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Comparison of diaphragmatic surgery at primary or interval debulking in advanced ovarian carcinoma: An analysis of 163 patients

Dimitris Tsolakidis, Frederic Amant, Karin Leunen, Isabelle Cadron, Patrick Neven, Ignace Vergote *

Division of Gynaecologic Oncology, Department of Obstetrics and Gynaecology, University Hospitals Leuven, Katholieke Universiteit Leuven, Leuven, Belgium

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ABSTRACT

Aims of the study and methods: Survival, complications and recurrences after diaphragmatic surgery at primary or interval debulking surgery were compared. One hundred and sixty three consecutive patients with stage III/IV ovarian cancer underwent diaphragmatic surgery between September 1993 and December 2007. Primary debulking was performed in group 1 (89) patients and interval debulking was performed in group 2 (74) patients. Cytoreductive outcome, overall survival (OS), disease-free survival (DFS) and post-operative complications were analysed.

Results: Despite differences in baseline mean age ($p = 0.015$), in FIGO stage III/IV ($p = 0.036$) and in mean largest diameter of metastatic disease at the beginning of debulking surgery ($p = 0.037$), the optimal debulking rates (residual tumour less than 1 cm) were similar ($p = 0.065$). Excision of diaphragmatic metastases was most frequently performed in group 1 (77.53%) and coagulation was most frequently performed in group 2 (58.10%). Similar overall survival and disease-free survival rates were found. After the propensity matching procedure, the largest diameter of metastatic disease at the time of debulking and no residual tumour (complete debulking) were demonstrated as independent prognostic factors for OS. Plaque-like lesions on the diaphragm metastases were significantly ($p = 0.015$) more associated with diaphragm recurrence than papillary lesions. Minor and major complications related to diaphragmatic surgery as well as mean operating time, post-operative care in intensive care unit and length of hospitalisation were significantly higher in group 1 rather than in group 2 ($p = 0.043$).

Conclusions: Diaphragmatic dissemination resulted in similar survival and cytoreductive rates after primary and interval debulking. However, the morbidity was less after interval debulking as fewer surgical procedures were performed.

1. Introduction

Involvement of the diaphragm was reported as the most common extrapelvic metastatic site (18–42%) amongst patients with advanced ovarian cancer.[1] The concept of maximum primary cytoreduction was firstly introduced by Meigs in 1934,[2] which is still considered the current surgical treatment of advanced stage epithelial ovarian cancer, despite the absence of

* *Corresponding author:* Address: Department of Obstetrics and Gynaecology, Division of Gynaecologic Oncology, University Hospitals Leuven, Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. Tel.: +32 16344208; fax: +32 16344629.
E-mail address: ignace.vergote@uz.kuleuven.ac.be (I. Vergote).
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prospective randomized controlled studies except one launched by EORTC-GCG.[3] No residual tumour (complete debulking) after primary debulking has been suggested as the only correct definition of optimal debulking.[4] However, 50–60% of patients with advanced disease are suboptimally cytoreduced (>1 cm) without any improvement in their prognosis.[5] Interestingly, diaphragm metastases were recorded as the second obstacle after portal metastases that preclude optimal cytoreduction according to 76.3% of 393 gynaecologist oncologists whose responses were evaluated in a SGO survey. This fact was attributed to the lack of training, limited experience and published evidence on the feasibility and safety of extensive debulking procedures like diaphragmatic surgery in the upper abdomen.[6] On the other hand, the introduction of neoadjuvant chemotherapy in advanced ovarian cancer, especially in patients with bulky tumours in the upper abdomen like diaphragm and with poor performance status resulted in response rates over 80% at the time of interval debulking.

To the best of our knowledge, no retrospective or prospective studies were found in the literature to compare primary with interval debulking involving diaphragmatic surgery in terms of cytoreductive, survival rates as well as intra- and post-operative morbidity in patients with advanced ovarian cancer. Furthermore, we tried to identify prognostic factors in this subgroup of patients with diaphragmatic disease and which type of diaphragmatic surgery is indicated.

2. Patients and methods

2.1. Patients

This retrospective analysis included 163 out of 303 consecutive patients (53.7%) with advanced ovarian carcinoma who underwent diaphragmatic surgery during their primary or interval debulking at the Leuven University Hospital between 1993 and 2007. With the approval of the local ethical committee, all patients gave their informed consent at the time of diagnosis that their medical records could be reviewed within the scope of this study.

2.2. Selection criteria for primary or interval debulking

Since 1993, we introduced diagnostic laparoscopy as a triage tool to diagnose and evaluate the resectability in patients suffering from advanced ovarian cancer with the goal to reach no residual tumour at the completion of primary or interval debulking, as this has been reported to be the most powerful determinant of survival amongst patients with stage III or IV ovarian carcinoma.[4,6] During the study period, 132 of 163 (80.9%) patients underwent diagnostic laparoscopy in order to select the appropriate candidates for interval debulking according to our published institutional inoperability criteria for primary debulking.[7] Analytically, 89 out of 163 patients underwent primary debulking (group 1), whereas the remaining 74 patients underwent interval debulking (group2). In the latter group, 64 out of 74 patients underwent diagnostic laparoscopy before initiation of neoadjuvant chemotherapy and the remaining 10 patients of the interval debulking group were referred to our institution after primary suboptimal debulking surgery and neoadjuvant chemotherapy in the referral hospitals.

2.3. Diaphragmatic surgery

We divided our patients into two groups based on the type of diaphragmatic surgery. In our department, diaphragmatic surgery consists of tumour ablation with the use of monopolar electrocoagulation, or excision with the use of stripping technique of diaphragmatic peritoneum or resection including diaphragmatic muscle and eventually pleura. The extent and the thickness of metastatic diaphragmatic disease determined our choice of diaphragmatic surgery. Of course, patient's general physical condition and sometimes intraoperative complications, such as hemodynamic instability or hypotension, during liver mobilisation, refrained us from excisional procedures in favour of coagulation.

Specifically, diffuse involvement of the diaphragm peritoneum by numerous superficial small implants more than 5 mm in horizontal diameter and an estimated thickness of more than 3 mm were preferentially treated by diaphragmatic stripping of the affected area. Smaller lesions as well as extensive thin fibrous plaques due to chemotherapy-induced fibrosis in patients with poor performance status were usually ablated using monopolar coagulation in spray mode. Full thickness resection with entry into the pleural cavity was applied in patients with infiltration of the muscle and sometimes the adjacent pleura.

All patients were staged according to the FIGO criteria and all operations were performed by two gynaecologist oncologists (IV, FA) and assisted by one of the other authors without any difference amongst them regarding their skills or the preferred method for treating diaphragmatic disease.

2.4. Peri-post-operative morbidity and mortality

Peri-operative morbidity and mortality were defined as any adverse event occurring within the first 30 days post-operatively. In this study, we used the Chassagne's glossary[8] and the NCI CTC version 2.0 classification system[9] for grading post-operative complications in our study population.

2.5. Chemotherapy

Within 4–6 weeks after primary debulking, all patients except one who died before initiation of chemotherapy received 6–8 cycles (median 6) platinum-based chemotherapy as single agent ($n = 2$) or in combination with cyclophosphamide ($n = 4$), paclitaxel or docetaxel ($n = 82$) and/or other drugs depending on the different ongoing protocols during the study period.

In the interval debulking group, within 10–20 d after diagnostic laparoscopy or laparotomy, all patients except one were treated before surgery with 3–4 cycles of neoadjuvant chemotherapy consisting of cisplatin or carboplatin as monotherapy ($n = 5$) or in combination with cyclophosphamide ($n = 1$) or paclitaxel or docetaxel ($n = 67$).

2.6. Follow-up

All patients after completing their therapy protocol were reassessed with clinical examination, measurement of serum CA125 levels and computed tomography scan every

3–4 months for the first 2 years and then semiannually for the next 3 years, in our outpatient clinics or by their referral gynaecologists.

2.7. Statistical analysis

Overall survival (OS) (time to death from any cause) and disease-free survival (DFS) (time to disease recurrence or death from any cause) were compared in both groups. In addition, we checked for differences in post-operative complications.

Survival curves were determined by the Kaplan–Meier method. OS was calculated from the day of diagnostic laparoscopy or cytoreductive surgery to the date of last contact or death. DFS was estimated until the day of first relapse or death according to the new guidelines for evaluating the response to treatment either with RECIST or CA-125 criteria. In order to avoid possible misspecification effects of parametric models, a semiparametric approach was chosen based on the Cox proportional hazards model.[10] All analyses were performed in the R statistical package (version 2.8.2) using the survival package (version 2.34-1).

We checked whether imbalances in the distribution of the baseline covariates in order to avoid biased statistical differences between the two treatment groups. To overcome the problem of covariate imbalances we used propensity score matching method[11] to create matched pairs between the two groups. To produce the matched pairs we used a genetic search algorithm[12] designed to find optimal balance between the baseline covariates. In addition to clarify if proportional hazards assumption made by the Cox model was or not appropriate, we calculated Scoenfeld residuals and tested for systematic trends with different choices of time-scale. In order to take into account the matching nature of our data set, we use a robust variance computation based on the grouped jackknife method.[10]

Log-rank and χ^2 tests were used to compare univariate prognostic factors. Multivariable analyses based on a logistic regression and on a generalised estimating equation analysis were used for comparing excision versus coagulation technique. The confidence intervals were based on the likelihood ratio test. Fisher exact test was used for categorical variables and Wilcoxon test for numerical ones. Differences were considered significant at p value < 0.05.

3. Results

Characteristics of patients, tumour and debulking surgery for both groups are summarised in Table 1. Mean age was higher in the interval debulking group (60.6 versus 56.6 years and more patients were of stage IV (26 versus 17). On the contrary, in the primary debulking group the mean diameter of metastatic disease was larger in comparison to the interval debulking group (12.1 versus 9.2 cm, respectively). However, the incidence of pre-operative pleural effusions was similar between the primary 16.8% (15 out of 89) and the interval debulking 17.6% (13 out of 74) group. Propensity scoring to create matched pairs between the primary and interval debulking groups was performed for the following variables: age, FIGO stage, largest diameter of metastases, histological type, tumour grade and WHO performance status. Coagulation of diaphragmatic peritoneum was the most frequently performed diaphragmatic procedure in group 2 (58.1% versus 22.4%) and on the other hand the frequency of bowel resections (29.2% versus 12.1%), lymphadenectomies (56.1% versus 39.1%) and spleenectomies (20.2% versus 8.1%) were significantly higher in group 1. Similar proportions of debulking to no residual ($p = 0.146$) or less <1 cm (0.065) were obtained at the end of the cytoreductive procedures in the two groups.

Intra- and post-operative complications related or not to diaphragmatic surgery are presented in Table 2. Interestingly, there were significant differences between the two groups, even after matching, in terms of post-operative pleural effusions ($p = 0.011$), necessity for chest tube placement ($p = 0.002$), intra-operative blood loss ($p < 0.001$), operating time ($p < 0.001$), post-operative hours in intermediate or intensive care unit ($p < 0.001$) and the length of hospitalisation ($p < 0.001$). On the contrary, there was no difference between the two groups with regards to the percentage of diaphragmatic relapses.

Post-operative morbidity was statistically more frequent ($p = 0.043$) in group 1. Specifically, minor or major complications were noted in 83 of the 89 (93.26%) patients compared with 56 of the 74 (82.35%) patients in the interval debulking group. Intra- and post-operative mortality was 0% in both groups. One patient died 108 days after primary debulking, from respiratory distress due to rapid disease progression and bilateral production of resistant malignant pleural effusions.

Univariate analysis for OS revealed that stage, serous histology, largest diameter in cm, residual tumour less than 1 cm and diaphragmatic recurrence, as first site of tumour relapse were significant predictors of OS. However, the same univariate analysis after the propensity score matching showed that only largest diameter of metastatic tumour and residual tumour less than 1 cm were the strongest prognostic factors for OS. In a multivariate model including largest size of metastatic disease, no residual tumour (complete debulking), residual tumour less than 1 cm (optimal debulking) and tumour histology, OS was significantly influenced by two variables: the diameter of metastatic disease and the absence of residual disease (complete debulking) either before or after adjusting for covariate imbalances (Table 3).

We also performed univariate analysis for various prognostic factors affecting DFS. Tumour grade, largest diameter of metastatic tumour and type of diaphragmatic lesions were found as independent prognostic factors without taking into account the covariate imbalances between the two groups. However, after the propensity score matching, WHO performance status, largest preoperative diameter of metastatic tumour and diameter of residual tumour less than 1 cm remained as independent prognostic factors for DFS. In a multivariate model including largest diameter of metastatic tumour, absence of residual tumour (complete debulking), residual tumour less than 1 cm (optimal debulking), tumour grade and type of diaphragmatic metastases, DFS was independently influenced by the diameter of residual disease equal to 0 cm or less than 1 cm, only after the propensity score matching procedure (Table 4).

After comparing the type of diaphragmatic surgery (coagulation versus excision), tumour load, diameter of metastatic disease, FIGO stage and type of diaphragmatic lesions (papillary versus plaque), we found that only the type of

Table 1 – Characteristics of patients, tumour and debulking surgery.

Parameter	Primary group 1 $n = 89$ (%)	Interval group 2 $n = 74$ (%)	p_1 value	p_2 value
Mean(SD) age (range)	56.6 (11.0) (26–79)	60.6 (10.0) (31–78)	0.015	0.677
WHO			0.097	0.223
0	62 (69.6)	42 (56.7)		
1	27 (30.3)	30 40.5)		
2	0 (0.0)	2 (2.7)		
FIGO stage			0.036	0.941
IIIB	8 (8.9)	2 (2.7)		
IIIC	64 (71.9)	46 (62.1)		
IV pleura	14 (15.7)	17 (22.9)		
IV other	3 (3.3)	9 (12.1)		
Histological epithelial type			0.566	0.66
Serous	82 (92.1)	68 (91.8)		
Mucinous	1 (1.1)	3 (4.0)		
Endometrioid	1 (1.1)	0 (0.0)		
Clear cell	3 (3.3)	1 (1.3)		
Undifferentiated	2 (2.2)	2 (2.7)		
Tumour grade			0.873	0.901
Grade 1	5 (5.6)	3 (4.1)		
Grade 2	13 (14.6)	10 (13.5)		
Grade 3	71 (79.7)	61 (82.4)		
Presence of ascites	74 (83.1)	33 (44.6)	<0.001	<0.0001
Large-small bowel resection	26 (29.2)	9 (12.1)	0.008	0.02
Lymphadenectomy	50 (56.1)	29 (39.1)	0.031	0.045
Spleenectomy	20 (20.2)	6 (8.1)	0.012	0.02
Type of diaphragmatic surgery			NA	NA
Coagulation	20 (22.4)	43 (58.1)		
Stripping	31 (34.8)	10 (13.5)		
Stripping + coagulation	31 (34.8)	19 (25.6)		
Resection including muscle	7 (7.8)	2 (2.7)		
Pre-operative pleural effusions			NA	NA
Right	7 (7.8)	6 (8.1)		
Left	3 (3.4)	1 (1.3)		
Bilateral	5 (5.6)	6 (8.1)		
Mean largest diameter of metastatic tumour (cm)	12.2	9.2	0.037	0.677
Largest diameter of residual tumour (cm)				
No residual	79 (88.7)	70 (94.6)	0.146	0.149
<1 cm	6 (6.7)	3 (4.0)	0.065	0.248
>1	4 (4.50)	1 (1.35)		
Mean preoperative serum CA-125 (U/mL)	1248	209	NA	NA
Mean post-operative serumCA-125 (U/mL)	274	126	NA	NA

NA: not available.
p_1: ignoring covariate imbalances.
p_2: taking into account covariate imbalances.

diaphragmatic metastases remained significantly different between the two groups ($p = 0.015$).

In a multivariate analysis, after adjusting of the covariate imbalances, the type of diaphragmatic lesions was the sole independent factor (odds ratio = 2.55 95% CI = 1.22–5.31) correlated to the type of diaphragmatic surgery.

Median follow-up (range) was 32 (1–158) months for the primary debulking and 28 (5–121) months for the interval debulking group. No statistically significant differences in survival were found between primary and interval debulking surgery with or without the propensity score matching (Figs. 1a and 1b).

4. Discussion

Since first proposal by Griffiths in 1975, optimal debulking surgery with no or less than 1 cm residual tumour at the end of cytoreductive operation remains the most important prognostic factor in patients with advanced ovarian cancer.[13,14]

Table 2 – Intra-and post-operative complications.

Parameter	Primary group 1 $n = 89$ (%)	Interval group 2 $n = 74$ (%)	p_1 value	p_2 value
Post-operative (<28 d)pleural effusions location				
Right	12 (13.4)	15 (20.2)		
Left	6 (6.7)	5 (6.7)		
Bilateral	47 (52.8)	17 (22.9)		
NA	0 (0.0%)	5 (6.7)		
Post-operative pleural effusion (nci-ctc v2)			0.011	0.003
Grades 1 and 2	15 (16.8)	27 (36.4)		
Grades 3 and 4	42 (47.1)	3 (4.0)		
NA	0 (0.0)	6 (8.1)		
Pneumothorax			0.167	0.131
Grades 1 and 2	3 (3.3)	2 (2.7)		
Grades 3 and 4	6 (6.7)	0 (0.0%)		
NA	0 (0.0)	5 (6.7)		
Pneumonia (nci-ctc v2)			0.727	0.002
Grades 1 and 2	3 (3.3)	2 (2.7)		
Grades 3 and 4	2 (2.2)	0 (0.0)		
NA	0 (0.0)	5 (6.7)		
Elevation of diaphragm			0.309	0.361
Right	38 (42.6)	20 (27.0)		
Left	2 (2.2)	2 (2.7)		
Bilateral	2 (2.2)	1 (1.3)		
NA	0 (0.0)	6 (8.1)		
Persistent pleural collections during follow-up			NA	NA
Right	10 (11.2)	8 (10.8)		
Left	2 (2.2)	0 (0.0%)		
Bilateral	6 (6.7)	0 (0.0%)		
Puncture of pleural fluid			0.311	0.016
Right	8 (8.9)	2 (2.7)		
Left	2 (2.2)	1 (1.3)		
Bilateral	1 (1.1)	6 (8.1)		
Chest tube			0.002	0.034
Right	11 (12.3)	0 (0.0)		
Left	1 (1.1)	1 (1.3)		
Bilateral	3 (3.3)	0 (0.0)		
NA	0 (0.0)	8 (10.8)		
Chest tube drainage (mean/median days) (range)	11.1/8.0 (5–48)	12.00/12.00 (12.0)	NA	NA
Site of diaphragm relapse				
No	51 (57.3)	44 (59.4)	0.548	0.628
Right	7 (7.8)	11 (14.8)		
Left	2 (2.2)	2 (2.7)		
Bilateral	6 (6.7)	6 (8.1)		
NA	23 (25.8)	11 (14.8)		
Mean (SD) intraoperative blood loss	2177 (1468)	1270 (761)	<0.001	0.005
Mean (SD) post-operative whole blood transfusion (ml)	534	389	0.431	0.722
Post-operative hours in intensive care unit mean	19.76 (29.2)	10.16 (10.0)	<0.001	<0.001
Mean (SD) duration of the operation (min)	355 (116.9)	272 (76.9)	<0.001	<0.001
Mean (SD) hospitalisation days	21 (20)	13 (5)	<0.001	0.001

NA: not available.
p_1: ignoring covariate imbalances
p_2: taking into account covariate imbalances

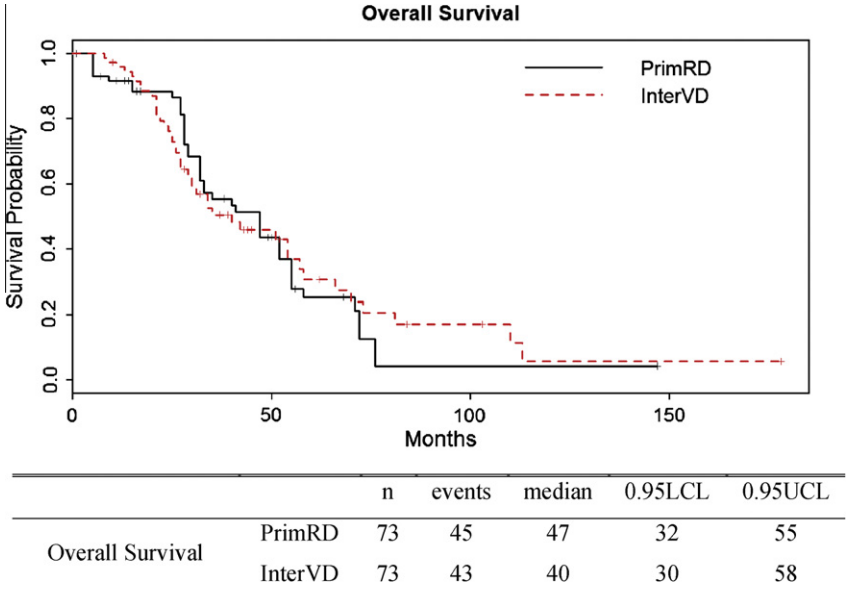
Unfortunately, in the majority of centres, the goal of optimal cytoreduction during primary debulking can be achieved only in 40–60% of cases, except for a few reports with primary optimal cytoreductive rates reaching up to 98.8%,[15–17] The latter high rates were attributed to the surgeon's skills and the recent introduction of more radical techniques for extirpation of

Table 3 – Multivariable analysis for the overall survival before and after the propensity score matching.

Variable	Hazard ratio	95% confidence interval (CI)	*p* value	Hazard ratio	95% CI	*p* value
Diameter of metastatic tumour	1.03	1.01–1.063	0.002	1.03	1.00–1.05	0.023
Diameter of residual tumour						
No versus >0 cm	2.28	1.16–4.49	0.016	3.48	2.18–5.57	<0.001
0–1 versus >1 cm	1.86	0.68–5.19	0.212	1.26	0.54–2.95	0.590
Histology						
Serous versus mucinous	4.72	1.45–15.41	0.003	4.96	0.99–24.90	0.110
Serous versus endometrioid	1.05	0.13–8.38				
Serous versus clear cell	6.18	1.87–20.36				
Serous versus undiferrentiated	2.98	0.91–9.73		2.60	0.19–35.2	

Table 4 – Multivariate analysis for disease free survival before and after the propensity score matching.

Variable	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Diameter of metastatic tumour	1.01	0.99–1.02	0.362	1.02	0.99–1.05	0.055
Diameter of residual tumour						
No versus >0 cm	1.66	0.90–3.05	0.099	2.83	1.60–5.01	<0.001
0–1 versus >1 cm	2.38	0.86–6.54	0.088	3.81	2.24–6.49	<0.001
Tumour grade			0.061			0.42
Grade 1 versus 2	2.60	0.87–7.81		2.04	0.62–6.65	
Grade 1 versus 3	3.25	1.17–8.98		1.64	0.55–4.88	
Type of diaphragmatic metastases papillary versus plaques	1.42	0.97–2.07	0.064	1.16	0.79–1.70	0.44

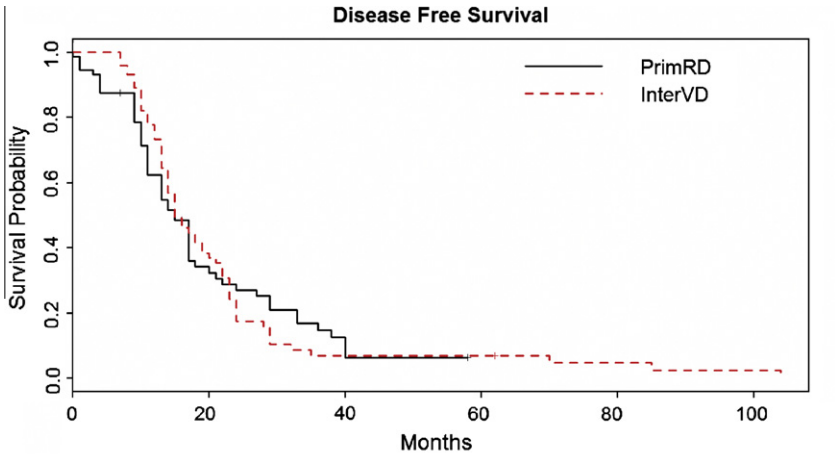


		n	events	median	0.95LCL	0.95UCL
Overall Survival	PrimRD	73	45	47	32	55
	InterVD	73	43	40	30	58

Fig. 1a – Kaplan–Meier overall survival curves.

metastatic disease in the upper abdomen.[18] Neoadjuvant chemotherapy has emerged in the last years as an alternative approach in order to improve cytoreductive outcome and survival rates associated with lower morbidity, there is no consensus for criteria for patients' selection for primary debulking or upfront neoadjuvant chemotherapy.[19]

Diaphragmatic dissemination has been reported in 42% of patients with tumour confined exclusively in the pelvic cavity and in 71% of those with bulky metastases extending beyond the pelvic brim,[20] and was reported as the second anatomic site that refrained 76.3% of gynaecologist oncologists from optimal cytoreduction.[5] In our centre, diaphragmatic involvement was



		n	events	median	0.95LCL	0.95UCL
Disease Free	PrimRD	73	57	15	13	18
Survival	InterVD	73	64	15	14	21

Fig. 1b – Kaplan–Meier disease free survival curves.

not a contraindication for primary cytoreduction surgery during the study period resulting in optimal cytoreductive rates over 90% either at the primary, or at the interval debulking group with diaphragm metastases comparable with those of other centres.[21,22]

In our patient population with diaphragm metastases, the median survival was 52 months in primary debulking group and 35 months in the interval debulking group. However, as prognostic factors were different between both groups, we also analysed survival after adjusting for baseline characteristics resulting in survival rates of 47 and 40 months, respectively. Despite the high rates of optimal cytoreduction, the survival rates of the current study were shorter than the 53% 5-year survival reported by Aletti[21] in 181 patients with stages III and IV and diaphragm disease, or the 59 months median survival reported by Dowdy and colleagues in 37 patients who underwent primary debulking with diaphragmatic peritonectomy,[22] or the 50 months median survival reported by Cliby and colleagues, in 30 patients with recurrent diaphragm disease.[1] Differences in the study period, the patients' characteristics, tumour extension, the applied type of diaphragmatic surgery, the type and cycles of chemotherapies might be the reasons of the aforementioned difference in the survival rates. Furthermore, the current series of diaphragmatic surgery during interval debulking are the first published series focusing on survival and associated complications that make impossible to make any comparison with other studies referred exclusively to this subgroup of patients.

Multivariate analysis revealed that the maximum diameter of metastatic tumour before debulking ($p = 0.023$) and the size of residual disease were independent prognostic factors for overall survival ($p < 0.001$) before and after the propensity score matching. The strong survival benefit of no residual disease versus less than 1 cm is demonstrated. These data are in accordance with other previous reports which emphasised the importance of complete debulking (no visible residual disease) compared to debulking to residual disease <1 cm)[17,21,23,24] or the size of the largest metastasis before cytoreduction.[4,25] In the current study plaque-like diaphragmatic lesions were more frequently associated with diaphragm relapse than papillary lesions. On the contrary, there was no difference in recurrence depending on the used technique (coagulation or resection). Some investigators related the dimensions of diaphragmatic tumours with the depth of invasion, suggesting that a diameter less than 4 cm rarely invades through the muscle.[26] Plaque-like diaphragmatic lesions, which are usually thick (>3–4 mm) and large (>4 cm), might invade the diaphragm muscle more often than papillary lesions. On multivariate analysis for the type of diaphragmatic surgery (excision versus coagulation) we found that the types of diaphragmatic lesions (papillary lesions versus plaques) were the only independent factor that influenced our decision regarding the type of diaphragmatic surgery.

Post-operative severe (grades 3 and 4 NCI-CTG v.2: symptomatic requiring thoracocentesis, chest tube or intubation) pleural effusions were predominantly observed after primary (47.1%) diaphragmatic resection compared with (4.0%) after interval debulking. We routinely placed chest tubes intra-operatively under direct visualisation when large diaphragmatic defects were present. The drain was removed after the fifth post-operative day or later depending on the results of serial chest X-rays. The incidence of chest tube drainage and thoracocentesis was also higher at primary surgery (29% versus 14%, respectively). This could be attributed to the higher rates of diaphragm stripping or resection at primary debulking or the more frequent occurrence of ascites at primary surgery. Our results concur with that of other reports.[22,27] In addition, in a multivariate analysis, Dowdy et al. found that entry in the pleural cavity was a significant predictor for the development of post-operative pleural effusions. Finally, operative time, blood loss, post-operative hospitalisation in the intensive care unit and length of hospitalisation were significantly higher after primary debulking. This could be attributed to the more frequent application of diaphragmatic stripping/resection,

bowel resection, lymphadenectomy and splenectomy in the primary debulking group. This is in concordance with the findings of the EORTC-NCIC-randomized study and retrospective-published studies.[3,28] According to the EORTC-NCIC study, neoadjuvant chemotherapy and interval debulking surgery resulted in similar overall and disease-free survival compared with primary debulking in a group of patients with very advanced Stage IIIc or IV ovarian carcinoma.[3]

The limitations of the current study are the non-randomized comparison of diaphragmatic surgery at primary and interval debulking surgery, although we made efforts to minimise selection bias and other confounders by using in our analysis the propensity score matching procedure. The strengths are of the large number of patients treated and the fact that all patients were selected with the same criteria and were operated by two senior surgeons. To the best of our knowledge, there are no other retrospective or prospective studies comparing diaphragmatic surgery at primary or interval debulking surgery. In conclusion, this study showed dissemination of ovarian cancer on diaphragm should not be considered as an obstacle to achieve complete cytoreduction. Diaphragmatic surgery consisting of coagulation, stripping of diaphragmatic peritoneum with or without resection of muscle is feasible and is associated with an acceptable morbidity both at primary and at interval debulking surgery.

Conflict of interest statement

None declared.

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