ECRONICON OPEN ACCESS

EC GYNAECOLOGY
Review Article

Splenectomy in Advanced Ovarian Cancer: Technique, Perioperative Considerations, and Impact on Chemotherapy and Oncologic Outcomes in A Single Tertiary Referral Institution

Blanca Segarra-Vidal[1]*, Tiermes Marina[2], Victor Lago[1] and Santiago Domingo[1]

[1]*Department of Gynecologic Oncology, La Fe University and Polytechnic Hospital, Valencia, Spain*

[2]*The Gynecology Oncology Unit, Institute Clinic of Gynecology, Obstetrics, and Neonatology, Hospital Clinic of Barcelona, Barcelona, Spain*

***Corresponding Author:** Blanca Segarra-Vidal, Department of Gynecologic Oncology, La Fe University and Polytechnic Hospital, Valencia, Spain.

Received: June 16, 2022; **Published:** July 27, 2022

Abstract

Advanced ovarian cancer frequently involves upper abdominal structures, including the spleen. To achieve complete surgical cytoreduction, the extensive upper abdominal procedures may be included in the gynecologic oncologist knowledge and surgical practice of the gynecological oncologist. This article presents the relevant anatomy and surgical methods required for a proactive approach to cytoreduction in the upper left quadrant. Moreover, as the spleen is the largest lymphoid organ and deleterious events resulting from splenectomy are a major concern in these patients, thus, the influence of splenectomy on chemotherapy treatment and oncological prognosis are also discussed.

Keywords: *Splenectomy in Advanced Ovarian Cancer: Technique; Perioperative Considerations; Impact on Chemotherapy; Tertiary Referral Institution*

Introduction

Ovarian cancer is frequently diagnosed at an advanced stage, with nearly 75% of cases at stage III–-IV at presentation [1]. The combination of surgery and systemic therapy is the cornerstone of its management [2]. Complete cytoreduction is one of the most important prognostic factors in advanced ovarian cancer [3,4]. For this purpose, surgery for advanced disease involves performing advanced and complex surgical procedures, including splenectomy [5]. In general, splenic metastasis are found in only 2.3 - 7.1% of patients with advanced ovarian cancer [6]. However, it has been described in up to 2 - 20% of cases, either during primary cytoreductive surgery or during a subsequent surgery for a relapse of ovarian cancer [5-11].

The immunological status of patients with ovarian cancer may be influenced by a number of factors. On the one hand, the spleen is the largest lymphoid organ in the human body, and it plays an important role in the innate and adaptive immune response, as it is the development and storage site for B and T lymphocytes and the site of production and release of immunoglobulins and immune mediators [12]. On the other hand, a standard regimen of chemotherapy for ovarian cancer often has an immunosuppressive effect due to myelosuppression. For all these reasons, spleen removal may influence the incidence of adverse events during systemic therapy, leading to many short- and medium-term complications like higher increased susceptibility to infections, thrombocytosis, and an increased number of damaged circulating red cells, leading to a state of hypercoagulability and increased risk of thromboembolism [13,14].

Anatomical considerations

The embryonic spleen develops within the dorsal mesogastrium, which in adults confers complex anatomical relationships and fixations on it.

The spleen is located in the left upper quadrant of the human body. It is protected by the left 9th, 10th, and 11th ribs, and the left diaphragm roofs covers its superior surface. It lies on the left colic flexure inferiorly, the stomach lies anterior to the spleen, and its medial boundary is the left kidney (Figure 1).

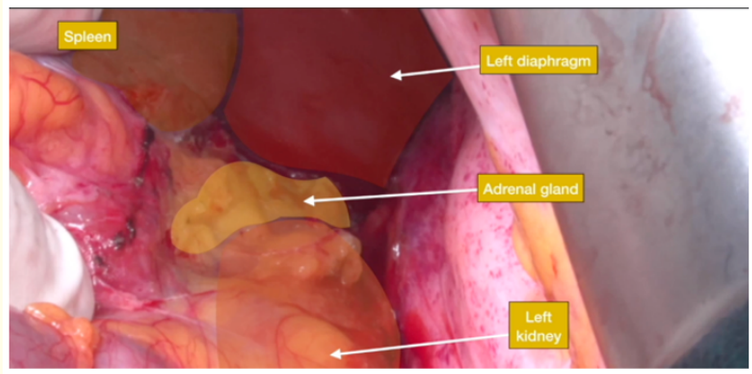


Figure 1: *The medial boundary of the spleen are the left adrenal gland and kidney, and the lateral boundary the left diaphragm.*

The spleen is surrounded by the peritoneum, except at the hilum. The hilum is often connected to or in contact with the tail of the pancreas and constitutes the left boundary of the omental bursa.

The spleen is suspended by multiple peritoneal reflections that extend into the neighbouring organs, forming various fixations (Figure 2): The splenophrenic ligament, the splenocolic ligament and, the gastrosplenic ligament carry the short gastric arteries and veins in the superior aspect, and the left gastro-epiploic artery and vein in the inferior aspect. The short vessels originate from the gastroepiploic artery, a branch of the splenic artery. The splenorenal ligament holds the splenic artery and vein, as well as the tail of the pancreas. The pancreatosplenic omentum is a portion of the greater omentum, extending between the pancreas and the spleen, that encloses the tail of the pancreas and the pedicle spleen vascular area that arises behind it.

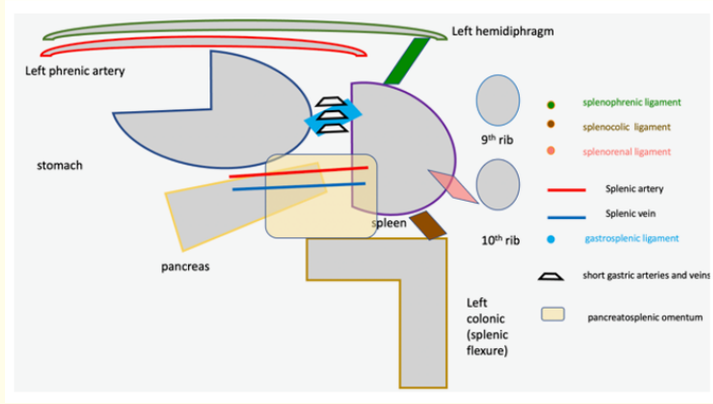


Figure 2: *The spleen ligaments and its relations.*

Vascular anatomy

The splenic artery runs from the celiac trunk behind the omental bursa, in front of the left kidney, and along the cephalic border of the pancreas. However, the splenic vein arises from the splenic hilum (Figure 3), usually with several tributary veins, and runs posterior to the body and tail of the pancreas, creating the portal system once the inferior and superior mesenteric vein join in. Hence, both vessels run along different pathways, joining in the tail of the pancreas, and making a curving towards the splenic hilum. This is crucial because as the tail of the pancreas can be involved in the tumour and should be removed with the spleen.

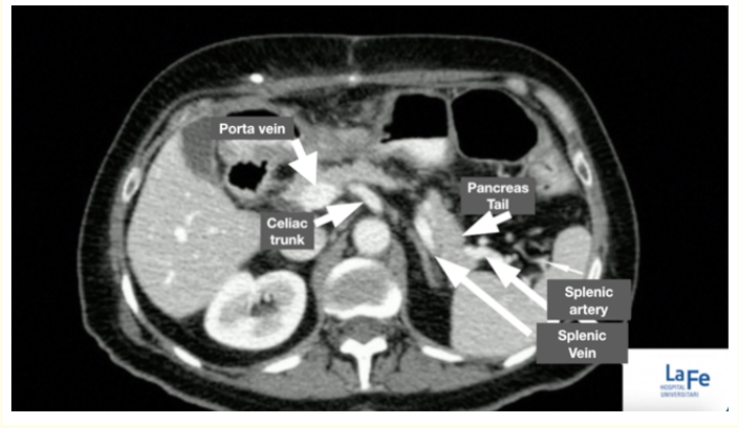


Figure 3: *Splenic artery and vein anatomy in CT.*

Surgical technique

Video link: https://ijgc.bmj.com/content/31/8/1190. Reproduced with permission from S.Domingo and T.Marina; published by International Journal of Gynecologic Cancer 2021;**31:**1190-1191.

The most crucial point is to secure surgical visibility by exposure of the left upper quadrant area. Cytoreduction surgery is performed through a xipho-pubic midline incision to allow a full exploration of the whole abdomen and pelvis, thus a splenectomy can also be performed enough through the same incision.

The splenectomy technique has two key points. The first is the dissection of its attachments; the second, the vascular supply.

The spleen and distal pancreas are carefully palpated to determine the extent of resection (Figure 4). To get free the spleen from the colon, the splenocolic ligament and splenic flexure are transected (Figure 5). The gastrosplenic ligament is opened by the end of the gastrocolic ligament resection during debulking surgery, and the short gastric vessels are dissected carefully (Figure 6).

Once this is done, the spleen is gently retracted medially and the peritoneal attachments are divided with sharp dissection or monopolar cautery, proceeding from the inferior pole, the splenorenal ligament (Figure 7), to the superior pole, the splenophrenic ligament (Figure 8).

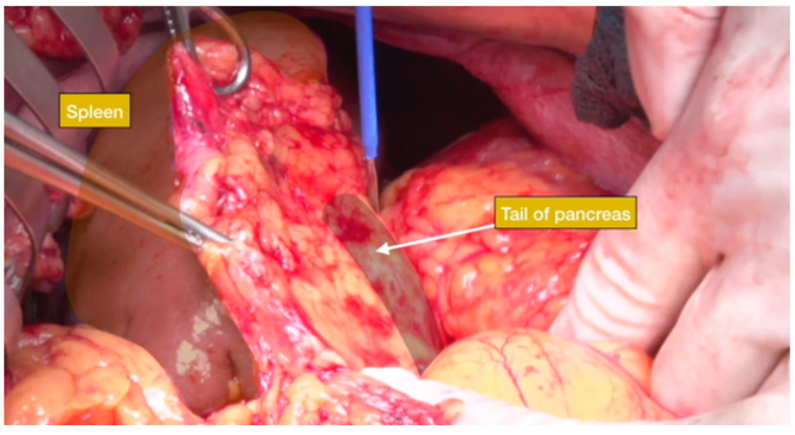


Figure 4: *The tail of the pancreas abuts against the hilum of the spleen.*

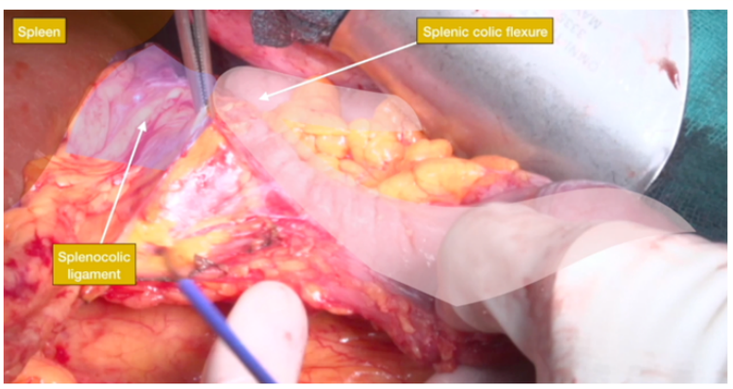


Figure 5: *The splenocolic ligament lies anterior to the spleen, the splenic flexure of the colon and the left kidney are taken inferiorly and medially to the spleen, respectively.*

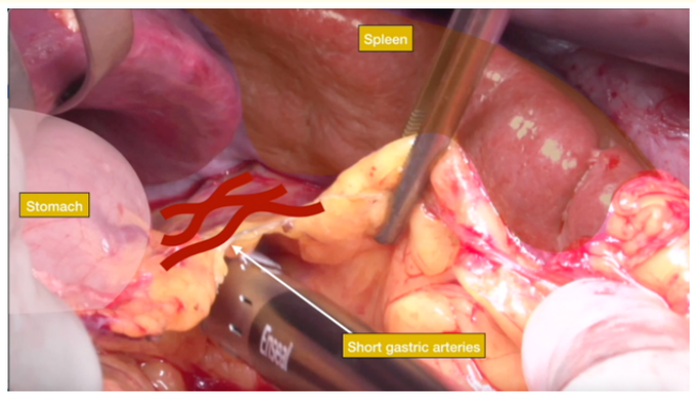


Figure 6: *The gastrosplenic ligament runs from the greater gastric curvature to the splenic hilum and carries the short gastric arteries and veins.*

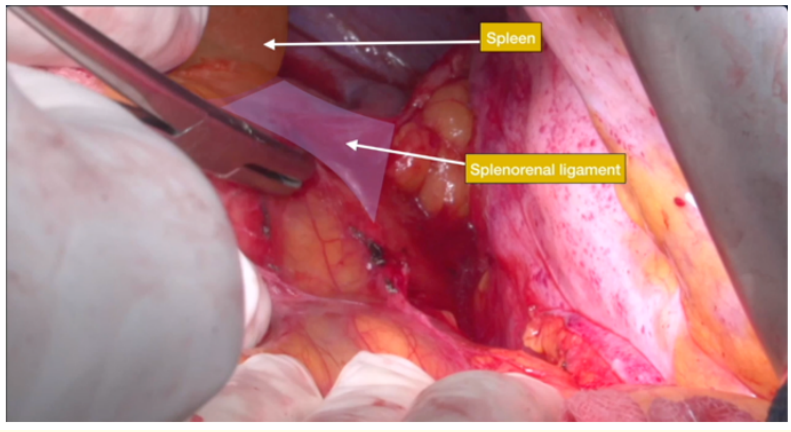


Figure 7: *The splenorenal ligament holds the splenic artery and vein, as well as the tail of the pancreas.*

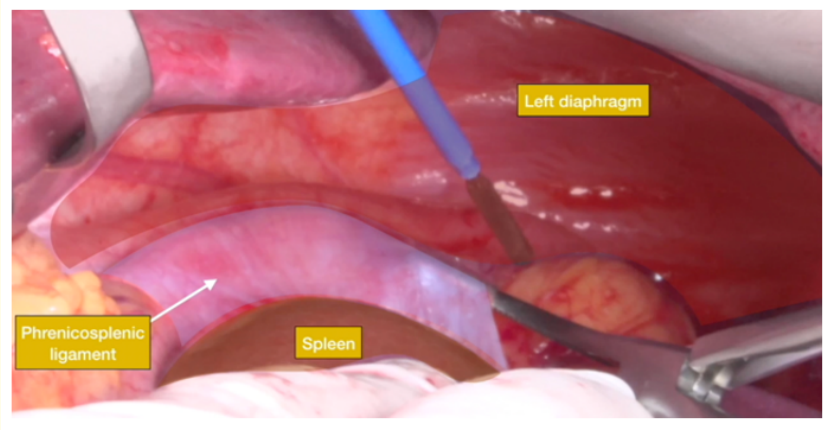


Figure 8: *The splenophrenic ligament is a peritoneal fold that fixes the spleen to the diafragma.*

These manoeuvres make it possible to externalise the pancreatosplenic block and the spleen is fully mobilised. At this point, the splenic artery and vein are identified, ligated separately, and divided (Figure 9). The splenic artery frequently branches as it gets close to the hilum of the spleen; therefore, care should be taken to ligate it before it branches, or to secure each branch of the artery. The artery is ligated separately and before the splenic vein, reducing the pressure within the vein when it is ligated and will also allowing additional blood sequestered within the spleen to return to circulation. Often, the tail of the pancreas will be close to the splenic vein, and a distal pancreatectomy can be performed if it is involved with a tumour.

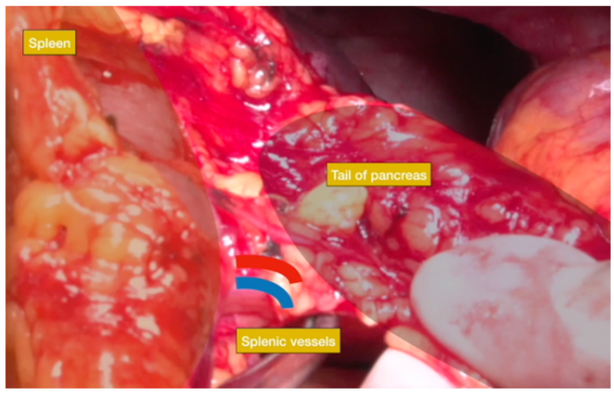


Figure 9: *The pancreatosplenic omentum is a portion of the greater omentum extending between the pancreas and the spleen that encloses the tail of the pancreas and the pedicle spleen vascular that arises behind it.*

Retrograde approach

The retrograde approach is the most common, and it is indicated when the tumour involves the gastrosplenic ligament or the colosplenic ligament, and there is a bulky omentum or there is a limited anterior vascular access. Moreover, the retrograde approach is usually performed to preserve the tail of the pancreas.

The splenophrenic ligament is released, allowing the spleen to be mobilised and the splenic hilum to be exposed. The tail of the pancreas is then separated from the pancreatic impression on the spleen, along with the avascular space between the two organs. The splenic vessels can be separately ligated while minimising the risk of pancreatic injury.

Anterograde approach

The anterograde approach to splenectomy is preferred when there is no tumour in the hilum or the anterior face of the spleen. However, it is associated with a higher risk of injury to the pancreatic tail.

When an en-bloc resection of the spleen and distal pancreas is required, a linear cutting stapler can be used to separate the spleen from the tail of the pancreas during splenectomy or to remove the pancreatic tail with the spleen. The ideal closure technique of the pancreas after distal pancreatectomy is not defined. It is postulated that standardised closure with a stapler device may prevent pancreatic fistula more effectively than would a hand-sewn closure of the remnant [15].

Step-by step splenectomy surgical technique

1. Release of inferior splenic adhesions (splenocolic ligament).
2. Gastrosplenic ligament section with short gastric vessel division.
3. *Splenic vessel dissection, avoiding the pancreas tail.
4. *Posterior (splenorenal) and cephalic (splenophrenic) dissection of the spleen.

*Interchangeable steps

Picture 1

Post-surgical care

After a splenectomy, several changes typically occur in the blood composition. Howell-Jolly bodies are seen in patients who have undergone a splenectomy. The white blood cell count is usually elevated on the first postoperative day and may remain elevated for months. The platelet count usually peaks on the first postoperative day and returns to normal levels after splenectomy [16].

Postoperative complications

The most frequent complication after splenectomy is left lower lobe atelectasis, which occurs in approximately 16% of patients. There are major abdominal complications, including intraabdominal collections, subphrenic hematoma and abscess; and other infectious complications such as anastomotic leaks or abscesses, sepsis, and overwhelming postsplenectomy infection; and hematologic complications such as deep-vein thrombophlebitis and portal system thrombosis [7,17].

Magtibay., *et al*. [10] reported that among 112 patients who underwent splenectomy during a cytoreductive surgery, the overall complication rate was 23% (26/112). Seven (6.3%) had wound infections, five (4.5%) had postoperative pneumonia, nine (8%) had thromboembolic events, and five (4.5%) had sepsis.; The authors suggested that when performed as part of cytoreductive procedures in patients with epithelial ovarian carcinoma, splenectomy was associated with modest but acceptable morbidity and mortality rates.

Infection

The spleen is the dominant site for the production of immunoglobulin M (IgM) antibodies required for opsonising encapsulated pathogens. Splenectomised patients are at increased risk of infectious processes and severe diseases caused by certain pathogens, so they must be vaccinated against *Streptococcus pneumoniae*, *Haemophilus influenzae B*, and *Neisseria meningitidis*. Vaccination should be given two weeks before elective splenectomy or two weeks after emergency splenectomy [18].

Hypercoagulable state

There is strong evidence that a hypercoagulable condition state occurs after a splenectomy. The incidence of thrombosis after splenectomy is approximately 5% and accounts for about 19% of cases in hospitalised patients. Thromboembolism can occur in up to 10% of patients. Extreme thrombocytosis may cause thrombotic events such as acute myocardial infarction, mesenteric vein thrombosis, and pulmonary embolism [19,20]. Due to the thrombotic risk after this procedure, antithrombotic prophylaxis with low-molecular-weight heparin is indicated, associated withing 100 mg of acetylsalicylic acid if the number of platelets is greater than 1,000,000/μL [17].

Postoperative pancreatic fistula (POPF)

Postoperative pancreatic fistula is one of the most frequent complications after distal pancreatectomy. Postoperative pancreatic fistula represents a failure of healing/sealing of a pancreatic-enteric anastomosis or a parenchymal leak not directly related to an anastomosis. In general, the following criteria according from the International Study Group of Pancreatic Fistula (ISGPF) are used for the diagnosis of POPF: output via an operatively placed drain of any measurable volume of drain fluid on or after postoperative day 3; and an amylase content more than three times the upper normal serum value [21].

The common symptoms related to POPF may be leucocytosis, abdominal pain, and colour change of drain fluid. In this clinical context, percutaneous drainage should be placed to avoid the worsening of POPF and subsequent abscess formation. Moreover, upper abdominal pain and distension, impaired bowel function, and fever > 38 °C can be combined [20].

Pancreatic pseudo abscesses due to pancreatic leak should be managed with percutaneous drains or with an internal endoscopically-inserted drain to avoid reoperation [22].

Influence of splenectomy on chemotherapy treatment and oncological prognosis

To determine the effect of splenectomy on subsequent chemotherapy treatment and prognosis in women with advanced ovarian cancer, we performed a retrospective study comparing two cohorts of patients in consisting of all women who underwent cytoreductive surgery for primary advanced or relapsed ovarian cancer at University Hospital La Fe of Valencia (Spain) between November 2011 and December 2019. Splenectomy was performed to achieve optimal cytoreduction. All procedures were performed by a gynecological oncology specialist with using the standardised technique, as explained previously. All women received systemic chemotherapy when they were completely recovered from surgery and their ECOG performance status was 2 or lower.

Statistical analysis

Data are summarised as mean and median for quantitative variables and as numbers and percentages for categorical variables. To compare differences in postoperative complications and adjuvant treatment between groups, explicative models were developed using multivariable regressions. Logistic, linear, and quantile regressions were performed depending on the nature of each outcome. Confounding factors such as age, duration of surgery, type of surgery, and pre-operative state were included in the model. Differences in the time to complete chemotherapy in both groups according to the number of cycles were assessed using the predicted marginal means of the model. Calibration of the models was assessed by plotting bootstrapped estimates of predicted versus observed values. In the univariate analysis of survival, only women with first diagnosis disease were included. Progression-free survival and overall survival were explored using Kaplan Meier curves and the log-rank test. All statistical analyses were conducted using R software (version 4.0.0), R -package rms (version 4.1 - 0), and R -package lsmeans (version 2.30). For all analyses, a two-sided p-value of less than 0.05 was considered statistically significant.

Results

Seventy-two out of 459 patients underwent splenectomy for advanced ovarian cancer at our institution between November 2011 and December 2019. The flowchart for patient selection is shown in figure 10 and the baseline characteristics and surgical data are summarised in table 1.

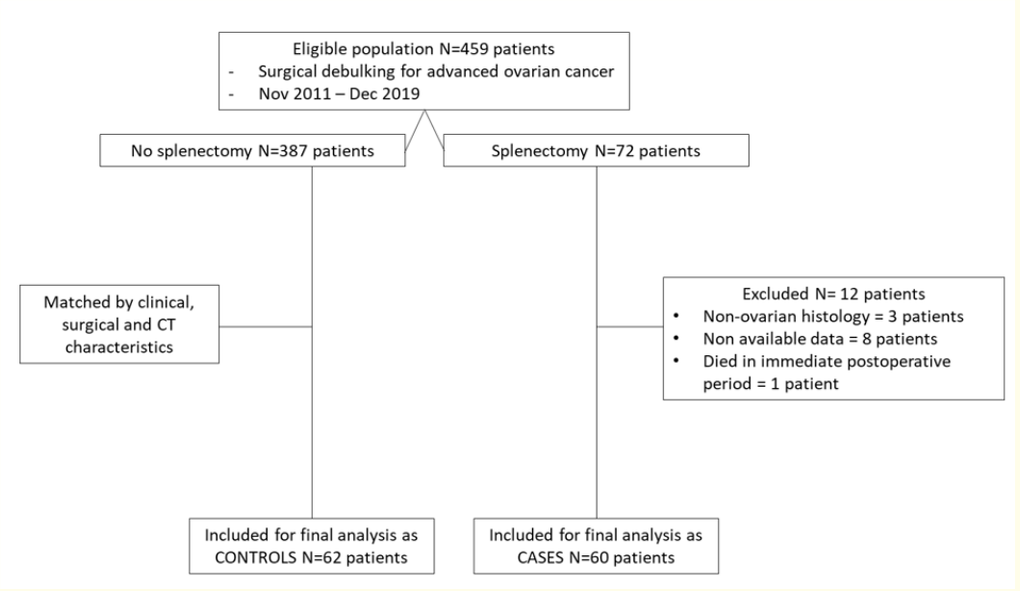


Figure 10: *Study flowchart. Case-control patient selection. CT=chemotherapy.*

Characteristics	Case group (N = 60)	Control group (N = 62)	P value
Age [Mean±SD (range)]	56,4 ± 9.8 (36-71)	56 ± 9.5 (32-74)	0.82
Body mass index (BMI) [Mean±SD (range)]	25 ± 4.6 (14.5-36.1)	24.5 ± 4.3 (16,5-35)	0.53
Stage, n (%)			0.82
- IIIB/C	44 (73.3)	42 (67.7)	
- IVA/B	12 (20)	16 (25.8)	
- Relapse	4 (6.7)	4 (6.5)	
Histological subtype, n(%)			0.54
- HG Serous	51 (85)	55 (88.7)	
- NO serous	9 (15)	7 (11.3)	
Type of surgery, n(%)			0.22
- Primary debulking	44 (73.3)	37 (59.7)	
- Interval debulking	12 (20)	21 (33.9)	
- Recurrence cytoreduction	4 (6.7)	4 (6.5)	
Residual disease, n(%)			0.07
- R0	42 (70)	43 (69.4)	
- R1	10 (16.7)	17 (27.4)	
- R2	3 (13.3)	2 (3.2)	
Pancreatic resection, n (%)	3 (5)	0	-
Intraoperative complications, n(%)	7 (11.7)	11 (17.7)	0.257
Surgical time (min) [Mean (range)]	397.5 (200-795)	340 (200-540)	<0.001
Postoperative complications, n(%)			
- Overall	19 (31.7)	12 (19.4)	0.18
- Pleural effusion	7 (11.7)	8 (12.9)	
- Pneumonia	3 (5)	0	
- Left subprhenic abscess	1 (1.7)	0	
Hospitalization stay (days) [Mean (range)]	9 (3-87)	7 (4-24)	0.12

Table 1: *Clinical and surgical base line characteristics.*
Abbreviations: n=number; SD= standard deviation.

There were no significant differences between the groups with respect to mean patient age, body mass index, FIGO stage, histological subtype, and residual disease. Differences between the groups were observed regarding the type of surgery despite no statistical significance (PDS 73.3% vs. 59.7% and IDS 20% vs. 33.9%; P = 0.22), but a clinical significance and surgical time with a statistical

significance [(397.5 vs. 340 min; *P* < 0.001; 95% CI -–(95.62–- -36.58)] was seen. For this reason, these variables were included in the model as covariables for the subsequent statistical analysis. There were no differences concerning intraoperative complications (11.7% vs. 7.7%; *P* = 0.26; 95% CI: 0.65–-5.48). No differences were observed regarding the postoperative complications (31.7% vs. 19.4%; *P* = 0.18; 95% CI 0.23–-1.3), with pleural effusion as the most common complication in both groups. The two cohorts were also comparable in terms of the length of hospital stay (9 vs. 7 days) and 30-day mortality (1.4% vs. 0%; *P* = 0.12; 95% CI: -3.88–-0.40).

Variables regarding the adjuvant chemotherapy treatment after surgery are shown in table 2. No differences were found in the period from surgery to adjuvant chemotherapy (mean time 48.6 vs. 42.7 days; *P* = 0.3; 95% CI -9.0–-2.78), in the time to complete chemotherapy for women who received only adjuvant treatment (104 vs. 116 days; *P* = 0.37) and for those who had received previous neoadjuvant treatment (54.4 vs. 55.4 days; *P* = 0.98). The mean number of chemotherapy cycles administered was 5.9 in the splenectomised group vs. 6.1 in the control group. Significant differences were found concerning women who completed at least six cycles (78.3% vs. 98.4%; P < 0.05; 95% CI 0.005–-0.522). Differences between the groups were found regarding cancelled chemotherapy cycles (30% vs. 11.3%; *P* = 0.037; 95% IC 0.054–-0.86). In contrast, no differences were detected neither either with respect to delayed cycles (50% vs. 32.3%; *P* = 0.16; 95% IC 0.23–-1.26), or for reduced dose cycles (23.3% vs. 22.6%; P = 0.61; 95% IC 0.28–-2.11).

Characteristics	**Case group (N=60)**	**Control group (N=62)**	**P value**
Type of chemotherapy, n (%)			0.26
- Neoadjuvant	13 (21.7)	19 (30.6)	
- Adjuvant	47 (78.3)	43 (69.4)	
IP chemotherapy, n (%)	9 (15)	21 (33.9)	**0.013**
Chemotherapy regimens, n (%)			
- CBDCA/CDDP-taxane IV/IP	57 (95)	60 (96.8)	
- Others	3 (5)	2 (3.2)	
Antiangiogenic, n (%)	26 (43.3)	17 (27.4)	0.07
Time from surgery to adjuvant chemotherapy (days) [Mean±SD (range)]	48.6±16.6 (27-113)	42.7±12.7 (22-78)	0.298
Time to complete chemotherapy (days) [Mean±SD]			
- Adjuvant treatment	104±30.8	116±18.7	0.372
- Neo + adjuvant treatment	54.4±16.3	55.4±39.2	0.983
Nº chemotherapy cycles [Mean±SD]	5.9±1.3	6.1±0.55	0.21
Pat complete at least 6 cycles adjuvant chemotherapy, n (%)	47 (78.3)	61 (98.4)	**<0.05**
Chemotherapy cycles delay, n (%)	30 (50)	20 (32.3)	0.156
- 1 cycle	21 (35)	9 (14.5)	
- 2 or more cycles	9 (15)	11 (17.7)	
Chemotherapy cycles cancel, n(%)	18 (30)	7 (11.3)	**0.037**

- 1 cycle	11 (18.3)	6 (9.7)	
- 2 o more cycles	7 (11.7)	1 (1.6)	
Chemotherapy reduced dose, n (%)	14 (23.3)	14 (22.6)	0.607
Blood transfusion, n (%)	1 (1.7)	1 (1.6)	-
Platelets transfusion, n (%)	0	0	-
Colony stimulating factors (CSF) (*), n (%)	13 (21.7)	20 (32.3)	
Re-admission during chemotherapy, n (%)	12 (20)	3 (4.8)	-
- Abdominal	10	0	
- Infectious	2	2	
- Thromboembolic event	0	1	
- Other	3	0	
Re-surgery during chemotherapy, n (%)	4 (6.7)	1 (1.6)	-
Chemotherapy mortality, n (%)	2 (3.3)	0	-

Table 2: *Chemotherapy characteristics.*

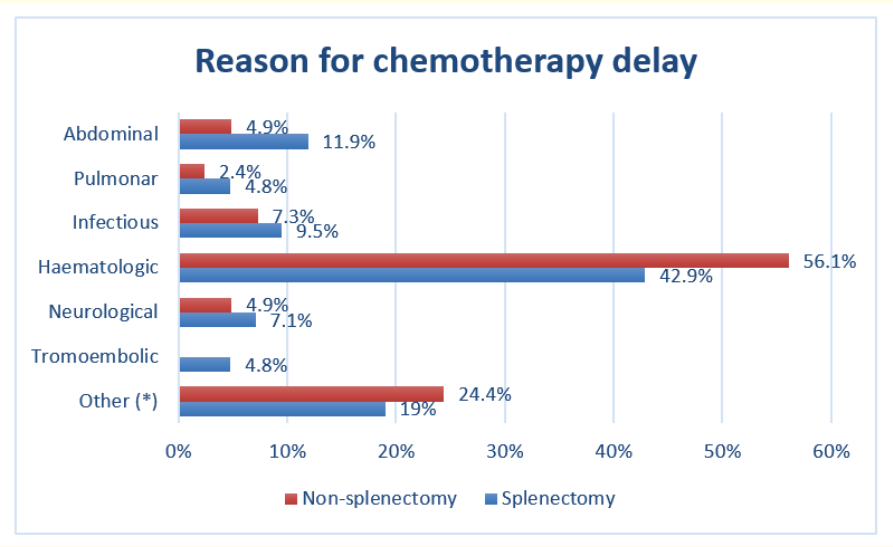
Abbreviations: N=Number; SD= Standard Deviation; IP=Intraperitoneal; N=Number; CBDCA=Carboplatin; CDDP=Cisplatin; CSF=Colony Stimulating Factor; Ns= Not Significant.

(*) Including granulocyte colony stimulating factor (G-CSF), erythropoietin (EPO) or both.

Regarding infectious complications, a total of 42 cycles were delayed among the 30 women who were required to delay at least one cycle in the splenectomy group in contrast to 41 cycles among the 20 women in the control group. Oof them, just four cycles (in four different women) in the splenectomy group (9.,5%) and three cycles (in three different women) in the control group (7.3%) had to be postponed due to an infectious process (Figure 11.1). Likewise, only two cycles (8.3%) were cancelled due to an infectious process out of a total of 24 cycles cancelled in the splenectomy group. The reasons for this were: infection of the intraperitoneal catheter port and lower urinary tract infection that required hospital admission (Figure 11.2).

Haematological toxicity was the main reason for the chemotherapy delay in both groups, while abdominal complications and neurological toxicity were the main reasons for the cancellation in the case and control groups, respectively (Figure 11). Regarding the need for transfusion, no significant differences were found between groups. Moreover, 21.7% of women in the case group required the administration of colony-stimulating factors compared with 32.3% in the control group. Finally, significant differences were found between groups for the rate of re-admission (20% vs. 4.8%) and reoperation-surgery (6.7% vs. 1.6%) during chemotherapy treatment. Intestinal complications were the reason for reoperation in three of the four women in the splenectomy group. Two women in the splenectomy group died during this period, which represents a mortality rate of 3.3%, while none of the women in the control group died.

Figure 11: *Multiple bar diagrams according to group: 11.1 Reasons for cycle delay. 11.2 Reasons for cycle reduction. 11.3 Reasons for cycle cancellation.*

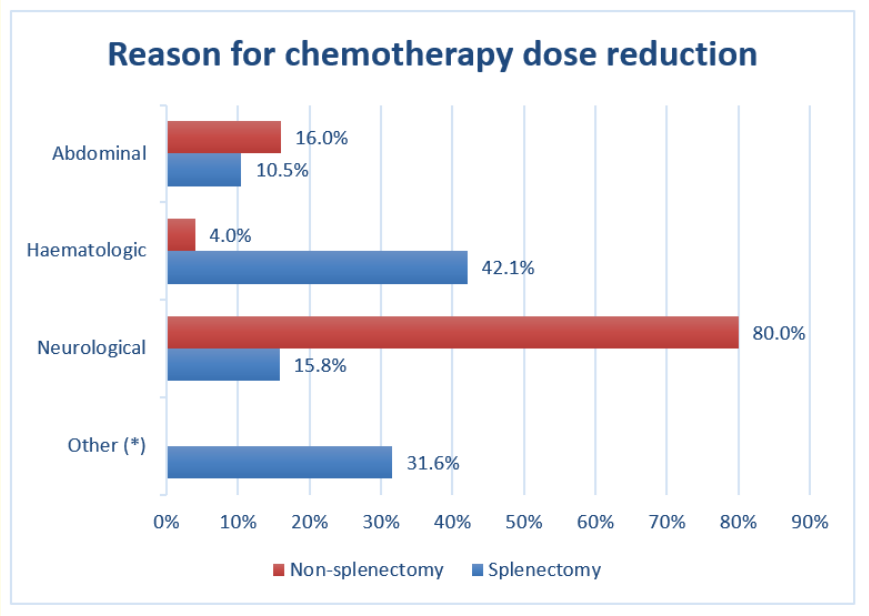


(*) Splenectomy: poor general status and asthenia, allergic reaction, abdominal collection/percutaneous drainage, ureteral catheter insertion, prolonged recovery period.

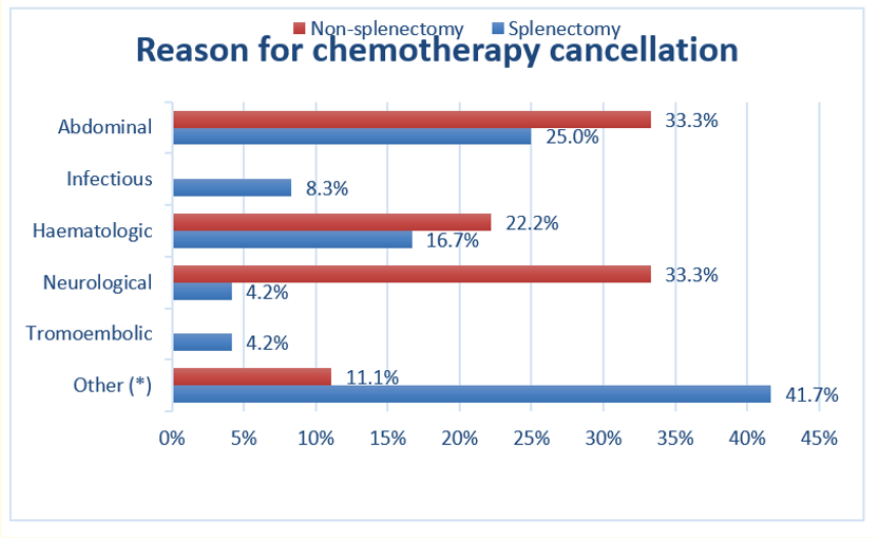
(*) Non-splenectomy: allergic reaction, paraneoplastic syndrome, poor general status and asthenia.

(*) Splenectomy: poor general status and asthenia, allergic reaction, abdominal collection/percutaneous drainage, ureteral catheter insertion, prolonged recovery period.

(*) Non-splenectomy: allergic reaction, paraneoplastic syndrome, poor general status and asthenia.



(*) Splenectomy: severe allergic reaction to platinum.



Long-rank=0.47

(*) Splenectomy: poor general status and asthenia.

(*) Non-splenectomy: poor general status and asthenia, ascites/paracentesis, catheter wound dehiscence, vesicovaginal fistula/surgical repair, wound dehiscence, colostomy.

Regarding survival, 41.7% and 31.7% of women were alive with disease and died due to disease, in the splenectomy group, compared to 35.5% and 22.6% in the control group, respectively. Only women with first- diagnosis disease were included in the survival analysis. The median follow-up for the entire cohort was 26 months (range 2–-107 months). Global median disease-free survival was 17 months (CI 15–-20) and median overall survival was 64 months (CI 46–-NA). The progression-free survival at 24 and 60 months was 20.47% vs. 30.3% and 4.26% vs..3% and the overall survival was 82.6% vs. 78% and 48.9% and 47.5% in the splenectomy and control groups, respectively. No significant differences were found in median progression-free survival (long-rank = 0.07) and overall survival (long-rank = 0.47) in the splenectomy group and the control group, respectively (Figure 12).

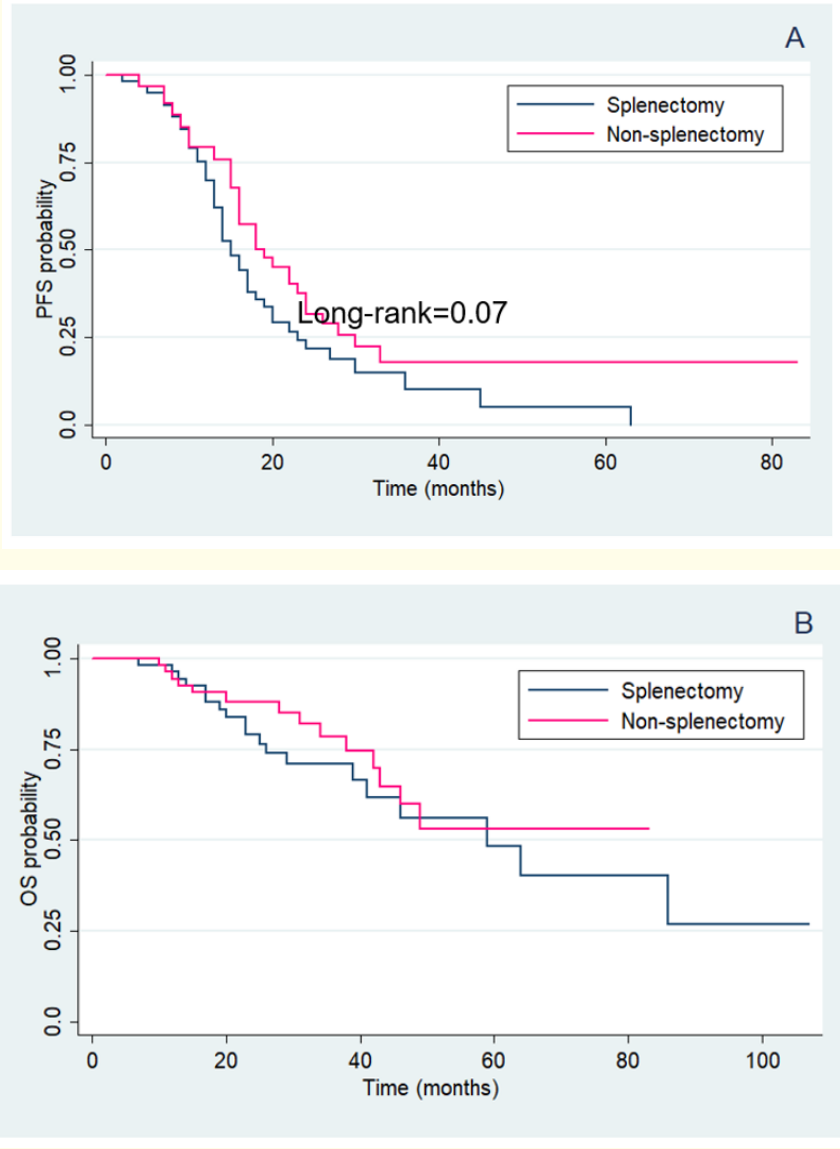


Figure 12: *Kaplan-Meier survival curves for PFS (A) and OS (B) by group.*

Discussion

In this retrospective study at a single tertiary institution the splenectomy rate is 15.7%, comparable to previously published series, ranging from 1.3 to 23.2% [5,11], with a trend showing an increase in its use. Up to 81.7% of splenectomies were performed during the last three years of the study period. The results showed intra- and postoperative complication rates of 11.7% and 31.7%, which were not statistically different from the control group after adjusting for other variables and are also consistent with the abovementioned publications. Only one complication, consisting of a left subphrenic abscess, could be unequivocally related to splenectomy.

One indicator related to oncological outcome is the optimal time interval between debulking surgery and the start of subsequent chemotherapy that has not been established, but it is recommended to be as short as possible and no longer than 4 - 6 weeks [23-29]. Some studies showed an association between delay and worse oncological prognosis, for both primary and interval surgery [23-29] while others did not [30-37]. Another indicator is the time to complete chemotherapy and delays during treatment: on-time completion of chemotherapy is correlated with increased survival and higher complete response rates, while a prolonged duration of adjuvant chemotherapy adversely affects progression-free survival and overall survival [38,39]. We did not observe significant differences in the time interval from surgery to adjuvant chemotherapy between both groups, either after primary debulking surgery or interval debulking surgery. Patients who underwent splenectomy during surgery had a lower likelihood of completing at least six cycles of chemotherapy and a higher likelihood of chemotherapy cycle cancellation compared to non-splenectomised women. However, if we focus on the reason for delay/cancellation or dose reduction, no differences between groups could be established. Hematologic toxicity (neutropenia) was the main reason for the delay in both groups; asthenia/poor general status was the main reason for cancellation in the splenectomy group, while abdominal disorders and neutropenia were observed in the control group; finally, neutropenia and neurotoxicity were the major causes for dose reduction in the splenectomy and control groups, respectively. None of these factors are directly linked to having been splenectomised (Figures 11.1, 11.2, 11.3).

Infections represent a major concern after splenectomy [10-13-40,41]. However, splenectomised women show similar infection rates during chemotherapy compared to non-splenectomised women.

Splenectomy did not influence the oncological outcome, as no differences were seen between groups for progression-free survival and overall survival, which is consistent with the previous publications [7,9-11,23-25,29,38-40].

The retrospective nature of the analysis is the main limitation, because the decision to perform a splenectomy or not resulted from any non measurable reasons. Moreover, throughout the time- frame of the study, the surgical and adjuvant treatment indications, the strategies of surveillance, and the treatment of recurrences varied.

In summary, we must perform a splenectomy during ovarian cancer debulking surgery to achieve an optimal surgery, following current protocol for post-operative care, if the direct benefit to the patient outweighs the risks.

This procedure does not seem to be related to a higher rate of complications, chemotherapy delay, or dose reduction during adjuvant treatment, nor does it have any negative impact on the oncological outcome.

Take-home messages

1. Upper abdominal surgery, including splenectomy or distal pancreatectomy, is required to minimise the size of residual tumour
2. The splenectomy technique has two key points: the dissection of its attachments and the vascular supply. It is also important to consider, the anatomical relationship with the pancreas tail.

3. Vaccination should be given two weeks before elective splenectomy or two weeks after emergency splenectomy.

4. Antithrombotic prophylaxis with low-molecular-weight heparin is indicated due to the hypercoagulable state that occurs after splenectomy.

5. The common symptoms related to a postoperative pancreatic fistula may be leucocytosis, abdominal pain, and colour change of drain fluid.

6. To achieve an optimal surgery, splenectomy must be performed during ovarian cancer debulking surgery, following the current protocol for post-operative care.

7. Splenectomy in the course of debulking surgery for ovarian cancer does not seem to have any negative impact on adjuvant chemotherapy or oncological outcome.

Conclusion

Advanced ovarian cancer frequently involves upper abdominal structures, including the spleen. To achieve complete surgical cytoreduction, surgery for advanced disease involves performing advanced and complex surgical procedures, including splenectomy. The splenectomy procedure does not seem to be related to a higher rate of complications, chemotherapy delay, or dose reduction during adjuvant treatment, nor does it have any negative impact on the oncological outcome.

Bibliography

1. Torre LA., *et al*. "Ovarian cancer statistics, 2018". *Clinical Cancer Investigation Journal* 68.4 (2018): 284-296.

2. Colombo N., *et al*. "Ovarian cancer". *Critical Reviews in Oncology/Hematology* 60.2 (2006): 159-179.

3. Melamed A., *et al*. "Associations between residual disease and survival in epithelial ovarian cancer by histologic type". *Gynecologic Oncology* 147.2 (2017): 250-256.

4. González Martín A., *et al*. "Exploratory outcome analyses according to stage and/or residual disease in the ICON7 trial of carboplatin and paclitaxel with or without bevacizumab for newly diagnosed ovarian cancer". *Gynecologic Oncology* 152.1 (2019): 53-60.

5. Jones NL., *et al*. "National trends in extended procedures for ovarian cancer debulking surgery". *International Journal of Gynecological Cancer* 28.1 (2018): 19-25.

6. Koh YS., *et al*. "Splenectomy for solitary splenic metastasis of ovarian cancer". *BMC Cancer* 4 (2004): 96-96.

7. Sun H., *et al*. "Splenectomy during cytoreductive surgery in epithelial ovarian cancer". *Cancer management and Research* 10 (2018): 3473-3482.

8. Fotopoulou C., *et al*. "Maximal effort cytoreductive surgery for disseminated ovarian cancer in a UK setting: challenges and possibilities". *Archives of Gynecology and Obstetrics* 294.3 (2016): 607-614.

9. Hanprasertpong J and Fujiwara K. "Splenectomy and surgical cytoreduction in epithelial ovarian cancer: a review". *European Journal of Cancer Care* 20.3 (2011): 287-293.

10. Magtibay PM., *et al*. "Splenectomy as part of cytoreductive surgery in ovarian cancer". *Gynecologic Oncology* 102.2 (2006): 369-374.

11. Zapardiel I., *et al*. "Splenectomy as part of primary cytoreductive surgery for advanced ovarian cancer: a retrospective cohort study". *International Journal of Gynecological Cancer* 22.6 (2012): 968-973.

12. De Porto AP., *et al*. "Assessment of splenic function". *European Journal of Clinical Microbiology and Infectious Diseases* 29.12 (2010): 1465-1473.

13. Weledji EP. "Benefits and risks of splenectomy". *International Journal of Surgery* 12.2 (2014): 113-119.

14. Filippova OT., *et al*. "Hematologic changes after splenectomy for ovarian cancer debulking surgery, and association with infection and venous thromboembolism". *International Journal of Gynecological Cancer* 30.8 (2020): 1183-1188.

15. Diener MK., *et al*. "Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a randomised, controlled multicentre trial". *Lancet* 377.9776 (2011): 1514-1522.

16. Lipson RL., *et al*. "The postsplenectomy blood picture". *American Journal of Clinical Pathology* 32 (1959): 526-532.

17. Ramirez PT and Dos Reis R. "Splenectomy in patients with advanced or recurrent ovarian cancer: open and laparoscopic surgical techniques and clinical outcomes". *Gynecologic Oncology* 104.2 (2007): 29-32.

18. Howdieshell TR., *et al*. "Surgical infection society guidelines for vaccination after traumatic injury". *Surgical Infections* 7.3 (2006): 275-303.

19. Qu Y., *et al*. "Management of postoperative complications following splenectomy". *International Surgery* 98.1 (2013): 55-60.

20. Lee EJ., *et al*. "Splenectomy and distal pancreatectomy in advanced ovarian cancer". *Gland Surgery* 10.3 (2021): 1218-1229.

21. Bassi C., *et al*. "Postoperative pancreatic fistula: an international study group (ISGPF) definition". *Surgery* 138.1 (2005): 8-13.

22. Fotopoulou C., *et al*. "European Society of Gynaecological Oncology guidelines for the peri-operative management of advanced ovarian cancer patients undergoing debulking surgery". *International Journal of Gynecological Cancer* 31.9 (2021): 1199-1206.

23. Alexander M., *et al*. "Timely initiation of chemotherapy: a systematic literature review of six priority cancers - results and recommendations for clinical practice". *Journal of Internal Medicine* 47.1 (2017): 16-34.

24. Mahner S., *et al*. "Prognostic impact of the time interval between surgery and chemotherapy in advanced ovarian cancer: analysis of prospective randomised phase III trials". *European Journal of Cancer* 49.1 (2013): 142-149.

25. Hofstetter G., *et al*. "The time interval from surgery to start of chemotherapy significantly impacts prognosis in patients with advanced serous ovarian carcinoma - analysis of patient data in the prospective OVCAD study". *Gynecologic Oncology* 131.1 (2013): 15-20.

26. Wright J., *et al*. "Variability in chemotherapy delivery for elderly women with advanced stage ovarian cancer and its impact on survival". *British Journal of Cancer* 98.7 (2008): 1197-1203.

27. Tewari KS., *et al*. "Early initiation of chemotherapy following complete resection of advanced ovarian cancer associated with improved survival: NRG Oncology/Gynecologic Oncology Group study". *Annals of Oncology* 27.1 (2016): 114-121.

28. Wright JD., *et al*. "Effect of radical cytoreductive surgery on omission and delay of chemotherapy for advanced-stage ovarian cancer". *Obstetrics and Gynecology* 120.4 (2012): 871-881.

29. Timmermans M., *et al*. "Interval between debulking surgery and adjuvant chemotherapy is associated with overall survival in patients with advanced ovarian cancer". *Gynecologic Oncology* 150.3 (2018): 446-450.

30. Flynn PM., *et al*. "Does the interval from primary surgery to chemotherapy influence progression-free survival in ovarian cancer?" *Gynecologic Oncology* 86.3 (2002): 354-357.

31. Gadducci A., *et al*. "Relationship between time interval from primary surgery to the start of taxane- plus platinum-based chemotherapy and clinical outcome of patients with advanced epithelial ovarian cancer: results of a multicenter retrospective Italian study". *Journal of Clinical Oncology* 23.4 (2005): 751-758.

32. Paulsen T., *et al*. "Influence of interval between primary surgery and chemotherapy on short-term survival of patients with advanced ovarian, tubal or peritoneal cancer". *Gynecologic Oncology* 102.3 (2006): 447-452.

33. Aletti GD., *et al*. "Is time to chemotherapy a determinant of prognosis in advanced-stage ovarian cancer?" *Gynecologic Oncology* 104.1 (2007): 212-216.

34. Anuradha S., *et al*. "Variations in adjuvant chemotherapy and survival in women with epithelial ovarian cancer - a population-based study". *Acta Oncologica* 55.2 (2016): 226-233.

35. Rosa DD., *et al*. "The interval from surgery to chemotherapy in the treatment of advanced epithelial ovarian carcinoma". *European Journal of Surgical Oncology* 32.5 (2006): 588-591.

36. Lydiksen L., *et al*. "Is it possible to define an optimal time for chemotherapy after surgery for ovarian cancer?" *Gynecologic Oncology* 133.3 (2014): 454-459.

37. Sorbe B. "Prognostic importance of the time interval from surgery to chemotherapy in treatment of ovarian carcinoma". *International Journal of Gynecological Cancer* 14.5 (2004): 788-793.

38. Starbuck KD., *et al*. "Prognostic impact of adjuvant chemotherapy treatment intensity for ovarian cancer". *PLoS One* 13.11 (2018): e0206913.

39. Seebacher V., *et al*. "The impact of the duration of adjuvant chemotherapy on survival in patients with epithelial ovarian cancer - a retrospective study". *PLoS One* 12.1 (2017): e0169272.

40. Buzelé R., *et al*. "Medical complications following splenectomy". *Journal of Visceral Surgery* 153.4 (2016): 277-286.

41. Cadili A and De Gara C. "Complications of splenectomy". *The American Journal of Medicine* 121.5 (2008): 371-375.

Volume 11 Issue 8 August 2022