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The impact of splenectomy and diaphragmatic surgeryon perioperative morbidity and overall survival of ovarian cancer patients

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ABSTRACT

Objectives: The prognosis of ovarian cancer (OC), among other factors, depends on residual disease after primary debulking surgery (PDS) and initial disease advancement. The main aim of our study was to evaluate the survival benefits of splenectomy and diaphragmatic surgery in OC patients, when the procedures result in resection to no macroscopic residual disease or minimal residual disease [tumor nodules below 2.5 mm according to Sugarbaker's completeness of cytoreduction score (CC) = 1].

Material and methods: The study included 25 OC patients after splenectomy procedures, 28 patients after diaphragmatic surgery and 17 patients who had undergone both splenectomy and diaphragmatic surgery. Patients' overall survival (OS) was compared with residual disease-matched controls (47 patients) who had upper abdomen involvement but no requirement for splenectomy and/or diaphragmatic surgery.

Results: Overall survival of patients after splenectomy was not significantly different from OS of patients who did not required splenectomy (36.1 vs 31.6 months; p = 0.85). No differences in OS were observed between patients who did and did not require diaphragmatic surgery (31.3 vs 41.8; p = 0.33). Similarly, we found no differences in OS between patients who underwent both splenectomy and diaphragmatic surgery and those patients who did not require either procedure (20.1 vs 31.6 months; p = 0.45). Splenectomies and diaphragmatic surgeries were associated with prolonged hospitalization and length of surgery, however, no specific morbidity related to the procedures was observed.

Conclusions: In the cases of advanced OC, diaphragm and spleen involvement do not hamper patient prognosis when adequately resected.

Key words: ovarian cancer surgery; splenectomy; diaphragmatic surgery; cytoreductive surgery; debulking surgery

INTRODUCTION

Ovarian cancer (OC) is the seventh most common cancer worldwide. It is estimated that almost 250,000 patients are diagnosed with ovarian cancer every year and that approximately 45% of cases have a five-year survival rate [1, 2]. Ovarian cancer is often asymptomatic to begin with, therefore most cases are already advanced at diagnosis [3]. Among all newly diagnosed OC cases, it is estimated that only 20–30% are early stage compared with 70% at stages III and IV [4].

Treatment of advanced OC is based on a combination of surgery and chemotherapy. The most important goal of surgical treatment in advanced ovarian cancer is complete resection (*i.e.*, no macroscopic residual disease) or when this is not possible, "optimal cytoreduction" of the tumor (*i.e.*, residual tumors less than 1 cm in diameter) [4]. The surgical goal of OC treatment should be achieved during primary debulking surgery (PDS) or during

interval debulking surgery (IDS) following neoadjuvant chemotherapy (NACT) [5]. Patients following PDS or IDS without macroscopic residual disease have been shown to have longer progression-free survival (PFS) and overall survival (OS) compared with those with sub-optimal cytoreduction [6].

Advanced OC affects the organs of the upper abdomen. Upper abdominal involvement is generally considered indicative of aggressive tumor biology [7]. Moreover, disease in the upper abdomen is often unresectable, although many patients can achievecomplete cytoreduction when procedures such as splenectomy or diaphragmatic stripping are performed [8]. However, OC prognosis is also related to how advanced the cancer was prior to these procedures. A recent study by Horowitz et al. [9], has shown that even when complete or optimal cytoreduction is achieved, a high initial disease burden results in a worse prognosis. These results suggest that the more advanced the disease, the less benefit there is from surgery. However, more aggressive surgery may be warranted if it results in no residual disease following surgery [9, 10].Although patients with OC have improved survival rates following ultra-radical surgery, studies also show that extensive surgical treatment may be associated with postoperative complications [10–12].

Objectives

The aim of our retrospective analysis was to evaluate the survival benefits of splenectomies and/or diaphragmatic stripping in OC patients, when these procedures result in either complete or “optimal” resection.

MATERIAL AND METHODS

We performed a retrospective analysis of patients who underwent PDS due to primary OC surgery for advanced ovarian cancer in the Clinical Division of Gynecological Oncology of the Franciszek Lukaszczyk Oncological Center in Bydgoszcz, Poland, between 2013 and 2017. Excluded were patients who were operated on for borderline tumors, those who had neoadjuvant chemotherapy, and thosewho had surgery due to recurring disease. We included only those patients who were diagnosed with advanced (at least IIIA) OC who had undergone PDS that resulted in either no gross residual disease (CC = 0 score) or minimal disease (CC = 1 score; tumor nodules below 2.5 mm after surgery) measured according to Sugarbaker’s completeness of cytoreduction (CC) surgery scoring [13].

All the patients had undergone longitudinal laparotomy extending from the xiphoid process to the pubic bone. Patients had undergone either bilateral/unilateral salpingoophorectomy and pelvic peritonectomy with retroperitoneal hysterectomy, or, in cases of a previous hysterectomy, vaginal vault resection. Additionally, a total omentectomy had been performed. Appendectomy was performed in cases of tumor infiltration or where there was suspicion of the mucinous type of ovarian cancer. Lymphadenectomy had always been performed in cases where enlarged or suspicious lymph nodes were found. In cases where the lymph nodes were unchanged, the primary surgeon had decided whether to perform lymphadenectomy. The resection of other organs was performed when necessary, depending on the degree of tumor infiltration, in order to remove all macroscopic lesions. In cases of diaphragmatic surgery, either diaphragmatic stripping (the removal of the diaphragmatic and upper abdomen peritoneum without full thickness resection of the diaphragm) or diaphragmatic resection (the removal of the diaphragmatic and upper abdomen peritoneum with full thickness resection of the diaphragm) were performed.

All surgeries were performed by accredited gynecological oncologists (in most cases, L.W.). In all cases, preoperative bowel preparation with mechanical bowel and preoperative enema was performed. All patients received an intravenous antibiotic prophylaxis composed of first-generation cephalosporin and metronidazole. Perioperative gentamicin was administered when bowel surgery was performed. Most patients who underwent extensive surgery received postoperative parenteral nutrition. The administration of transfusions of red blood cell concentrates (RCC) depended on each patient’s clinical performance; however, the majority of patients whose postoperative hemoglobin concentration was below 8 d/dL received RCC. Following surgery, patients were scheduled for first-line chemotherapy consisting of intravenous carboplatin and paclitaxel. Anti-angiogenic treatment composed of bevacizumab was administered only for patients with suboptimal debulking (residual tumors > 1 cm), therefore, patients meeting our study’s inclusion criteria had not been treated with bevacizumab.

To compare the effects of splenectomy and diaphragmatic surgery on patient survival, the total study cohort was divided, by identifyingboth those who had, and those who had not undergone one or other of the above-mentionedprocedures, as well as those who had undergone both. Meaning, we identified three study groups and three respective control groups; and we analyzed patient outcomes in the following manner: study group 1: patients who had splenectomies; control group 1: patients who had not undergone splenectomies;

study group 2: patients who had undergone diaphragmatic surgery; control group 2: patients who had not undergone diaphragmatic surgery; study group 3: patients who had undergone both splenectomy and diaphragmatic surgery; control group 3: patients who had not undergone either splenectomy or diaphragmatic surgery.

Final histopathological diagnosis was undertaken on all the tumors removed during surgeries, and each tumor was classified according to the World Health Organization Classification of Tumors (WHO). Disease stages were assessed according to the 2014 International Federation of Gynecology and Obstetrics (FIGO) classification system. Cases that had been treated prior to 2014 were reclassified using FIGO's 2014 classifications.

The following variables were compared between the study and control groups: patient age, disease stage, rate of bowel resections, residual disease, proportion of high grade serous ovarian cancer, length of surgery and length of hospital stay, surgery complexity score according to Aletti et al. [14], the rate of serious adverse events (grade 3 or more according to the Clavien-Dindo classification [2]), the median number of RBC concentrates transfused, and the median overall survival (mOS) [14, 15].

The Mann-Whitney test was used to compare the groups studied with respect to ordinal data. Nominal data comparisons between the groups were made using the Fisher-exact test. The Freeman-Halton extension was used for 3 × 2 and 4 × 2 contingence tables. Information on any patients who died was retrieved from the database of the National Health System of Poland. Survival analyses were conducted using the Kaplan-Meier survival curves and differences in patients'median overall survival (mOS) were compared using the log-rank test.

RESULTS

Patient characteristics

We identified 83 patients who met the study's inclusion criteria. Of these patients, 28 had undergone diaphragmatic-surgery, 25 had undergone splenectomies,17 had undergone both diaphragmatic stripping and splenectomies, and 47 had undergone neither splenectomy nor diaphragmatic stripping/resection.

There were no differences in the distribution of patient ages and disease stages between the analyzed groups of patients (Tab. 1.) The groups were similar to each other in the

rate of bowel resections and proportion of high-grade serous carcinomas (Tab. 1). We found no difference in the rates of no gross residual disease between patients who had undergone and had not undergone splenectomies. On the other hand, the patients who required diaphragmatic stripping or diaphragmatic stripping and splenectomy revealed lower rates of no gross residual disease when compared to their respective control groups (Tab. 1). For patients who underwent splenectomy or diaphragmatic stripping, the duration of surgery and length of hospital stay were significantly longer when compared to patients who had neither of the above-mentioned surgical procedures (Tab. 1). Similarly, when splenectomy or diaphragmatic stripping were performed, the procedure resulted in higher surgical complexity scores according to Aletti et al. [14] (Tab. 1). The rates of serious adverse events and RBC transfusions were similar between the studied groups and their respective control groups (Tab. 1). The median follow-up period for patients was 65 months days (range 0.2–81.0).

We found no differences in mOS between patients who had a splenectomy, diaphragmatic surgery, or both procedures when compared to their respective control groups (Tab. 1). When the patients with no gross residual (CC = 0) and minimal residual (CC = 1) disease were analyzed separately, the difference in survival did not differ when compared to controls. Survival curves for the analyzed study groups and control groups are presented in Figure 1.

DISCUSSION

The most important prognostic factors in OC are initial disease burden and residual disease following surgery. These two factors are related to each other, because initial disease advancement influences the success of surgery and the amount of residual disease. However, initial disease burden has been shown to be an independent prognostic factor in OC, while prognoses of patients with the same residual disease following surgery are associated with preoperative cancer burden [11]. However, in our study we have shown that OS rates for OC patients following splenectomy and/or diaphragmatic stripping during PDS that result in no gross residual (CC = 0) or minimal residual disease (CC = 1), are similar to OS rates for OC patients with the same amount of residual disease but without spleen and diaphragmatic involvement.

Similar results were obtained by Eisenhauer et al. [8], who found no difference in survival rates of patients with extensive upper abdominal procedures, including splenectomy

and diaphragmatic stripping, when comparing to patients with less extensive surgery with similar residual disease. In one of the largest studies concerning diaphragmatic surgery in ovarian cancer, Muallem et al. [16], have shown no difference in patient survival whether diaphragmatic resection/stripping was performed or not, in groups of patients with similar residual disease [17]. Furthermore, in a study by Said et al. [17], the group of patients who underwent PDS with splenectomy, despite having a higher number of complications after the surgery, showed no significant differences in progression-free survival and OS when compared to patients who did not require splenectomy [16].

In contrast to these results, in our previous study, we found significantly shortened survival of ovarian cancer patients who underwent bowel resection compared to residual disease matched patients without bowel surgery [18]. Shortened survival was especially apparent in the group of patients with ultra-radical surgery that included total colectomy despite either no residual disease or minimal residual disease [12].These results suggest that despite higher initial tumor burden, performing selected upper abdomen surgical procedures can achieve similar survival outcomesto those patients with less advanced disease. However, in the case of bowel surgery, despite complete tumor resection, patient prognosis is worse when compared to patients with similar residual disease who did not require bowel resection. We suggest the reason that some of the surgical procedures are associated with patient survival while others are not, may be linked to surgery-related adverse events and/or differences in tumor biology.

In our study, the duration of the operation and the length of hospitalization were longer after the diaphragmatic procedures. This is also confirmed by other studies [19, 20]. The prolongation of surgery with diaphragmatic surgery is due to the greater complexity of cytoreductive surgery. However, despite longer and more complex surgery, no differences in the number of patients affected by severe adverse events and no differences in specific adverse events were found between the study groups. In a study by Muallem et al. [16], regarding diaphragmatic surgery in advanced OC, the authors reported higher rates of postoperative complications in the group of patients who underwent diaphragmatic surgery compared to controls. However, the group of patients in the above-mentioned study was not balanced — the rate of bowel resection in the group of patients with diaphragmatic surgery was significantly higher than in the control group. In contrast, in our study, the rate of bowel resection was similar between the study groups. Nevertheless, most of the adverse events reported in the Musallam et al. [16], study were notdirectly related to the diaphragmatic

surgery [18].Only pleural effusion was significantly more commonly observed in the group of patients with diaphragmatic surgery. In other published findings, the most common complications that occur after cytoreductive surgeries in the upper abdomen with diaphragm stripping are pulmonary complications, and the most frequently described complication in this group is pleural effusion [21, 22]. In a study by Shuang Ye et al. [23], the authors reported pleural effusion, pneumonia, and pneumothorax in 25.8%, 16.1%, and 7.3% (respectively) of patients following diaphragmatic surgery [24]. Zapardiel et al. [20], demonstrated similar results; but the rate of pleural effusion after diaphragmatic surgery in their study was as high as 37.9%. In our study, we only found a few patients with pleural effusion that required thoracocentesis. The low rate of pleural effusion in our study can be explained by the lack of routine chest X-ray examination and no pleural drainage following diaphragmatic surgery in our institution. Therefore, we only included patients who required thoracocentesis due to symptomatic hydrothorax.

Our study revealed a longer operation times and longer duration of hospital stay when splenectomy was performed during PDS. Similar results are found in work by other authors [24]. However, in our splenectomy cases, we did not find higher rates of adverse events compared with rates for our non-splenectomy patients. Splenectomy can be associated with some specific adverse events, like overwhelming post-splenectomy infection syndrome or pancreatic fistula formation [25]. Although these complications may be fatal, the results of our study and other studies suggest these adverse events are infrequent [26]. Other adverse events reported in ovarian cancer patients following splenectomy include infection, formation of abscesses, anastomotic leaks, deep vein thrombophlebitis, and portal vein thrombosis [27, 28]. However, these adverse events seem to be associated with prolonged surgery and surgery complexity, and not with splenectomy *per se*.

In summary, both splenectomy and diaphragmatic surgery in OC patients are associated with prolonged surgery times, however, specific severe adverse events are infrequent. This contrasts with bowel surgery, where serious adverse events are more common postoperatively. In addition, serious adverse events associated with bowel resection, like anastomotic leakage, may be fatal or result in delays in adjuvant administering chemotherapy [18, 29].

The second reason for OC patients having differing prognoses according to which surgical procedures are performed, may be related to differences in tumor biology. Although in recent years, our knowledge about the molecular mechanisms of ovarian cancer spread has

increased [30], little is known about the relationship between tumor biology and the types of OC spread. Ovarian cancer is a heterogeneous disease. There are a number of histopathological types of OC, and for each tumor type, the course of the disease is different [31]. In addition, there are different molecular subtypes within single histopathological types. The Cancer Genome Atlas (TCGA) Research Network distinguished four transcriptional subtypes of high grade serous ovarian cancer (HGSOC), namely: immunoreactive, differentiated, proliferative, and mesenchymal [32]. Further analysis by Konecny et al. [33], revealed differences in patient survival rates among the types, showing that best survival is associated with the immunoreactive subtype, while the proliferative and mesenchymal types had the worst survival rates. Wang et al. [34], also correlated surgical outcomes with the molecular subtypes of HGSOC. They showed that the mesenchymal subtype was associated with the lowest rate of complete debulking, while patients suffering from the immunoreactive subtype of HGSOC had the highest rate of no gross residual disease. The lower rate of complete resection in the case of mesenchymal subtype of HGSOC may be caused by its different dissemination pattern. When compared with other subtypes, the mesenchymal subtype is more commonly characterized by an upper abdominal and military dissemination pattern [34]. In a study by Ohsuga et al. [35], patients with the mesenchymal subtype of HGSOC were more commonly diagnosed at an advanced stage, had ascites more frequently, showed diffuse peritoneal lesions, and omental cake-like masses. All these features were less frequently found in cases of the immunoreactive histopathological subtype of HGSOC [35]. Thus, it is possible that different types of OC are associated with diaphragm/spleen metastases while other types with bowel involvement. Therefore, despite successful surgical resection, it is possible thatdiffering prognoses of OC patients following diaphragm/spleen surgery and bowel resection may be attributed to tumor biology. Currently, the decision whether to perform cytoreductive surgery in OC is mainly based on the technical possibilities of resection and on the condition of patients. Growing evidence suggests that tumor biology will be used in future for planning surgical treatment of ovarian cancer [36]. We believe that future novel research concerning tumor biology will also lead to surgical treatments becoming more tailored to the tumor biology of individual OC patients.

CONCLUSIONS

In conclusion, the results of our study suggest that diaphragm and spleen involvement by OC do not hamper patient prognosis when adequately resected. Therefore, these

procedures should be considered in OC patients when cytoreduction to either no gross, or minimal residual disease is feasible. However, the association between surgical procedures and patient prognosis requires further study.

Conflict of interest

All authors declare no conflict of interest.

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Table 1. Comparison of ovarian cancer patients who had primary debulking surgery resulting in no gross residual or minimal residual disease (tumor nodules < 2.5 mm), according to the type of upper abdomen surgery performed

	Without splenectomy n = 58	With splenectomy n = 25	p value	Without diaphragmatic surgery n = 55	With diaphragmatic surgery n = 28	p value	Without splenectomy and diaphragmatic surgery n = 47	With splenectomy and diaphragmatic surgery n = 17	p value
Age Median (range)	62 (36–86)	59 (37–76)	0.521	62 (36–86)	58 (26–76)	p = 0.146	63 (36–86)	58 (26–76)	p = 0.264
FIGO IIIA IIIB IIIC IVA IVB	 1 (1.7%) 10 (17.2%) 39 (67.2%) 5 (8.6%) 3 (5.2%)	 1 (4%) 1 (4%) 21 (84%) 1 (4%) 1 (4%)	0.353	 1 (1.8%) 9 (16.4%) 40 (72.7%) 4 (7.3%) 1 (1.8%)	 1 (3.6%) 2 (7.1%) 20 (71.4%) 2 (7.1%) 3 (10.7%)	p = 0.427	 1 (2.1%) 9 (19.1%) 33 (70.2%) 3 (6.4%) 1 (2.1%)	 1 (5.9%) 1 (5.9%) 14 (82.4%) 0 (0%) 1 (5.9%)	0.711
Rate of bowel resection	56 (97%)	23 (92%)	0.58	51 (93%)	28 (100%)	0.295	46 (98%)	17 (100%)	1.000
Residual disease CC = 0 CC-1	 32 (55.2%) 26 (44.8%)	 10 (40%) 15 (60%)	0.23	 34 (61.8%) 21 (38.2%)	 8 (28.6%) 20 (71.4%)	0.005	 28 (59.6%) 19 (40.4%)	 4 (23.5%) 13 (76.5%)	0.022
High grade serous ovarian cancer Yes No	 39 (67.2%) 19 (32.8%)	 21 (84%) 4 (16%)	0.181	 39 (70.9%) 16 (29.1%)	 21 (75%) 7 (25%)	0.798	 32 (68.1%) 15 (31.9%)	 14 (82.4%) 3 (17.6%)	0.353
Duration of surgery Minutes (range)	280 (125–615)	345 (215–700)	< 0.001	245 (125–590)	352 (200–700)	p < 0.001	245 (125–590)	350 (220–700)	< 0.001
Length of hospital stay	15 (7–228)	19 (8–80)	0.022	15 (7–228)	21 (8–80)	p = 0.011	14 (7–228)	23 (8–80)	< 0.001
Surgery complexity score	7 (5–10)	10 (7–15)	< 0.001	7 (5–10)	10 (7–15)	p < 0.001	7 (5–10)	12 (9–15)	< 0.001
Patients with serious adverse events	14 (24%)	4 (16%)	0.564	11 (20%)	7 (25%)	0.778	10 (21%)	3 (18%)	1.00
Severe adverse events Wound infection	 8 (13.8%) 2 (3.4%)	 2 (8%) 0 (0%)	 0.51 0.57	 6 (10.9%) 3 (5.5%)	 4 (14.3%) 0 (0%)	 0.72 0.41	 4 (8.5%) 3 (6.4%)	 1 (5.9%) 0 (0%)	 1.00 0.55

Sepsis	1 (1.7%)	1 (4%)	1.00	1 (1.8%)	1 (3.6%)	1.00	0 (0%)	0 (0%)	1.00
Thrombo-embolic events	2 (3.4%)	0 (0%)	0.57	1 (1.8%)	1 (3.6%)	1.00	1 (2.1%)	0 (0%)	1.00
Pleural effusion that required thoracocentesis	1(1.7%)	0 (0%)	1.00	1 (1.8%)	0 (0%)	1.00	1 (2.1%)	0 (0%)	1.00
Bowel perforation	1(1.7%)	0 (0%)	1.00	1 (1.8%)	0 (0%)	1.00	1 (2.1%)	0 (0%)	1.00
Bowel obstruction	2 (3.4%)	1 (4%)	0.57	2 (3.6%)	1 (3.6%)	1.00	2 (4.3%)	1 (5.9%)	1.00
Wound dehiscence	2 (3.4%)	0 (0%)	0.57	2 (3.6%)	0 (0%)	0.54	2 (4.3%)	0 (0%)	0.99
Pelvic abscess	1(1.7%)	1 (4%)	1.00	1 (1.8%)	1 (3.6%)	1.00	1 (2.1%)	1 (5.9%)	1.00
Fistula	2 (3.4%)	0 (0%)	0.57	0 (0%)	1 (3.6%)	0.33	0 (0%)	0 (0%)	
Anastomotic leak									
30 Day mortality	0 (0%)	0 (0%)	1.00	0 (0%)	0 (0%)	1.00	0 (0%)	0 (0%)	1.00
100 Day mortality	0 (0%)	0 (0%)	1.00	0 (0%)	0 (0%)	1.00	1 (2.1%)	1 (5.9%)	0.99
Median RBC concentrate transfusion	2 (0–18)	2 (0–10)	0.138	2 (0–18)	2 (0–10)	0.149	2 (0–18)	2 (0–10)	0.182
Median overall survival Months (range)	31.6 (0.2–81.0)	36.1 (2.4–74.9)	p = 0.853	41.8 (0.2–81.0)	31.3 (2.4–65.5)	p = 0.338	31.6 (0.2–81.0)	20.1 (2.4–65.5)	p = 0.45
Survival Hazard ratio (95% CI)		1.059 (0.574–1.953)			1.320 (0.728–2.395)			1.309 (0.620–2.763)	
Patients with no gross residual disease (CC = 0) Median overall survival Months (range)	31.2 (0.2–79.9) [n = 32]	49.9 (23–72) [n = 10]	p = 0.256	44.0 (0.2–79.9) [n = 34]	30.7 (2.8–65.5) [n = 8]	p = 0.256	41.8 (0.2–79.9) [n = 28]	37.8 (3.4–65.5) [n = 4]	p = 0.311
Patients with minimal residual disease (CC = 1) Median overall survival Months (range)	31.6 (1.16–74.9) [n = 26]	15.4 (2.3–54.3) [n = 15]	p = 0.22	31.6 (1.16–70.7) [n = 21]	20.1 (2.3–74.9) [n = 20]	p = 0.433	31.6 (1.16–70.7) [n = 19]	15.4 (2.3–59.3) [n = 13]	p = 0.21

RBC — red blood cell concentrates; post-surgery residual disease was evaluated using

Sugarbaker’s completeness of cytoreduction score. Therefore, CC0 corresponds to no gross residual disease after the surgery while CC1 refers to tumor nodules below 2.5 mm after the surgery, according to the completeness of cytoreductive (CC) surgery scale [13]. The surgery complexity score was assessed according to Aletti et al. [14]. Adverse events were reported according to Clavien-Dindo classification, and only three or more grade adverse events were recorded as serious adverse events [15]

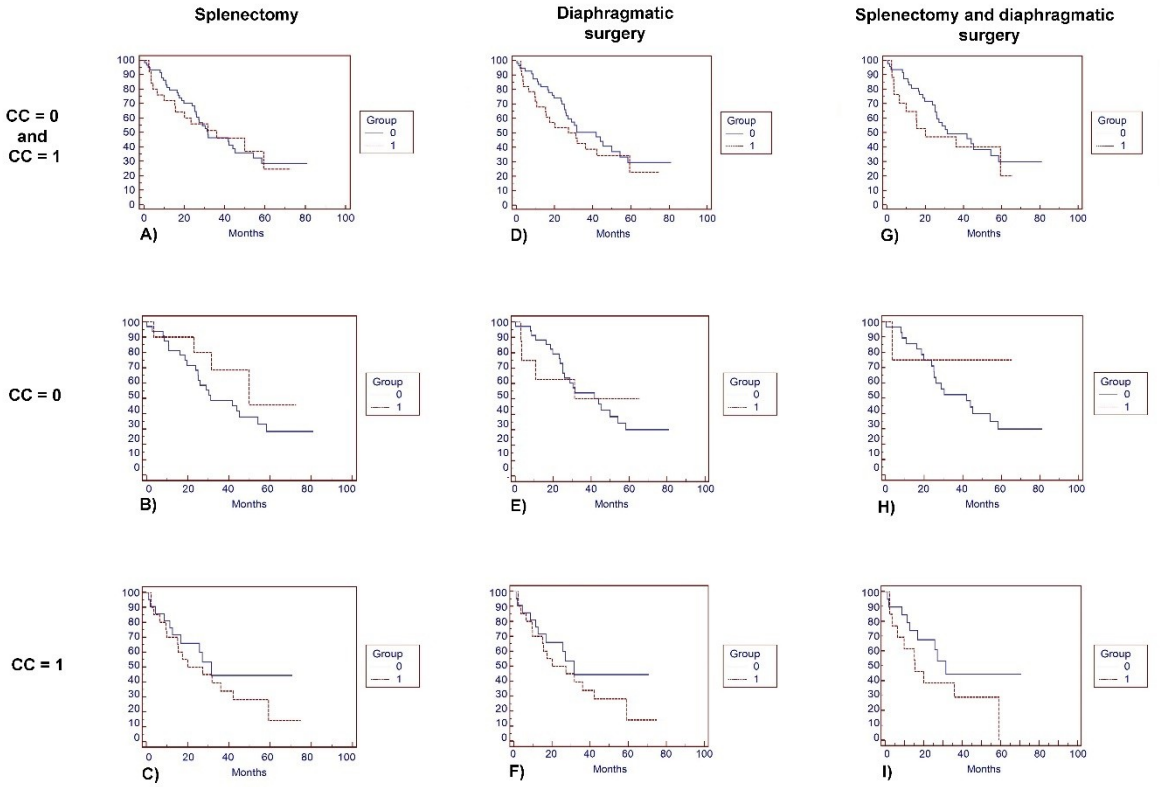

Figure 1. Survival curves of ovarian cancer patients who had primary debulking surgery resulting in no gross residual or minimal residual disease (tumor nodules < 2.5 mm), according to the type of upper abdomen surgery. (**A**) Patients with both no gross residual (CC = 0) and minimal residual disease (CC = 1). Group 0: patients who did not undergo splenectomy (n = 58), median overall survival (mOS) = 31.6 months (range: 0.2–81.0); Group 1: patients undergoing splenectomy (n = 25), mOS = 36.1 months (range: 2.4–74.9), p = 0.853; (**B**) Patients with no gross residual disease (CC = 0). Group 0: patients who did not undergo splenectomy (n = 32), median overall survival (mOS) = 31.2 months (range: 0.2–79.9); Group 1: patients undergoing splenectomy (n = 10), mOS = 49.9 months (range: 23–72), p = 0.256; (**C**) Patients with minimal residual disease (CC = 1). Group 0: patients who did not undergo splenectomy (n = 26), median overall survival (mOS) = 31.6 months (range: 1.16–74.9); Group 1: patients undergoing splenectomy (n = 15), mOS = 15.4 months (range: 2.3–54.3), p = 0.22; (**D**) Group 0: patients who had no diaphragmatic stripping (n = 55), mOS = 41.8 months (range:0.2–81.0); Group 1: patients who had diaphragmatic stripping (n = 28), mOS = 31.3 months (range:2.4–65.5), p = 0.338; (**E**) Patients with no gross residual disease (CC = 0). Patients who had no diaphragmatic stripping (n = 34), mOS = 44 months (range:0.2–79.9); Group 1: patients who had diaphragmatic stripping (n = 8), mOS = 30.7

months (range:2.8–65.5), p = 0.256; (**F**) Patients with minimal residual disease (CC = 1). Patients who had no diaphragmatic stripping (n = 21), mOS = 31.6 months (range: 1.16–70.7); Group 1: patients who had diaphragmatic stripping (n = 20), mOS = 20.1 (range: 2.3–74.9), p = 0.256; (**G**) Group 0: patients who had neither diaphragmatic stripping nor splenectomy (n = 47), mOS 31.6 months (range:0.2–81.0); Group 1: patients who had both splenectomy and diaphragmatic stripping (n = 17), mOS = 20.1 months (range:2.3–74.9), p = 0.450; (**H**) Patients with no gross residual disease (CC = 0). Patients who had neither diaphragmatic stripping nor splenectomy (n = 28), mOS 41.8 months (range: 0.2–79.9); Group 1: patients who had both splenectomy and diaphragmatic stripping (n = 4), mOS = 37.8 months (range: 3.4–65.5), p = 0.311; (**I**) Patients with minimal residual disease (CC = 1). Patients who had neither diaphragmatic stripping nor splenectomy (n = 19), mOS 31.6 months (range: 1.16–70.7); Group 1: patients who had both splenectomy and diaphragmatic stripping (n = 13), mOS = 15.4 months (range:2.3–59.3), p = 0.21