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Diaphragmatic peritonectomy vs. full thickness resection with pleurectomy during Visceral-Peritoneal Debulking (VPD) in 100 consecutive patients with stage IIIC–IV ovarian cancer: A surgical-histological analysis

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HIGHLIGHTS

- Ovarian cancer involves the muscle in 28% and the pleura in 19.4% of the patients
- No significant difference was found between peritonectomy and pleurectomy
- Pleural involvement should not discourage a complete resection

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ABSTRACT

Objective. To compare the surgical and histological outcomes of diaphragmatic peritonectomy vs. full thickness resection with pleurectomy during Visceral-Peritoneal Debulking.

Methods. Service evaluation protocol (Trust number 3265). All patients with stage IIIC–IV ovarian cancer who had diaphragmatic surgery between April 2009 and November 2013 were included. Clinical notes and histology reports were reviewed. Additional histology sections were undertaken. Patients were divided in Groups 1 (peritonectomy) and 2 (pleurectomy). The outcomes of interest were: surgical (intra- and post-operative morbidity, pulmonary morbidity, mortality, rate of complete resection) and histological (rate of diaphragmatic peritoneum, muscle and pleural involvement, rate of microscopic diaphragmatic free margins).

Results. Sixty four patients had diaphragmatic peritonectomy (Group 1), 36 patients full thickness diaphragmatic resection with pleurectomy (Group 2). There was no significant difference in the rate of mortality (3% in both groups), overall intra- and post-operative morbidity (32.8% vs. 38.8%), pulmonary morbidity (9.3% vs. 19%, $P = 0.14$). Histology showed tumor invasion in the diaphragmatic peritoneum (96%), muscle (28%) and pleura (19.4%). Microscopic free margins were seen in 86% vs. 92% in Groups 1 and 2.

Conclusions. Our study demonstrated that, in patients with ovarian cancer, diaphragmatic involvement extends to the muscle in almost 30% and to the pleura in 20% of the patients. Overall and specific morbidity was not significantly different when comparing peritonectomy vs. pleurectomy.

1. Introduction

Ovarian cancer is an aggressive disease. It is estimated that 200,000 women are diagnosed globally every year, with approximately 7000 new cases being diagnosed in the UK during 2010 [1–2]. Most cases present with disease spread to the entire abdomen, largely due to a poor screening system and the late onset of symptoms. The standard of treatment is the combination of surgery and chemotherapy. Many studies have proven that the residual disease following surgery is the strongest independent prognostic factor. In addition, a complete resection (CR) of all visible disease strongly correlates with best survival rates [3–12]. To achieve the highest rate of CR, gynecological oncologists are commonly performing upper abdominal surgery [13–14]. Involvement of the diaphragm in patients with stage III–IV ovarian cancer is common, with an estimated incidence of 40–91% [15–18]. Computerized Tomography (CT) scan is considered the standard pre-operative test to stage

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patients with ovarian cancer. However no specific radiologic features have been described to recognize the presence of tumor implants on the diaphragm and/or the pleura. Recently a few groups have suggested the use of thoracoscopy to identify the presence of pleural disease. Diaphragmatic surgery in the context of ovarian cancer debulking was described two decades ago [19–21]. The current literature suggests that diaphragmatic surgery enhances CR rates and the inability to perform these procedures often represents the sole limit to a CR [22–25]. Most commonly diaphragmatic surgery is limited to the stripping of the peritoneum. Sometimes, depending on extent of the disease, it may involve full thickness resection of the muscle with access to pleural cavity. Allegedly, entering the pleural cavity increases the morbidity of the procedure [26–28]. In this study we compare the surgical morbidity of patients who underwent diaphragmatic peritonectomy to patients who had a full-thickness resection of the diaphragm with pleura. Since there are no clear diagnostic tests and no data on the depth of diaphragmatic disease, we specifically analyzed the histological involvement by layers.

2. Methods

The study was a service evaluation project and obtained Trust approval (number 3265). The study group included all patients with FIGO stage IIIC–IV epithelial ovarian cancer who had diaphragmatic surgery during Visceral Peritoneal Debulking (VPD) at the Oxford University Hospital between April 2009 and November 2013. The pre-operative inclusion and exclusion criteria, the surgical technique and the goal of VPD have been previously reported [29]. Briefly, VPD was undertaken only if a CR was deemed suitable. To rule out the presence of disease precluding a CR, an exploratory laparoscopy (Karl Storz, Tuttlingen, Germany) always preceded a xifo-pubic laparotomy. Presence of diaphragmatic disease was suggested by CT scan and confirmed by exploratory laparoscopy. The surgical intention was to perform a peritonectomy. However, all patients also consented to a full thickness resection. The final decision was based on the direct inspection, palpation and dissection of the lesion at time of surgery. If no cleavage plane was found, if the peritonectomy left tumor behind or if disease was seen on the pleura once opened, a full thickness resection with pleurectomy was performed. Our surgical technique only supports resection of cancer, no coagulation or ablation. In patients with pleurectomy, the pleural space was examined to see if additional lesions had to be resected. We used a 0 PDS running suture to reconstruct the pleura and a mesh was utilized only if the diaphragmatic ends were under tension when suturing. To decrease the risk of pneumothorax the anesthetist manually ventilated the patient and a 10 Ch. Foley catheter was placed in the pleura. The aim was by Valsava maneuver and by suction through the Foley catheter which was removed at time of last stich. No chest drain was electively placed. Post-operatively all patients had serial chest x-rays to verify the absence of pneumothorax. We identified 100 consecutive patients from our prospectively maintained Ovarian Cancer data-base who had either diaphragmatic peritonectomy, full thickness resection with pleura or both and whose histology slides and block were available. Based on the type of surgery, patients were divided into Group 1 (diaphragmatic peritonectomy) and Group 2 (diaphragmatic full thickness resection with pleurectomy). We also divided the patients in group A (up-front surgery) and group B (neo-adjuvant chemotherapy). The endpoints of this study were: 1. compare the surgical morbidity and mortality of Group 1 vs. 2; 2. assess the depth of histological involvement in the diaphragm layers (peritoneum, muscle, pleura). For the latter purpose, our dedicated Gynaecologic Oncology Pathologist (SM) performed additional sections of the specimens. We also aimed at detecting the presence of muscular tissue and eventually tumor involvement in the specimens of patients in Group 1 who are meant to have peritoneum only. Solely for the histological assessment of the muscular layer we had to exclude from the analysis patients in Group 1 who had no muscular tissue present in the specimen. Although it was not the primary endpoint of this surgical-histological study, we included survival outcomes for all patients. The data were analyzed using the chi-square test or Fisher's exact test for categorical variables, and the Student's t-test for continuous variables. Survival outcomes were measured with the Kaplan-Meier method and compared with the Mantel-Cox test. A P value of 0.05 or < was considered statistically significant.

3. Results

A flowchart of the patients in this study is reported in Fig. 1. Patient demographics, tumor characteristics and surgical details are shown in Table 1. Sixty four patients were in Group 1 and 36 in Group 2. There were no statistically significant differences between the two groups with regards to age, treatment type and histology. Forty three patients were in group A and 57 in group B. In group A, significantly more patients had peritonectomy than pleurectomy (74.4% vs. 25.6%, P = 0.012). Double the patients had pleurectomy in group B than group A, but the difference only approached statistical significance (group B 70% vs. group A 30%, P = 0.061). However, we did find that patients with stage IV disease were more likely to have pleurectomy (P = 0.03). The extent of surgical intervention was similar between the

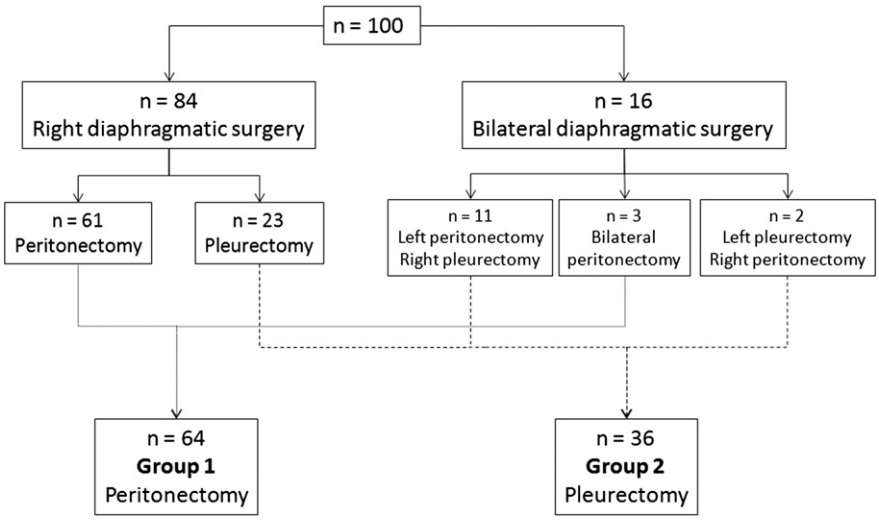

Fig. 1. Flowchart of 100 patients with diaphragmatic surgery during VPD.

Table 1
Patients, tumor characteristics and surgical details.

	Group 1 n = 64	**Group 2 n = 36**	P -value
Age, median (range)	63 (23-84)	64 (22 -77)	P =0.35
FIGO Stage			
IIIC	54 (84%)	23 (64%)	
IV	10 (16%)	13 (36%)	P =0.03
Treatment Type*			
Group A (up-front surgery, n=43)	32 (50%) *(74.4%)*	11 (30%) *(25.6%)*	*P=0.012*
Group B (interval surgery, n=57)	32 (50%) *(56.1%)*	25 (70%) *(43.8%)*	*P =0.09*
	P=0.202	P=0.061	
Histology			
Serous	55	30	
Endometrioid	5	3	P=0.76
Mucinous	3	1	
Clear cell	1	2	
Surgical details	**Group 1 n = 64**	**Group 2 n = 36**	P -value
CR, n (rate)	56 (87.5%)	33 (92%)	*P = 0.26*
Large bowel resection	33 (51.5%)	25 (69.4%)	*P = 0.08*
Small bowel resection	8 (12.5%)	3 (8.3%)	*P = 0.63*
Anastomosis	30 (46.8%)	23 (63.8%)	*P = 0.10*
Hepatic resection	8 (12.5%)	7 (19.4%)	*P = 0.35*
Splenectomy	4 (6.2%)	14 (38.8%)	*P = 0.05*
Cholecystectomy	3 (4.6%)	1 (1.5%)	*P =0.63*
Mean duration of surgery (minutes)	425 (200 – 875)	457 (210 -780)	*P =0.19*
Mean intra-operative blood loss (ml)	599 (100 – 2800)	743 (200 – 2000)	*P = 0.01*
Mean hospital stay (days)	12.4 (6 – 91)	11.3 (6 – 32)	*P =0.71*

*Data in red and italics represent comparison of Group A vs. B.

groups, except for a greater number of splenectomies in Group 2 (P = 0.05) All patients had a CR. As reported in Table 1, surgical outcomes were not statistically different other than the mean intra-operative blood loss (599 ml Group 1 vs. 743 ml Group 2, P = 0.01). Overall 4 patients experienced intra-operative complications. One occurred in Group 1, where the patient became hypotensive and developed an unexplained high lactate necessitating premature reversal of anesthesia and recovery in ITU. Eventually she recovered smoothly and had uneventful surgery later on with diaphragmatic surgery. The other three occurred in Group 2. Two patients had vascular injury: one right hepatic vein at the inset in the IVC and one had an injury of the supra-hepatic portion of IVC. The hemorrhage was stopped by digital pressure. Both injuries were immediately exposed over vascular clamps and repaired with running 5–0 Prolene sutures. The vessel damages were <5 mm and the blood loss was minimal as a result of good exposure and the prompt clamping. The last patient had a dehiscence of the pleural repair after a large pleurectomy, with prolapse of the liver in the chest. Although the complication occurred 3 days after the surgery, we identified the cause of the complication and classified it as intra-operative. The patient returned to theater and the diaphragm was fixed. At that time it was clear that a 2–0 PDS had been incorrectly used, rather than the usual 0 PDS suture. The patient recovered after 12 days in ITU and 7 days on the ward. Overall morbidity was not significantly different between the 2 groups (32.8% vs. 38.8%, P = 0.54). Of note, only 6% of the patients in Group 1 and 11% in Group 2 (P = 0.38) experienced grade 3b or > morbidity. Mortality rate was 3% in each group. Table 2 shows the most significant complications associated to this type of surgery.

Table 2
Grade III–IV surgical morbidity (Clavien–Dindo classification).

Type of complication	Group 1 n = 64	Group 2 n = 36	P-value
Pulmonary morbidity	6 (9.3%)	7 (19%)	P = 0.14
Post-operative pleural effusion	4 (6%)	4 (11%)	P = 0.38
Pneumothorax	1 (1.5%)	2 (5.5%)	P = 0.26
Lobar collapse	0	1 (2.7%)	P = 0.18
Thromboembolism	1 (1.5%)	0	P = 0.45
Non-pulmonary morbidity	4 (6%)	4 (11%)	P = 0.38
Anastomotic leak with digestive fistula	1	1	P = 0.67
Ureteric fistula	1	1	P = 0.67
Sepsis	1	1	P = 0.67
Wound dehiscence	1	1	P = 0.67

Pulmonary morbidity occurred in 9.3% of Group 1 and in 19% of Group 2 patients (P = 0.14). Rate of post-operative pleural effusions and pneumothorax were not significantly different. All pulmonary complications were treated conservatively and settled before discharge. The return to theater rate in Group 1 was 6% vs. 14% in Group 2 (P = 0.2). Depth of involvement and microscopic status of the margins are reported in Table 3. All patients had diaphragmatic surgery based on CT scan and macroscopic inspection of the peritoneal surface at laparoscopy and confirmed at laparotomy. Despite such careful protocol, overall 4% of our patients had no disease found in the final specimen of the diaphragmatic peritoneum. Surprisingly, one out of these 4 patients, in Group 2, had no disease on the peritoneum but had diffuse microscopic disease on the pleural side. All remaining 96 patients had disease confirmed on the peritoneum. When examining the presence of muscular tissue in the final specimen, 7 patients in Group 1 were excluded due to the absence of any muscle, leaving 57 patients for analysis. In Group 2, as expected, muscular tissue was present in all specimens at histology and harbored disease in 47%. In Group 1, 11 specimens out of 57 (19.2%) showed disease present in the muscle. This difference resulted statistically significant (P = 0.008). The analysis of pleural involvement only included specimens from patients in Group 2 and showed disease present in one fifth of the patients. Remarkably, only 4 of the patients with pleural involvement at histology also showed grossly visible disease on the pleura at time of surgery. No significant difference was found in the rate of microscopic disease free margins (86% in Group 1 vs. 92% in Group 2). Finally, the sizes of the specimens were plotted against the rate of involvement to investigate if the size would increase the detection rate. According to Fig. 2, the size of the peritonectomy specimen significantly correlated with the presence of disease. To the contrary, no significant correlation was found with the pleurectomy specimens. Survival outcomes are reported through Kaplan-Meier curves in Fig. 3. At

Table 3
Histological analysis of diaphragmatic specimens: depth of involvement by layers and status of microscopic margins.

	Group 1 n = 64	Group 2 n = 36	Specimens n = 100	P value
Specimen size, mm, mean (range)	123 (55–280)	128 (50–240)	100	P = 0.808
Peritoneum				
Disease	61 (95.3%)	35 (97.2%)	96	P = 0.54
No disease	3 (4.7%)	1 (2.8%)	4	
Muscle				
Disease	11 (19.2%)	17 (47%)	28	P = 0.008
No disease	46 (80.8%)	19 (53%)	65	
No muscle present	7	0	7	
Pleura				
Disease	n/a	7 (19.4%)	7	n/a
No disease	n/a	29 (80.6%)	29	
Status of margins				
All negative	55 (86%)	33 (92%)	88	
At least one positive	6 (9%)	3 (8%)	9	
No disease seen	3 (5%)	0	3	

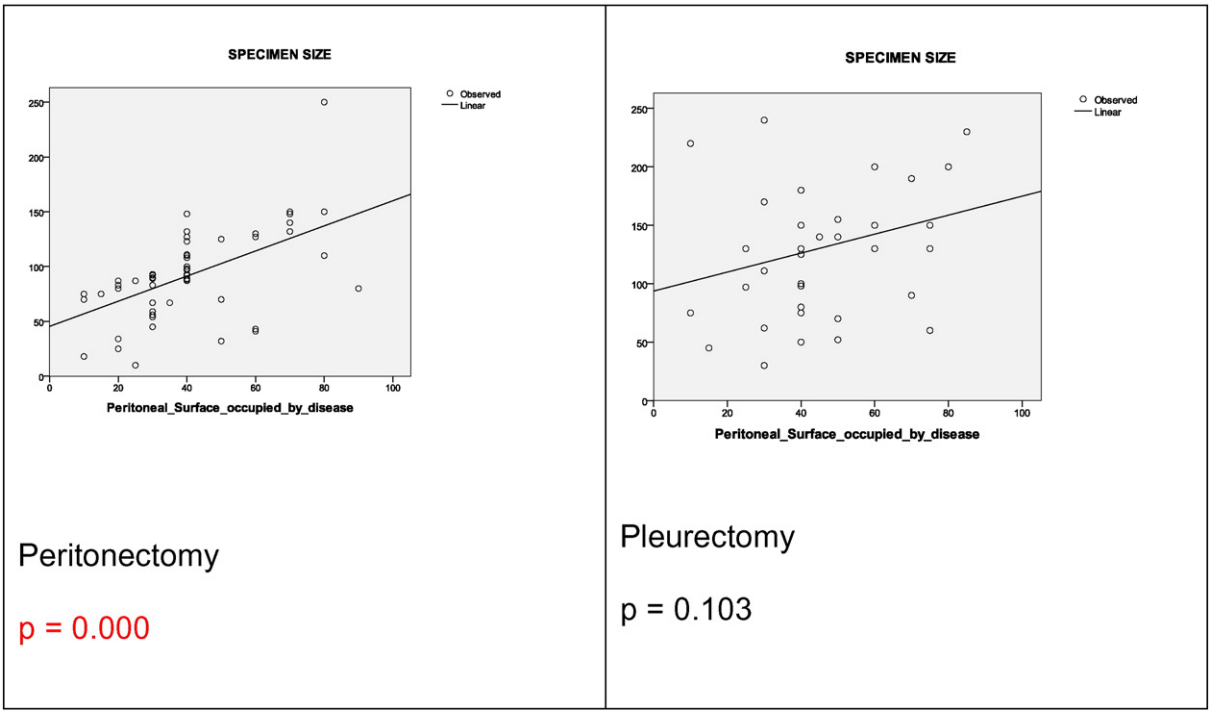

Fig. 2. Correlation between the maximum size of the specimen and the percentage of peritoneal surface involved by disease.

35 months median follow-up no significant difference was found with regards to overall survival (51% Group 1 vs. 48% Group 2).

4. Discussion

Traditionally there has been a perception that accessing the pleural cavity at time of abdominal surgery is per se associated to higher perioperative morbidity [30,31]. The results of this study fail to show a significant difference in the surgical morbidity of diaphragmatic peritonectomy and full thickness resection with pleurectomy. The absence of a significant difference in morbidity supports the surgeon aiming at CR of ovarian cancer even when this means accessing the pleural cavity. Despite similar complexity of surgery, intraoperative blood loss was significantly higher in Group 2 ($P = 0.01$). We attribute this finding to the higher rate of patients in Group 2 who had VPD after neo-adjuvant chemotherapy, which, in our opinion, makes tissue planes less amenable for resection. Patients with stage IV, irrespective if they had positive pleural cytology or parenchymal disease, were more likely to require pleurectomy than patients with stage IIIC ($P = 0.03$). We also found that splenectomy was more likely in the pleurectomy group ($P = 0.05$), probably because more patients in this group (36%) had concomitantly left diaphragmatic surgery and possibly more disease on that side. The rate of pneumothorax and pleural effusion in our study is lower than any other study published so far [6,32] and was not affected by the access to the pleural cavity in Group 2. Of note, the study protocol included regular post-operative chest radiographies for all patients in the study irrespective of symptoms. So it provides a true estimate of the rate of pleural effusion and pneumothorax. The meticulous closure of the pleura combining maximal lung expansion with negative pressure in the pleura is probably the key factor to avoid pneumothorax. With regards to the pleural effusion we are completing a review on the risk factors of complication after diaphragmatic surgery. Provisional analysis shows an interesting correlation with the presence of disease on the pleural side and the status of the margins at histology. Similarly our data show that a chest drain was not required in most patients [33]. The histological analysis confirmed the presence of disease in 95% in Group 1 and 97% in Group 2. When assessing the extent of disease by layers, the peritoneum was involved in 96% of all patients, the muscle in 30% of the patients who had muscle in the specimen and the pleura in 19.4% of patients in Group 2. Our results indicate that, overall, in 35% of the patients with diaphragmatic disease, the invasion breaches the peritoneum and involves the muscle and/or the pleura. In these patients performing the peritonectomy alone is likely to leave disease behind, mainly in the muscle. In Group 2, 80% of the patients had no disease found on the pleura, but 66% of them had disease in the muscle or the pleura. We found that the larger the peritonectomy specimen, the more extensive the peritoneal involvement by tumor. The latter was not true of pleurectomy specimens which showed no correlation. Despite a high rate of muscle invasion we found no significant difference in the rate of microscopic margins involvement between the 2 groups, which was overall high (90.7%). There was no difference in term of survival outcomes between the two groups, probably a reflection of the high rate of CR (100%). No data are present in the literature on the involvement of the peritoneum, muscle and pleura. Hence no standard test is available to pre-operatively identify depth of involvement. It is therefore important to know that a peritonectomy alone would have left disease behind in 1/3 of our patients due to the involvement of the muscle or the pleura. Another novel finding is that half of the patients with pleural involvement at histology had no visible disease at surgery. The implication is that a pre-operative thoracoscopy, as suggested by other groups [34], could be unsuitable to identify pleural disease. The method we use to triage patients for pleurectomy based on the intra-operative surgical findings, is not accurate enough. In fact 18 patients in Group 2 (50%) only had peritoneal involvement and underwent full thickness resection because a dissection plane was not found at surgery. Twelve patients out of these 18 (66.6%) were in group B, supporting the concept that neo-adjuvant chemotherapy makes tissue dissection more challenging and may disguise the presence of disease [29]. This study reports the results of a prospective collected data base. The consecutiveness of the patients, the consistency of the protocol and the use of the same surgical technique in both groups should protect the study from major biases. However the retrospective nature of the study and the lack of a randomization may limit the results. In 2001, diaphragmatic metastasis prevented 81% of the

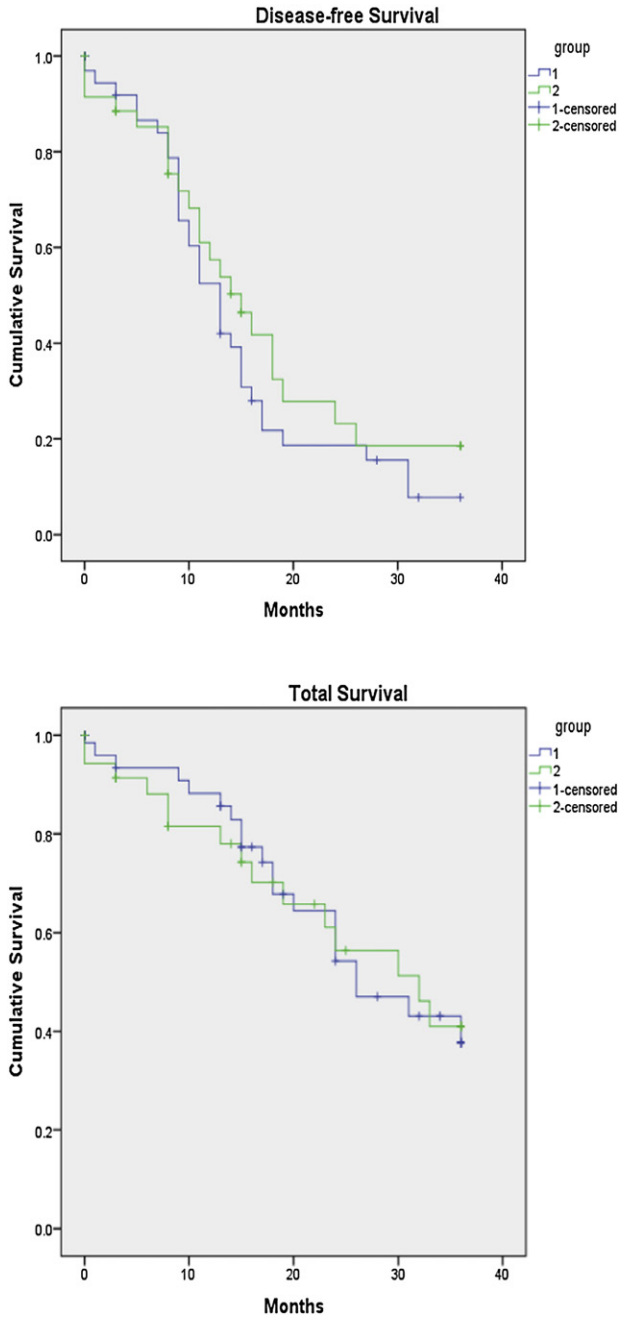

Fig. 3. Kaplan Meier survival curves Groups 1 and 2.

SGO members from achieving a CR in patients with ovarian cancer [35]. Since that review, many papers have published on the technique of diaphragmatic peritonectomy and full thickness resection, showing an increase in the rate of CR [28–29,36–37]. Few papers also reported an impact on disease free and overall survival [23,30,38]. What remains to be defined is to how to select patients who require pleural resection. In one third of our study group, the peritonectomy would have failed to achieve a CR leaving microscopic disease in the muscle or the pleura. Usually the aim of debulking surgery is to remove all visible disease. So it is unclear whether microscopic residual disease holds any impact on the survival outcomes. To other end of the spectrum, 50% of patients who had pleurectomy had no disease beyond the peritoneum. The findings of similar morbidity between the 2 techniques should not stop the investigators from improving the selection process. At this stage all surgeons attempting at CR of patients with known diaphragmatic disease have to be familial with both techniques and the potential complications. With this respect an exploratory laparoscopy is very useful in identifying the presence and extent of diaphragmatic disease.

Contribution to authorship

HS: Assisted with surgery, data collection, performed data analysis and wrote the manuscript.

FF: Assisted with surgery, data collection, performed data analysis and helped write the manuscript.

SM: Reviewed the slides, performed additional sections and provided all histological information.

KG: Assisted with surgery, data collection, helped perform data analysis.

RGC: Assisted with surgery, data collection, helped perform data analysis.

RT: Designed the project, performed the surgery, supervised the analysis and wrote the manuscript.

Details of ethics approval

Service evaluation protocol was approved by the Oxford University Hospital (OUH) Trust (number 3265).

Conflict of interest

There is no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2015.12.004.

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