent debulking procedures in the framework of primary treatment of ovarian cancer. The 268 Patients in the diaphragm surgery group were divided in 3 subgroups: 1) Stripping of the diaphragm peritoneum, 2) resection of diaphragm muscle, 3) Coagulation.

Patient characteristics of the entire cohort are summarized in Table I. The median age at the first diagnosis of a very advanced stage was 59 years, with a range of 19 to 89 years. Using the old FIGO staging system, 71.5% of patients had stage III and 24.3% had stage IV disease at first diagnosis. The rate of stage IV disease was doubled (33.2%) in the group of patients with diaphragm surgery versus those without diaphragm surgery (15.3%, p<0.001). According to our finding the rate of HGSOC type was almost identical in both study groups (67.9% vs. 67%) respectively.

249 patients (92.9%) had the final histological diagnosis of papillary serous carcinoma. This tumor histology was significantly higher in the group of patients who needed diaphragm surgery in comparison with those who did not need it (92,9 %vs. 78.4% respectively, <P=0.001). Other tumor histology types were generally fewer in this collection, endometroid ovarian cancer was diagnosed only in 2 (0.7%) cases of the diaphragm intervention group and in 6 (2.2%) cases of the non-diaphragm intervention group. Mucinous ovarian cancer was the less frequent histological type in this cohort and with 2 patients (0.7%) in the diaphragm interventions group vs. 4 patients (1.5%) in the non-diaphragm intervention group.

We observed a statistically significant higher rate of massive ascites (>500 ml) in the diaphragm surgery group (43.6%) versus the non-diaphragm surgery group (21.6%) (p<0.001).

Cancer antigen (CA)-125 was preoperatively measured in 510 patients (95.1%). The median preoperative CA-125 value was almost 4-fold higher in the diaphragm surgery group (753 U/mL) compared with the non-diaphragm surgery group (198 U/mL) (p<0.001).

Table I. Characteristics of 536 AOC-patients who underwent PCS with and without diaphragm surgery.

Characteristics		All patients n=536 (%)	Diaphragm surgery n=268 (%)	Without diaphragm surgery n=268 (%)	p-value
Age at first diagnosis [years]		Median 59 (18-89)	Median 60 (18-89)	Median 58 (20-86)	0.372
CA-125		446.85 U/mL	753 U/mL	198 U/mL	<0.001
	Ovarian	490 (91.4%)	248 (92.5%)	242 (90.3%)	

Tumour type	tubal	15 (2.8%)	4 (1.5%)	11 (4.1%)	
	peritoneal	31 (5.8%)	16 (6%)	15 (5.6%)	
FIGO	III	383 (71.5%)	175 (65.3%)	208 (77.6%)	<0.001
	IV	130 (24.3%)	89 (33.2%)	41 (15.3%)	
	Not defined	23 (4.3%)	4 (1.5%)	19 (7%)	
Grading	1-2	139 (25.9%)	74 (27.6%)	65 (24.3%)	
	3	362 (67.5%)	182 (67.9%)	180 (67%)	
	Not defined	35 (6.5%)	12 (4.5%)	23 (8.6%)	
Histology	Serous papillary	459 (85.6%)	249 (92.9%)	210 (78.4%)	<0.001
	Mucinous	6 (1%)	2 (0.7%)	4 (1.5%)	
	Endometrioid	8 (1.5%)	2 (0.7%)	6 (2.2%)	
	Clear cell	6 (1%)	1 (0.37%)	5 (1.9%)	
	Mixed	3 (0.6%)	1 (0.37%)	2 (0.7%)	
	Undifferentiated	4 (0.7%)	0 (0%)	4 (1.5%)	
	Other/ Unknown	50 (9.3%)	13 (4.9%)	37 (13.8%)	
Ascites	No ascites	198 (36.9%)	69 (25.7%)	129 (48%)	<0.001
	< 500 ml	160 (29.9%)	81 (30.2%)	79 (29.5%)	
	≥ 500 ml	175 (32.6%)	117 (43.6%)	58 (21.6%)	<0.001
	Unknown	3 (5.6%)	1 (0.37%)	2 (0.7%)	

II. Surgical characteristics:

Adding the diaphragm surgery resulted in a significantly ($p<0.001$) longer surgery time: the median operating time was 282.5 minutes versus 244 minutes in the diaphragm and non-diaphragm surgery groups, respectively. The patients in the diaphragm surgery group also underwent statistically significantly more surgical efforts and more complicated procedures compared with the non-diaphragm group (Table II).

We observed a higher rate of bowel resection in the group of patients who underwent a diaphragm surgery (71.3 % vs. 47.4 %, p<0.001, respectively). Whereas, there was no difference concerning the Anus praetor rate in both groups. We performed 8 (3%) atypical liver resections (resection of liver parenchyma), in the diaphragm group; whereas in the non-diaphragm surgery group there were only 3 (1.5 %) cases with atypical liver resection.

In the study period from 2007 to 2013, we performed 63 (11.8%) partial liver capsule resections within the framework of primary cytoreduction surgery for advanced ovarian cancer, 49 of these patients were in the group of diaphragm interventions (18.4% of diaphragm interventions group) and 14 patients were in non- diaphragm group (5.2% of the group of cases) (p<0.001). Splenectomy was indicated and performed in 86 (16%) patients of the whole cohort, the incidence was higher in the diaphragm surgery group with 65 cases (24.3%) compared with only 21 cases (7.8%) in the group of non-diaphragm intervention (p<0.001). We observed only one lung partial resection in the diaphragm group.

Cholecystectomy was performed in the diaphragm intervention group [27 patients (10.1%) compared to 13 patients (4.9%) in the other group], this difference was statistically significant (p= 0.03). The stomach partial resection was more required in the diaphragm interventions group to achieve a complete tumor resection with 7 cases (2.6%) compared with only 1case (0.4%) in the non-diaphragm surgery group, but this result was not statistically significant (P = 0.068).

Table II: Surgical Characteristics in all AOC cases

Characteristics	All patients n=536 (%)	Diaphragm surgery n=268 (%)	Without diaphragm surgery n=268 (%)	p-value
Surgery duration [Minutes]	Median 265 (30-592)	Median 282,5 (30-592)	Median 244 (30-540)	<0.001
Bowel resection	318 (59.3%)	191 (71.3%)	127 (47.4%)	<0.001
Atypical liver resection	12 (2.2%)	8 (3%)	4 (1.5%)	
Partial resection of liver capsule	63 (11.8%)	49 (18.4%)	14 (5.2%)	<0.001
Cholecystectomy	40 (7.5%)	27 (10.1%)	13 (4.9%)	0.03
Splenectomy	86 (16%)	65 (24.3%)	21 (7.8%)	<0.001
Partial Stomach resection	8 (1.5%)	7 (2.6%)	1 (0.4%)	0.068
Lung partial resection	1 (0.2%)	1 (0.4%)	0	
Anus praetor(colostomy)	71 (13.2%)	36 (13.4%)	35 13.1%)	

III. Surgical outcomes:

CTR was achieved in 66% of all patients. This rate did not differ significantly between the group with diaphragm surgery and the group without diaphragm intervention (65.7% vs. 66.4%), respectively.

Suboptimal debulking (the largest dimension of the largest residual tumor measured 1- 10mm) was performed in 27.2% of patients in the diaphragm surgery group and in only 18.3% of patients in the group without diaphragm surgery, but this difference was not statistically significant (p=0.86).

The rate of residual tumor > 10 mm was higher in the group of PCS without diaphragm intervention compared with the group of diaphragm surgeries (13% vs. 6%) respectively (p<0.00).

The most common residual tumor site in both groups was the B2- region, which includes central middle abdominal part (intestine/mesenteries) with 61 cases (72.6%) out of 84 cases in the non-diaphragm interventions group and 68 patients (76.45%) out of 89 patients in the diaphragm surgery group. The second most common site of residual tumor in the group without diaphragm surgery was A3, which represents the right upper abdomen = the region of right diaphragm, with 44 cases (52.4%). B3-region (middle upper abdomen) was the second most common site of residual tumor in the group of diaphragm interventions 32 (36%).

All residual tumor locations are summarized in table III.

Table III. Tumor residual rate and location

The outcome of PCS (residual tumor)		Diaphragm surgery n=268 (%)	Without diaphragm surgery n=268 (%)	All patients n=536 (%)
Residual tumour	No residual	176 (65.7%)	178 (66.4%)	354 (66%)
	< 10 mm	73 (27.2%)	49 (18.3%)	122 (22.8%)
	≥ 10 mm	16 (6%)	35 (13%)	51 (9.5%)
	Unknown	3 (1.1%)	6 (2.2%)	9 (1.7%)

Localizations of residual tumor		With diaphragm N =89, (%)	Without diaphragm N= 84, (%)	P Value
Sites according to IMO (intraoperative mapping of ovarian cancer)	A 1	13 (14.6)	22 (26.2)	0.062
	A2	22 (24.7)	27 (32.1)	0.313
	A3	26 (29.2)	44 (52.4)	0.002
	B1	19 (21.3)	31 (36.9)	0.02
	B2	68 (76.4)	61 (72.6)	0.63
	B3	32 (36)	36 (42.9)	0.43
	C1	11 (12.4)	18 (21.4)	0.153
	C2	23 (25.8)	27 (32.1)	0.404
	C3	21 (23.6)	29 (34.5)	0.132

IV. Postoperative complications:

The overall complication rate was 44.2%, all grades of complications according to Chassagne's glossary for complications of treatment in gynecological cancers and the National Cancer Institute Common Toxicity Criteria version 2.0 classification system were included.

The postoperative complication rate was 38.8% when no diaphragm surgery was performed and this rate rose to 49.6% in the diaphragm intervention group (p=0.04).

The most frequent complications in our cohort were the infection/sepsis (12.7% of all patients) and pleura effusion (19.8% of all patients). The logistic regression analysis showed a 2-fold increased risk of infection/sepsis after PCS with intestinal resection (OR= 2.097, 95% CI= 1.131-3.887, P-Value= 0.022), cholecystectomy (OR= 2.295, 95% CI= 0.995-5.295, P-Value= 0.059) and in residual tumor after surgery (OR= 1.914, 95% CI= 1.1-3.33, P-Value= 0.026). Diaphragm surgery was a risk factor too for infection/sepsis (OR= 1.674) but this result was not statistically significant.

The risk of postoperative pleura effusion rose about two- fold in the most of aggressive procedures of PCS: diaphragm surgery (OR= 2.0, 95% CI= 1.284-3.116, P-Value= 0.002), intestinal resection (OR= 2.487, 95% CI= 1.531-4.038, P-Value< 0.001), cholecystectomy (OR= 2.468, 95% CI= 1.222-4.982, P-Value= 0.019), and splenectomy (OR= 2.734, 95% CI= 1.642-4.554, P-Value< 0.001); and with the tumor residual after surgery (OR= 1.948, 95% CI= 1.255-3.024, P-value= 0.004).

These results are presented in the tables IV and V.

Table IV. Multivariate analysis of correlations between PCS-surgical procedures and the postoperative infection/sepsis and pleura effusion.

Postoperative complication	Surgical procedure	Odds Ratio	95% Confidence Interval		p-value
			lower	upper	
Infection/sepsis	Diaphragm surgery	1.674	0.954	2.936	0.093
	Intestinal resection	2.097	1.131	3.887	0.022
	Cholecystectomy	2.295	0.995	5.295	0.059
	Splenectomy	1.062	0.514	2.194	0.852
	Tumor residual	1.914	1.100	3.330	0.026
Pleura effusion	Diaphragm surgery	2.000	1.284	3.116	0.002

	Intestinal resection	2.487	1.531	4.038	<0.001
	Cholecystectomy	2.468	1.222	4.982	0.019
	Splenectomy		2.734	1.642	4.554
	Tumor residual	1.948	1.255	3.024	0.004

Postoperative infections were diagnosed in 13.4% of patients in the diaphragm intervention group and only in 7% in the non-diaphragm surgery group (p=0.02). Here, we observed all kinds of infections even any elevated temperature ≥ 38.0° C on at least one occasion in the patient's body temperature curve.

The incidence of thromboembolic events was nearly doubled in the diaphragm intervention group (6.7 % vs. 3.35%) in comparison with the non- diaphragm surgery group. However, the overall rate of this complication was not too high and it showed no statistically significant difference between the two groups of patients. A low rate of sepsis was observed in both groups too, here, the non-diaphragm surgery group showed at least twice as high as a rate of sepsis than in the group of diaphragm interventions (3.3% vs. 1.5% respectively), here, too, it was not without statistically significant.

Postoperative pleura effusion was the most frequent, directly with diaphragm surgery associated complication, which increased significantly in the diaphragm surgery group (68 patients, 25.4%) comparing with the group of patients who did not undergo any diaphragm intervention (38 patients, 14.2%), (P=0.002).

There were no recorded cases of postoperative lung edema in the diaphragm intervention group and only 2 cases in the other group. Postoperative pneumonia was reported in 21 of the patients in the entire collection, 12 (4.5%) of them belonged to the diaphragm surgery group and 9 (3.3%) to the other group (p= 0.6)

We have not noticed any significant differences in both groups regarding postoperative pneumothorax or wound dehiscence (1.9% in both groups and 3.7% vs. 4.1%, respectively).

The rate of postoperative anastomoses insufficiency was elevated in diaphragm intervention group compared to non-diaphragm intervention group (4.5 % vs. 1.9%, respectively).

Table V. Postoperative complications of PCS with and without diaphragm interventions

Characteristics	All patients n=536 (%)	Diaphragm surgery n=268 (%)	Without diaphragm surgery n=268 (%)	P value
Postoperative complications	237 (44.2%)	133 (49.6%)	104 (38.8%)	0.04
Thrombo-embolic events	27 (5%)	18 (6.7%)	9 (3.35%)	0.114
Postoperative infection	55 (10.3%)	36 (13.4%)	19 (7%)	0.02
Postoperative sepsis	13 (2.4%)	4 (1.5%)	9 (3.3%)	0.16
Postoperative pneumonia	21 (3.9%)	12 (4.5%)	9 (3.3%)	0.6
Postoperative pleura effusion	106 (19.8%)	68 (25.4%)	38 (14.2%)	0.002
Postoperative lung oedema	2 (0.3%)	0	2 (0.6%)	0.241
Postoperative pneumothorax	10 (1.9%)	5 (1.9%)	5 (1.9%)	1.0
Postoperative ileus	18 (3.35%)	10 (3.7%)	8 (3%)	0.81
Bowel perforation	7 (1.3%)	5 (1.9%)	2 (0.75%)	0.4

Anastomosis insufficiency	17 (3.2%)	12 (4.5%)	5 (1.9%)	0.13
Wound dehiscence	21 (3.9%)	10 (3.7%)	11 (4.1%)	0.8
Postoperative cardiac arrhythmia	29 (5.4%)	16 (6%)	13 (4.9%)	0.7
Postoperative bleeding	16 (3%)	5 (1.9%)	11 (4.1%)	0.13
Neurologic complications	24 (4.5%)	16 (6%)	8 (3%)	0.1
Postoperative organ failure	18 (3.35%)	8 (3%)	10 (3.7%)	0.6
Postoperative fistula	6 (1.1%)	4 (1.5%)	2 (0.75%)	0.686
30-day mortality	14 (2.6%)	3 (1.1%)	11 (4.1%)	

V. Postoperative mortality

The mortality rate was lower in the diaphragm intervention group than this rate in the other group.

There were three (1.1%) recorded postoperative death cases in the group of patients who underwent a diaphragm intervention, unfortunately the rate increased to 11 cases (4.1%) in the group of patients, where no diaphragm intervention was performed (p=0.2). By concerning the death cases in the study arm (the group of diaphragm interventions), we could recognize the following scenarios:

- The first mortality case in the diaphragm group was a 74-year old patient who underwent a modified posterior exenteration, bilateral salpingo-oophorectomy (BSO) (to confirm the diagnosis of primary ovarian cancer), omentectomy (to reduce the chance of symptomatic ascites), total colectomy with Ileostomy (to avoid the rapid development of ileus) an infrared coagulation of bladder peritoneum and diaphragm (modified procedure by multiple comorbidities). Tumor residual < 5 mm for a stage IV, serous ovarian carcinoma. She suffered perioperative on coronary heart disease in 3 coronary arteries. Patients suffered already from two myocardial infarcts in

1997 and 2006 and a coronary stent was performed. On the 15th postoperative day, the patient experienced a new and her 3rd myocardial infarct. The cardiologist tried to catheterize right coronary artery without success, because of complete occlusion in following to her chronic atherosclerosis. a coronary bypass could not be performed because of the critical instable situation of the patient. At the same day, she develops a multi-organic failure and a cardiac shock and died few hours later in intensive care unit.

- The second case was a 59-years old patient who had cardiac failure in stage I-II according to the classification of New York Heart Association (NYHA) and coronary heart disease with paroxysmal atrial fibrillation. In the frame of PCS, the patient underwent a modified posterior exenteration, omentectomy, splenectomy, bilateral pelvic and para-aortic node dissection, and right diaphragm peritonectomy for a stage IV serous ovarian carcinoma with tumor residual < 2 mm. On postoperative day 2, she developed right ventricular dysfunction, pulmonary hypertension, and cardiac and respiratory failure. Her cardiopulmonary status continued to worsen, and she died on postoperative day 9.
- The Third Patient was a 73-Year-old patient, who had a diagnosis of primary ovarian cancer stag FIGO IV (Iva; according to the new classification from 2014) due to a preoperative malignant pleural effusion. As a comorbidity, she had only an arterial hypertension. She underwent a modified posterior exenteration, omentectomy, splenectomy, bilateral pelvic and para-aortic node dissection, and right diaphragm peritonectomy, with residual tumor of 10 mm.

  On the 1st postoperative day, she could be extubated successfully. Later, she starts to complain of abdominal pain. A CT scan showed a pneumoperitoneum with signs of bowel perforation. For this reason, we performed an urgent relaparotomy. Intraoperatively, we discovered a duodenal perforation therefore, a duodenal resection and a post pyloric gastrojejunostomy was performed. Postoperative the patient stayed under intensive monitoring in the ICU. over the time the gas exchange began to drop gradually and she developed delirium, massive respiratory insufficiency and Lung edema despite of intubation and tracheotomy. She died on the 21th postoperative day.

VI. Outcomes of PCS with diaphragm interventions

According to the type of diaphragm surgery, we recognized 3 subgroups of patients in this arm:

1. Diaphragm resection, i.e. complete full-thickness resection of diaphragm or any kind of partly diaphragm resections.
2. Diaphragm stripping: i.e. diaphragm peritonectomy without resection of diaphragm muscles.
3. Infrared coagulation of peritoneal carcinomatosis on the surface of the diaphragm

VI. a. Characteristics of patients who underwent PCS with diaphragm interventions:

The mean age of patients at first diagnosis of EOC, who underwent a diaphragm intervention as an essential part of PCS was 60 years, this ranged from (27 to 80) years in the diaphragm resection group and (18-89) in the diaphragm stripping group.

According to the FIGO-classification, FIGO III incidence rate was higher in diaphragm stripping group with (69%) compared to (62.5%) in diaphragm resection group, nevertheless, this result was not statistically significant.

In the same way, FIGO IV was more often diagnosed in the diaphragm resection group than in the diaphragm stripping group (35% vs. 30.3%, respectively) with no significant difference. 50% of the patients in the small group of only infrared-coagulation of diaphragm had the FIGO IV-stage at the time of PCS.

The rate of high-grade cancers (grade 3) was almost the same in all 3 subgroups of diaphragm interventions and ranged between 65.8% and 69.7%.

Table VI. Characteristics of 268 AOC-patients who underwent PCS with diaphragm surgery

Characteristics		Diaphragm resection n=120 (44.8%)	Diaphragm stripping n=142 (53%)	Infrared coagulation n=6 (2.2%)	p-value
Age at first diagnosis [years]		Median 60 (27-80)	Median 60.5 (18-89)	Median 71 (49-79)	
Tumour type	Ovarian	113 (94.2%)	131 (92.3%)	4 (66.7%)	0.061
	fallopian	1 (0.8%)	3 (2.1%)	0	
	Peritoneal	6 (5%)	8 (5.6%)	2 (33.3%)	
FIGO	III	75 (62.5%)	98 (69%)	2 (33.3%)	0.274
	IV	43 (35.8%)	43 (30.3%)	3 (50%)	
	Not defined	2 (1.7%)	1 (0.7%)	1 (16.7%)	
Grading	1-2	37 (30.8%)	35 (24.6%)	2 (33.3%)	0.937
	3	79 (65.8%)	99 (69.7%)	4 (66.7%)	
	Not defined	4 (3.3%)	8 (5.6%)	0	

Histology	Serous papillary	112 (93.3%)	132 (93%)	5 (83.3%)	0.011
	Mucinous	0	1 (0.7%)	1 (16.7%)	
	Endometrioid	0	2 (1.4%)	0	
	Clear cell	1 (0.8%)	0	0	
	Mixed	1 (0.8%)	0	0	
	Unknown	6 (5%)	7 (4.9%)	0	
Ascites	No ascites	27 (22.5%)	41 (28.9%)	1 (16.7%)	
	< 500 ml	42 (35%)	37 (26%)	2 (33.3%)	0.547
	≥ 500 ml	51 (42.5%)	63 (44.4%)	3 (50%)	
	Unknown	0	1 (0. 7%)	0	
CA-125 median U/mL		721	821	566	0.9

Serous papillary was the most dominant histological type in all diaphragm procedure groups, this histological type was diagnosed in 112 (93.3%) cases in the diaphragm resection group vs. 132 (93%) cases in the stripping group. Its incidence dropped to 83.3% (5 patients) in the group of infrared-coagulation only.

We observed similar incidence rates of massive ascites (>500 ml) in both study subgroups who underwent diaphragm surgery (resection vs. stripping) (42.5%, 44.4%), respectively. Whereas 50% of infrared-coagulation patients had massive ascites >500 ml.

The preoperatively measured tumor marker CA-125 values were elevated in the resection group compared to the stripping group without significant difference (137 vs 117 U/ml, respectively) (p=0.9).

IV. b. Characteristics of PCS with diaphragm interventions:

The operating time differed between the group of infrared-coagulation (median 200 minutes) and the other two groups of diaphragm interventions. Nevertheless, we observed a longer operating time in the diaphragm resection group compared to the stripping group the mean operating time in the resection group was 295 minutes vs. 282 minutes in the diaphragm stripping group. In the study arm, many other surgical procedure in the framework of PCS were indicated and performed. These procedures are listed in Table VII.

123 appendectomies were performed in the diaphragm intervention group, 73 (51%) cases had a diaphragm stripping and the other 50 (41.7%) cases had a diaphragm resection, this result was not statistically significant.

Bowel resection (appendectomies are excluded here) as a part of PCS in this study arm were more utilized in the diaphragm resection subgroup with 75.8% vs. 66.9% in the diaphragm stripping subgroup. 83.3% of infrared-coagulation group underwent an intestinal resection as a part of PCS, all of them as a total colectomy with different small bowel resection and ileostomy/jejunostomy.

Partial resection of pancreas tail was not a common procedure and performed only in 2 patients (1.7%) in diaphragm resection group and in one other patient (0.7%) in the stripping group. The resection rate of ligamentum falciforma hepatis was obviously higher in the diaphragm resection group compared to the stripping group (67% vs. 48%, p=0.008) respectively. This procedure was performed in 50% of infrared-coagulation group too.

Partial gastrectomy was although more indicated in the diaphragm resection group 5.8% vs. 0% in the diaphragm stripping group (p=0.021), which perhaps reflected the more massive tumor infiltration in the upper abdomen in EOC-patients, who underwent diaphragm resection to achieve a CTR.

The partial resection of any liver segment and the partial stripping of liver capsule showed similar rates in both groups of diaphragm interventions

(2.5% vs. 3.5% and 19.2% vs. 18.4% for diaphragm resection and stripping groups, respectively).

About one fourth of the patients with diaphragm interventions underwent splenectomy in each subgroup [31 patients (25.8%) in the resection group compared to 33 patients (23.2%) in the diaphragm stripping group].

Only the partial cystectomy and ureter resections were more indicated in the diaphragm stripping group than in the group of diaphragm resections, however, these procedures were collectively rare indicated.

Table VII: Operation characteristics of diaphragm surgery subgroups

Surgical procedures	Diaphragm resection n=120 (44.8%)	Diaphragm stripping n=142 (53%)	Infrared coagulation n=6 (2.2%)	p-value
Op-duration [Median-Minutes]	295 (42-592)	282 (30-559)	200 (175-215)	0.018
Appendectomies	50(41%)	73(51.4%)	2(33.3%)	0.233
Intestinal resection	91(75.8%)	95(66%)	5(83.3%)	0.226
Pancreas partial resection	2(1.7%)	1(0.7%)	0	0.736
Ligamentum falciforum resection	81(67.5%)	69(48.6%)	3(50%)	0.008
partial hepatectomy	3(2.5%)	5(3.5%)	0	0.809
Liver capsule resection	23(19.2%)	26(18,4)	0	0.496
Partial stomach resection	7(5.8%)	0	0	0.012
Splenectomy	31(25.8)	33 (23.2)	1 (16.7%)	0.806

Bladder resection	1(0.8%)	4(2.8%)	1(16.7%)	0.030
Ureter resection	0	1(0.7%)	1 (16.7%)	<0.001
Postoperative complications	58 (48.3%)	71 (50%)	4 (66.7%)	0.395
30-day mortality	0	2 (1.4%)	1 (16.6%)	<0.001

IV. C. Complications of PCS with diaphragm interventions:

As we reported previously, the PCS with diaphragm intervention associated in this study with slightly but statistically significant increase in overall postoperative complications.

Taking all grades of complications according to Chassagne's glossary for complications of treatment in gynecological cancers and the National Cancer Institute Common Toxicity Criteria version 2.0-classification system into account, we registered 58 cases (48.3%) and 71 cases (50%) with postoperative complications in the diaphragm resection group and stripping group, respectively. Two thirds of patients with infrared-coagulation experienced some degree of postoperative complication.

Postoperative infections (as defined previously in our methods section) were diagnosed in 16.6% of patients in the diaphragm coagulation group. This rate diminished gradually to 15.5% and 10.8% in the diaphragm stripping and resection group (P=0.02), respectively.

We observed an increased rate of postoperative thrombotic emboli reaching to 2 out of 6 patients who underwent a diaphragm infrared coagulation compared with 7.7% in diaphragm resection group and 5.2% in the diaphragm stripping group (p=0.07).

The incidence of postoperative pneumothorax was low in the diaphragm resection and diaphragm stripping group (2.5%,1.4%) respectively, while there were no recorded cases in the coagulation group. At the same time, the incidence of postoperative pleural effusion was highest (33.3%) in the diaphragm infrared-coagulation group and dropping to (26.6% and 24%) in the diaphragm resection and stripping group respectively. But this did not show any significant difference.

We observed an almost threefold increase in the diagnosed postoperative wound dehiscence (5.6%) in the stripping group versus (1.6%) in the resection group. This difference was statistically insignificant.

The rate of increase of Anastomosis insufficiency in the diaphragm intervention group compared to the other group without diaphragm intervention was significantly high, but this rate was similar in the diaphragm intervention subgroups [5 reported cases in the resection group (4.15%) and 7 cases (5.2%) in the stripping group].

Table VIII: Complication in the diaphragm intervention group in PCS:

Characteristics	Resection group N= 120	Diaphragm stripping n=142	Infrared n=6	p-value
Postoperative complications	58 (48.3%)	71 (50%)	4 (66.7%)	p=0.395
Thrombo-embolic events	9(7.7%)	7(5.2%)	2 (33.3%)	p=0.07
Postoperative infection	13(10.8%)	22 (15.5%)	1 (16.6%)	p=0.02
Postoperative sepsis	2 (1.7%)	1 (0.7%)	1 (16.6%)	p=0.124
Postoperative pneumonia	3 (2.5%)	8 (5.6%)	1 (16.6%)	p=0.117
Postoperative pleura effusion	32 (26.6%)	34 (24%)	2 (33.3%)	p=0.734
Postoperative pneumothorax	3 (2.5%)	2 (1.4%)	0	p=0.788

Anastomosis insufficiency	5 (4.16%)	7 (5.2%)	0	p=0.828
Wound dehiscence	2 (1.66%)	8 (5.6%)	0	p=0.199
Postoperative bleeding	2 (1.66%)	3 (2.1%)	0	p=0.908
Neurologic complications	11 (9.1%)	4 (2.8%)	1 (16.6%)	p=0.049
30-day mortality	0	2 (1.4%)	1 (16.6%)	p<0.001

On the other hand, we observed a higher rate (3-fold) of postoperative neurological complication in patients who underwent a diaphragm resection 11 patients (9.1%) compared to 4 (2.8%) in the stripping group and 2 patients (33.3%) in the infrared-coagulation group (p=0.04).
The 30-day patient's mortality rate was clearly higher in the group of those treated only with infrared contact coagulation (one out of six patients,16.6%), whereas in diaphragm stripping it dropped to 1.4%. Compared to no recorded mortality in the resection group. (p<0.001).

IV. d. Surgical outcome in PCS with diaphragm intervention:

Diaphragm resection was associated with an increased rate of CTR (73.3%) compared with (61.3%) in diaphragm stripping. This rate dropped dramatically in the infrared-coagulation group with (16.7%) (p<0.001).
The incidence of suboptimal debulking (the largest dimension of the largest residual tumor measured 1- 10mm) was, as expected, observed more often in the coagulation group (66.7%) than in the other group, where the rate dropped to 28.2% in the stripping group and to 24.2% in the resection group of patients. But this difference was not statistically significant (p=0.86). The same was observed regarding the rate of residual tumor > 10 mm, which was higher in the group of patients who underwent

an only-infrared coagulation of diaphragm with 16.7%, whereas this rate was lowest in the resection group, with (2.5%). (Table IX).

The median follow-up time for the entire cohort reached 22 months (range=1-98.4 months).

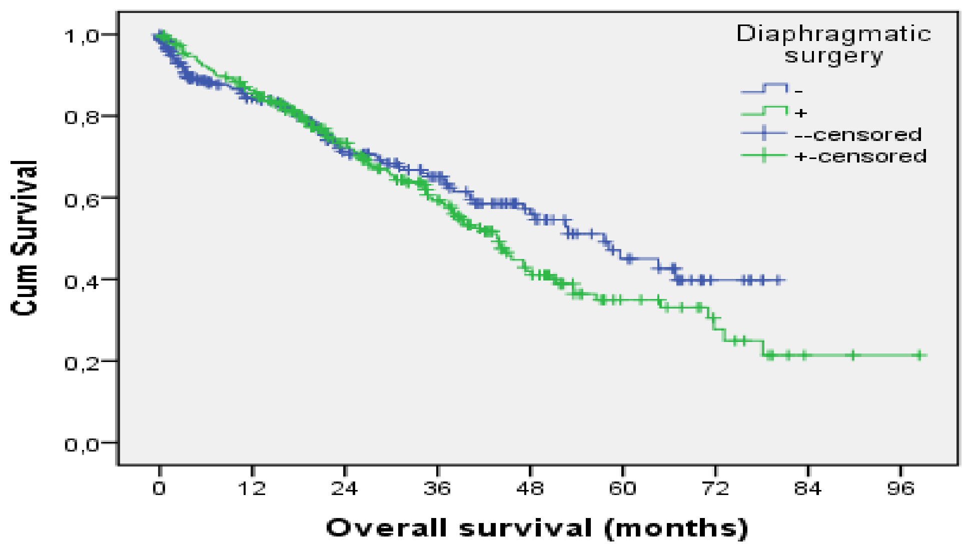
Table IX: Residual tumor rate in PCS patients with diaphragm intervention.

Surgical procedures		Diaphragm resection n=120 (44.8%)	Diaphragm stripping n=142 (53%)	Infrared coagulation n=6 (2.2%)	p-value
Residual tumour	No residual	88 (73.3%)	87 (61.3%)	1 (16.7%)	p=0.075
	< 10 mm	29 (24.2%)	40 (28.2%)	4 (66.7%)	
	≥ 10 mm	3 (2.5%)	13 (9.2%)	1 (16.7%)	
	Unknown	0	2 (1.4%)	0	

IV. d. I. Overall and progression-free survival in diaphragm and non-diaphragm interventions groups:

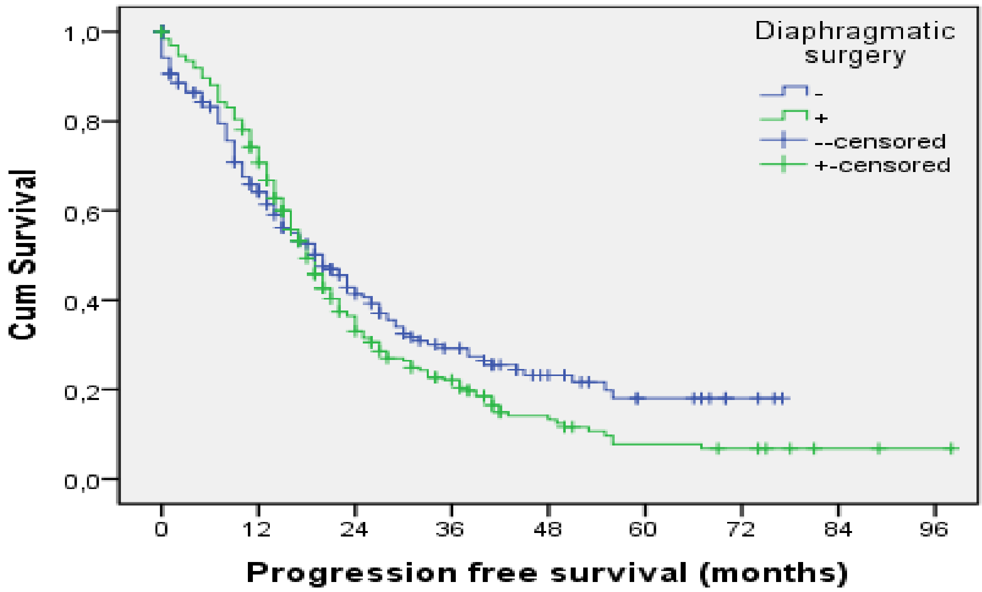
The median overall survival (OS) in patients who did not undergone diaphragm intervention was 57.6 months (95%CI= 47.3-67.9 months) versus 43.9 months (95%CI=38.9-48.9 months) in patients who had diaphragm surgery (p=0.188). The 5 years (OS) was 45% (34.5 - 55.5) in the group without diaphragm surgery versus 35% in the group of patients who had a diaphragm intervention (26.6- 43.3).

Figure I : Overall survival AOC-patients underwent PCS with and without diaphragm intervention



The median PFS in the PCS-group without diaphragm intervention was higher than PFS in the diaphragm intervention group, 20 months (95% CI=15.8-24.2 months) versus 18 months (95%CI= 16.1-19.9), (p=0.21) respectively. Figure II

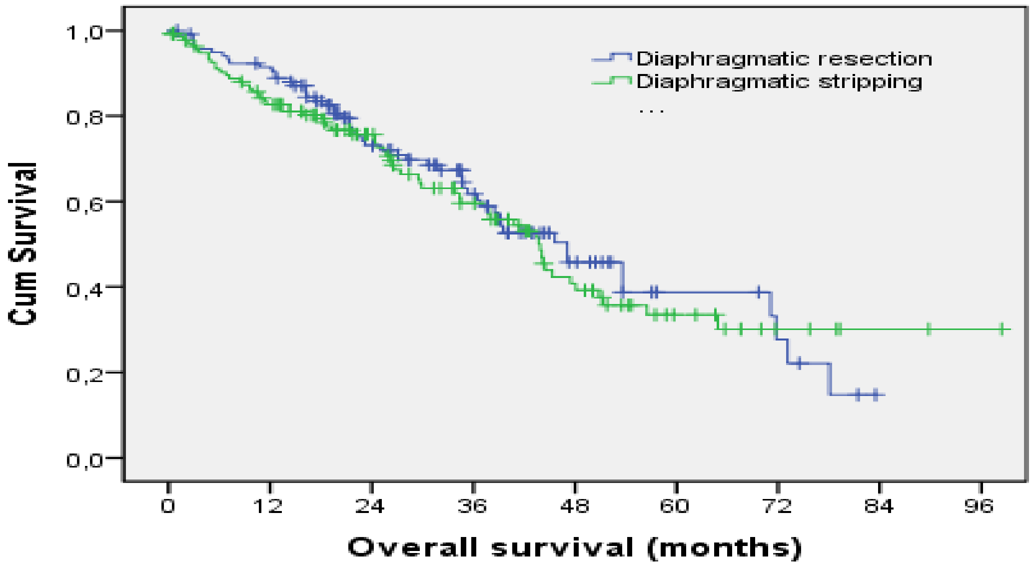
Figure II: PFS in PCS patients with and without diaphragm intervention



IV. d. II. Overall and progression-free survival in diaphragm interventions subgroups (stripping versus full resection):

The diaphragm resection subgroup of patients showed a slightly longer median OS of 47.1 month (95% CI=36.9-57.3 months) versus 43.9 months in the diaphragm stripping subgroup (95% CI=38.2-49.6 months), however, this result was not statistically significant (p=0.63). The same OS was observed in terms of 5-years overall survival, which was 38.7% (25.3-52.2%) in the diaphragm resection subgroup versus 33.5% in the diaphragm stripping subgroup (22.5 -44.5%). Figure III shows the OS in both subgroups of diaphragm interventions.

Figure III: Overall survival the diaphragm intervention subgroups



IV. d. III. Overall and progression free survival according to the postoperative residual tumor:

In this study, the median OS of patients who achieved a complete resection was 57.6 months, this dropped to 29.9 months in patients with residual tumor up to 10 mm (suboptimal debulking) after PCS and again to 19.6 months in patients with residual tumor >10 mm, (p=0.001). The estimated median 5-year overall survival was 46.3% (95% CI: 37.8- 54.8) for patients with CTR after PCS and it declined dramatically to 21.9% (95% CI:10.7-33.1%) for patients with residual tumor up to 10 mm (95% CI:0- 27.7%) and then to 10.2% if the residual tumor exceeded 10 mm, (p=0.001).

The results of evaluated PFS were in line with the OS-outcomes and showed the same trend. PFS in patients who underwent an optimal primary cytoreduction (no residual tumor) reached 22 months compared to 14 months when the optimal cytoreduction could not be achieved and the remained residual tumor was up to 10 mm. The 3-year progression-free survival was 30.7% and 10.4% for patients with optimal debulkig and suboptimal debulking, respectively. Figures IV and V represent these results.

Figure IV: Overall survival in optimally and suboptimally debulked patients.

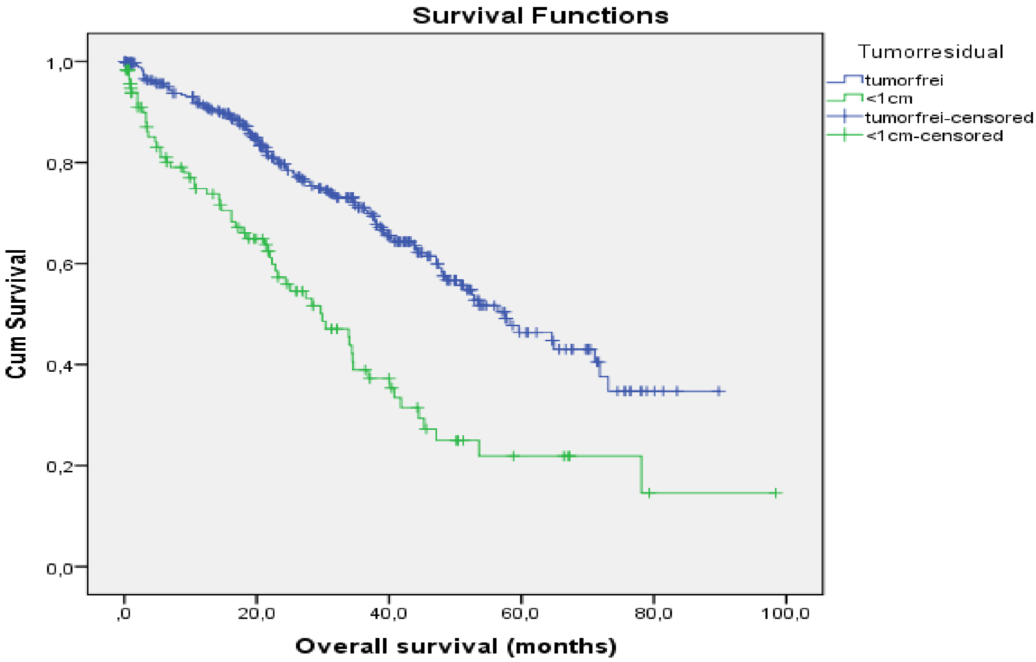
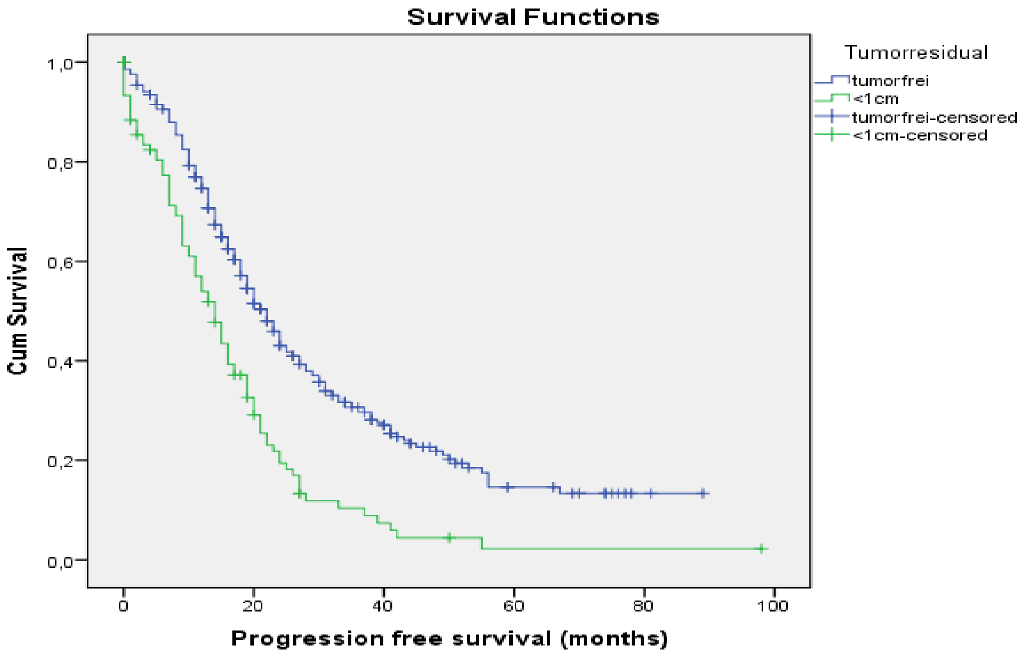


Figure V: PFS in optimally and suboptimally Cytoreduction patients



Even in the diaphragm interventions group, we could clearly notice the CTR as a strong factor predicting survival. Our study showed a higher median OS in the optimally debulked patient group with diaphragm intervention of 53 months (95%CI: 39.7- 67.5) compared with 29 months (95%CI: 20.5- 39.3%) in the group of suboptimally debulked patient (residual tumor ≤ 10 mm) and 26 months (95%CI: 13.8- 39.3%), (p=0.001) in the group with residual tumor > 10 mm group.

The PFS was 20 (95%CI: 17.4- 22.6) months in the optimally debulked group in comparing with 15 (95%CI: 12.3- 17.7) and 15 months (95%CI:8.3- 21.7) in the groups of patients with residual tumor ≤10 mm and > 10 mm respectively. These results illustrated in Figure VI and VII.

Figure VI: OS in optimal and suboptimal PCS with diaphragm surgery

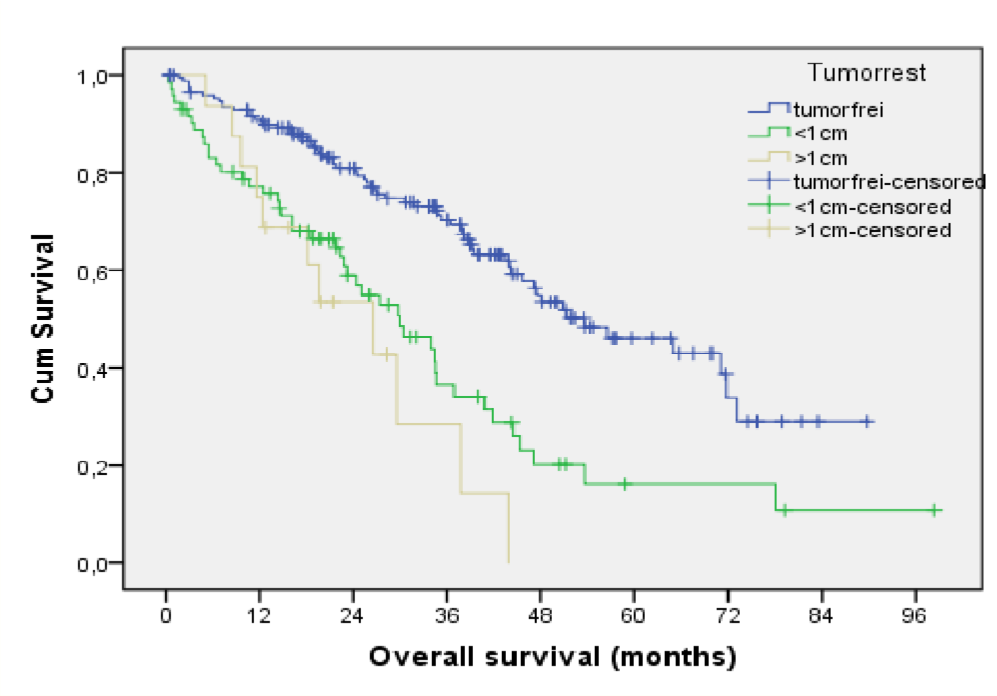
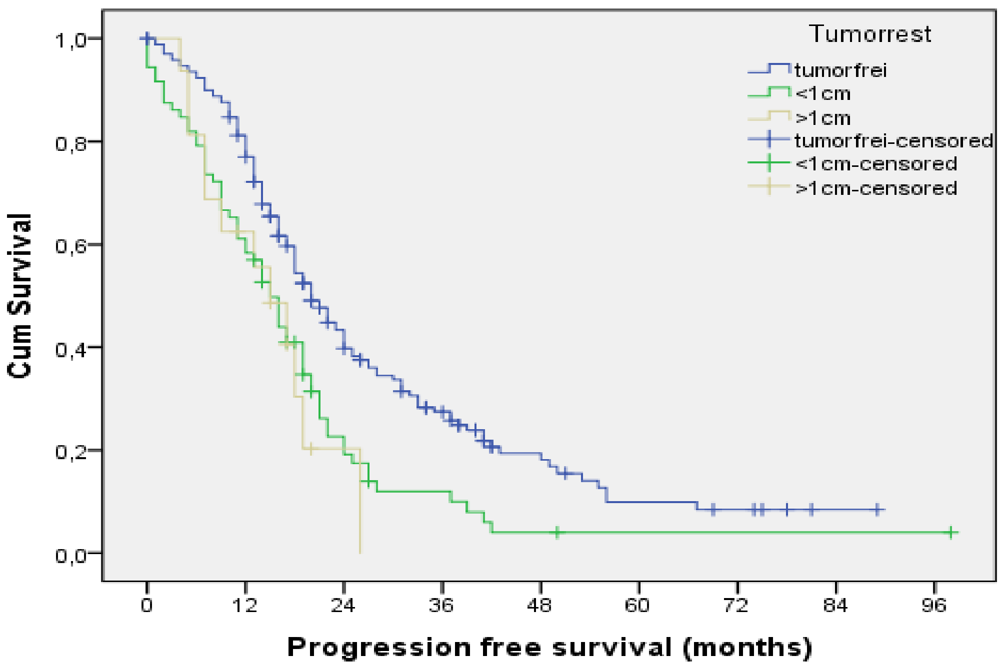


Figure VII: PFS in optimal and suboptimal PCS with diaphragm surgery



Discussion:

Primary cytoreductive surgery is the cornerstone of the initial treatment of patients with EOC. The goal of such surgery should be the complete macroscopic disease resection (35). That means in many cases the utilization of many radical and aggressive procedures to be able to achieve this goal. Diaphragms are involved in 44 %- 91% (36), (37) of primary AOC cases. As previously suggested by many authors (38), (39), a thorough knowledge of the anatomy of the upper abdomen and of the liver mobilization maneuvers, are necessary to a good and ultimate visualizing and debulking of the diaphragm, and to diminishing the risk of major injuries of vessels (retro-hepatic caval veins, hepatic ileus, suprahepatic veins, diaphragm vessels) with severe hemorrhage. Thanks to the advances made in anesthesiological techniques, the permanent evolution of pre-, intra- and postoperative care of such patients, and the advance made in surgical techniques for AOC, like the no-touch isolation technique, en-bloc-low abdomen- resection or the techniques of upper abdomen surgery, has become possible to achieve the CTR in up to 70% of patients (40, 41). In this way, it is very difficult nowadays to accept the diaphragm disease as a reason for residual tumor by PCS.

In the present study, we aimed to focus on the diaphragm surgery as one of the most important and needed procedure in the frame of upper abdomen interventions as part of PCS for AOC. To the best of our knowledge, this study presents the largest cohort of AOC-patients who underwent a diaphragm surgery compared with the ones who did not undergone a diaphragm surgery for PCS.

Unfortunately, we could not find any other study which compared the PCS with and without diaphragm surgery, but only some studies which focused on PCS with different types of diaphragm surgery as a collective without a control group.

Our study was able to identify statistically significant predictors for diaphragm interventions in PCS. Patients with apparent preoperatively FIGO IV (pleura effusion), serous papillary tumors, massive ascites (>500 mL) and very high preoperative CA-125 value (more than 500 U/ml) might be candidates to undergo a diaphragm surgery to achieve the CTR.

This correlate to some extent with the result of other authors like Chi et al.(42), who observed that in patients with CA-125 values greater than 500 U/mL, extensive upper abdominal surgery might be required to achieve a residual disease status < 1 cm, which was considered at the time of this study as an optimal debulking.

In our study, optimal resection was defined as no residual macroscopic tumor at the end of surgery. To achieve this target, in almost half of our patients diaphragm surgery was needed. Moreover, one of the diaphragm surgery techniques was needed in 60% of patients to achieve a residual tumor status of less than or equal to 10 mm (sub-optimal debulking). To achieve a complete cytoreduction diaphragm intervention was indicated in 93.2% (356/382) of optimally debulked patients in Heitz et al.study (43). In Chi study, 50% (57/113) of patients required extensive upper abdominal surgery to accomplish a tumor resection to residual tumor less than or equal to 1 cm. The same results were concluded by other studies about PCS for AOC (19, 20).

In our collective, we performed diaphragm stripping in 53% of cases in the diaphragm interventions group, diaphragm resection in 44.8% and infrared coagulation in only 2.2%. of cases,

In the Benedetti Panici et al. study (44), the diaphragm was involved in 51.9% of patients in a collective of 126 patients, who had upper abdominal tumor spread and needed one of the upper abdominal surgeries to achieve a CTR. diaphragm stripping was indicated in 28.9% of patients and diaphragm resection in 31.4% of patients. Ye et al.(45) implemented the diaphragm stripping in 82.7% (124/150) of patients and a diaphragm resection in 17.3% (26/150) of patients, while Zapradiel et al.(29), performed the diaphragm stripping in 70.5% and full-thickness resection in 29.5% of cases.

Adding diaphragm surgery to the procedures performed during PCS resulted in our study in a statistically significant increase of bowel resection (71%) [OR= 2.754, 95%CI= 1.897- 4.001), p<0.001], cholecystectomy (10.1%), partial resection of liver capsule (3%), partial gastrectomy (2.6%), and splenectomy (24.3%) compared to the other group of patients who did not undergo a diaphragm intervention.

Ye et al. (45) reported about (35.3%) bowel resection, (12%) splenectomy. (0.7%) cholecystectomy in a series of 150 patients who underwent diaphragm stripping and diaphragm resection as part of PCS, the same was observed by Chereau et al. (46) with (68%) bowel resection, (31%) splenectomy, (18%) cholecystectomy, (4%) distal pancreatectomy, (9%) partial liver resection and (3%) partial gastrectomy.

Because of these extensive surgical procedures, the overall postoperative complications increased (49,6% vs. 38,8%) in the group of diaphragm interventions vs. the group without diaphragm intervention and the operating time was longer in the diaphragm intervention group of our study with a median operating time (282.5 minutes vs. 244 minutes) in the diaphragm intervention group vs. non-diaphragm intervention group respectively. We believe that the increased rate of complications in the diaphragm intervention group and the prolonged operating time was associated with the increased rate of other operative procedures.

The median operating time in the Ye et al. (45) study was 260 (190–300) minutes. He reported a 38% overall complication rate in patients who underwent an upper abdominal surgery, 19% of them were sever complications. The operating time was slightly longer in the resection

group in the Zapardiel study (29). He attributed it also to the extensive disease spread in the upper abdomen, requiring additional time for debulking and performing a diaphragm resection in the group of patients.
We did not observe any statistically significant differences neither in terms of postoperative complications, nor in terms of the surgical procedures performed between the 2 major diaphragm surgery subgroups.
By contrast, Zapradiel et al. (29) reported a significant increase in the rate of rectosigmoid resection (75.9% vs. 57.6%) in stripping group and resection group, respectively. (P=0.05). and 8 hemicolectomies (10.1%) in the stripping group vs. none in the resection group (P=0.06). Tsolakidis et al.(47) performed 29% bowel resections, 55% pelvic and/or para aortic lymphadenectomy, and 26% splenectomy in the stripping group.
Focusing on complications directly related to diaphragm surgery, postoperative pleural effusion was the most frequent complication mentioned by many authors like Tsolakidis et al.(47), who reported about (16.9%) of pleura effusion, followed by pneumothorax (6.6%), and pneumonia (2.2%). Similarly, Chereau et al. (46) reported even a higher rate of pleural effusion with (37%), (5%) of pulmonary embolism, (4%) of pneumothorax, and (2%) of pulmonary infection.
In the study by Ye et al. (45) pleura effusion and pneumothorax rate reached (33.3%) and (7.3%), respectively with (14%) of patients with symptomatic pleural effusion requiring drainage. In the study by Dowdy et. al. was in (48) (12.5%) of patients required a postoperative thoracentesis or chest tube placement. In a group of 69 diaphragm surgeries in the Devolder et al. study (49), pleura effusion was diagnosed in (59%) of patients.
Our findings were in line with these studies. The rate of postoperative pleural effusion reached (25.4%). This was the most frequently diagnosed complication in the group of patients, who underwent any kind of

diaphragm surgery. The incidence of pneumonia and pneumothorax was lower (4.5%) and (1.9%), respectively in the same group of patients.
Furthermore, Benedetti Panici et al. (44) diagnosed postoperative pleura effusion in (31%) of patients after a diaphragm stripping and in (39%) of patients after diaphragm resection.
Many authors (27, 51) attempted to detect the cause of the postoperative pleural effusion, Fanfani et al. (50) claimed the strict linkage between liver mobilization and postoperative pleural effusion (52.3% vs. 16%; p=0.0027) which is also mentioned in Eisenhauer et al. study (52). By using multivariate analysis, they found that pleural effusion was statistically well predicted only by hepatic mobilization. Unfortunately, they did not define which kind or classify the extent of liver mobilization, which resulted in a higher rate of pleural effusion.
Liver mobilization was routinely performed in most cases in our cohort even in apparent absence of the involvement of diaphragm for a good exploration of the diaphragm surface to identify any lesions, but we could not notice any relationship between liver mobilization and pleural effusion.
In this study, a longer progression-free and overall survival was noticed in the non-diaphragm surgery group in comparison with the diaphragm surgery group. These results were not statistically significant, and they show the big difference between the two groups regarding the spread pattern of peritoneal carcinomatosis, which was clearly more massive and extensive in the diaphragm surgery group. Despite this difference, we succeeded in achieving an equal CTR in both study groups
CTR was obtained in (73.3%) and (61.3%) in diaphragm resection and stripping groups, respectively. In the Zapardiel study these rates reached (29) only (63.6%) in diaphragm resection group and (36.7%) in the diaphragm stripping group. Fanfani et al. (50) could achieve in 100% of his patients an optimal cytoreduction at the end of surgery. It is worth

mentioning that the definition of optimal cytoreduction in their study was a residual tumor less than 10 mm. Debulking to no residual tumor was achieved in 90%, 86% and 100% in diaphragm coagulation, stripping and resection group, respectively in the Tsolakidis et al. study (47).

We observed in the present study better results in term of OS and PFS in the diaphragm resection group, this is probably due to the higher rate of CTR in this group of patients compared with the group of diaphragm stripping.

The median OS and PFS were 47.1 months and 43.9% vs. 20.7 months and 24.3% for diaphragm resection and stripping groups, respectively.

Similarly, Zapardiel et al. (29) reported an OS rate of 58.2% vs. 78.8% in the stripping and resection group respectively, and PFS rate by 27.8% vs. 39.4% in stripping and resection groups respectively.

Tsolakidis et al. (47) reported no statistically significant difference in terms of PFS between his study groups with 15, 15, 17 months and median OS of 40, 42, and 50 months in coagulation, stripping, and combination stripping with coagulation groups, respectively.

Aletti et al.(27) reported a benefit form treatment of diaphragm disease in terms of OS in all patients with diaphragm disease (53% vs. 15%) and (55% vs. 28%) in patients with diaphragm disease who were optimally cytoreduced., CTR defined as less than 10 mm of residual tumor.

We observed a similar OS advantage of 53 months vs. 29 months in the diaphragm intervention subgroup with CTR vs. suboptimally debulked subgroup, respectively.

Furthermore, Fanfani et al.(50) claimed a benefit of diaphragm surgery even in patients who underwent interval and secondary cytoreductive surgery with a median OS, calculated from the second surgery, respectively, of 24 months (range 18–38 months) and 24 months (range 18–67 months).

In conclusion, we found the diaphragm surgery at the time of PCS for AOC may be needed in 50% of patients to achieve a complete cytoreduction to no macroscopic residual tumor. The findings in the present study correlate with the results of other studies considering diaphragm surgery as acceptable, feasible and in most cases as an essential intervention to achieve CTR or sub-optimal debulking.

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Eidesstattliche Versicherung

Ich, Jumana Muallem (geb. Almuheimid), versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Upper abdominal surgery in advanced epithelial ovarian cancer diaphragm surgery in Focus.

selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik und Resultaten entsprechen den URM und werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Betreuer, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Anteilserklärung

Jumana Muallem (geb. Almuheimid) hatte folgenden Anteil an der folgenden Publikation:

Publikation 1: Muallem MZ, Almuheimid J, Richter R, Braicu EI, Osman S, Sehouli J., Diaphragm Surgery in Advanced Ovarian, Tubal and Peritoneal Cancer. A 7-Year Retrospective Analysis of the Tumor Bank Ovarian Cancer Network, Anticancer Res. 2016 Sep;36(9):4707-13.

Beitrag im Einzelnen:
Mitwirkung bei der Erhebung der primären Daten, Aufbau, Korrektur und Aktualisieren der Datenbank, Literatur Recherche und Mitwirkung bei Manuskripterstellung.

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Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

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Unterschrift des Doktoranden/der Doktorandin

Mein Lebenslauf ist in der elektronischen Version der Dissertation aus datenschutzrechtlichen Gründen nicht enthalt

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