Risk Factors for Anastomotic Leakage in Advanced Ovarian Cancer Surgery: A Large Single-Center Experience

Barbara Costantini, MD¹, Virginia Vargiu, MD², Francesco Santullo, MD³, Andrea Rosati, MD⁴, Matteo Bruno, MD⁵, Valerio Gallotta, MD⁵, Claudio Lodoli, MD⁵, Rossana Moroni, MD⁴, Fabio Pacelli, MD⁵, Giovanni Scambia, MD¹,⁵, and Anna Fagotti, PhD¹,⁵

¹Division of Gynecologic Oncology, Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; ²Department of Oncology, Gemelli Molise Spa, Campobasso, Italy; ³Surgical Unit of Peritoneum and Retroperitoneum, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; ⁴Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; ⁵Università Cattolica del Sacro Cuore, Rome, Italy

ABSTRACT

Background. Cytoreductive surgery is currently the main treatment for advanced epithelial ovarian cancer (OC), and several surgical maneuvers, including colorectal resection, are often needed to achieve no residual disease. High surgical complexity carries an inherent risk of postoperative complications, including anastomosis leakage (AL). Albeit rare, AL is a life-threatening condition. The aim of this single-center retrospective study is to assess the AL rate in patients undergoing colorectal resection and anastomosis during primary surgery for advanced epithelial OC through a standardized surgical technique and to evaluate possible pre/intra- and postoperative risk factors to identify the population at greatest risk.

Methods. A retrospective analysis of clinical and surgical characteristics of 515 patients undergoing colorectal resection and anastomosis during primary surgery for advanced epithelial OC between December 2011 and October 2019 was performed. Several pre/intra- and postoperative variables were evaluated by multivariate analysis as potential risk factors for AL.

Results. The overall anastomotic leakage rate was 2.9% (15/515) with a significant negative impact on postoperative course. Body mass index $<18$ kg/m², preoperative albumin value lower than 30 mg/dL, section of the inferior mesenteric artery at its origin, and medium–low colorectal anastomosis ($<10$ cm from the anal verge) were identified as independent risk factors for AL on multivariate analysis.

Conclusions. AL is confirmed to be an extremely rare but severe postoperative complication of OC surgery, being responsible for increased early postoperative mortality. Preoperative nutritional status and surgical characteristics, such as blood supply and anastomosis level, appear to be the most significant risk factors.
Compared with the colorectal cancer literature, there is a paucity of data on risk factors for AL during OC surgery, with few showing statistical significance, such as previous pelvic irradiation, poor nutritional status, and distance of anastomosis from anal verge.6,17

Recently, a multicenter retrospective study identified the at surgery, additional small bowel resections, and hand-sewn anastomosis as other possible risk factors.20

The aim of this study is to assess the AL rate in patients receiving colorectal resection and anastomosis during primary surgery (PDS or IDS) for OC, through a standardized surgical technique, in a high-volume tertiary cancer center specialized on OC treatment. In addition, we evaluated several possible pre/intra- and postoperative risk factors for AL.

METHODS

This study is a single-center retrospective, observational cohort study.

All pre-, intra-, and postoperative characteristics of patients who underwent primary surgery (PDS or IDS) for advanced epithelial OC at the Department of Gynecologic Oncology, Fondazione Polyclinico Universitario A. Gemelli IRCCS, between December 2011 and October 2019, were collected. All demographic and surgical variables were retrieved from our prospective electronic database (REDCAP).

Informed consent was obtained from all women for their data to be registered and analyzed for scientific purposes. The trial was approved by our Ethics Committee (protocol ID no. 3304).

Patients Clinical and Surgical Data

The enrolled population included all patients with histological diagnosis of epithelial ovarian, fallopian, or peritoneal cancer (FIGO stage IIIB–IVB) who underwent rectosigmoid resection and anastomosis with curative intent. All patients received preoperative mechanical bowel preparation.

Patients with end-colostomy or end-ileostomy were excluded from the study.

Several system scores, clinical and surgical variables, helpful in predicting operative and postoperative risk, were used to classify patients’ risk.

Patients with American Society of Anesthesiologists (ASA) score > 2, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) ≥ 2, and Age-Adjusted Charlson Comorbidity Index (ACCI) score > 2 were considered at high risk of postoperative complications.

Preoperative albumin level below 30 mg/dL and preoperative hemoglobin values below 10.0 g/dL were indicative respectively of severely poor nutritional status and moderate to severe anemia.

Nutritional status was also assessed by body mass index (BMI) classification (divided into the following categories: underweight patients with BMI < 18 kg/m², normal weight–overweight with BMI 18–30 kg/m², and obese patients with BMI ≥ 30 kg/m²).

CA-125 value and Predictive Index Value (PIV) at initial diagnosis were considered as potential indicators of tumor burden. To identify the disease with the greatest tumor burden, the cutoffs were set to CA-125 ≥ 1000 U/mL and PIV ≥ 6.

A cutoff of 60 years was used, based on the median age of the study population. Suspcion of AL, suggested by clinical signs such as abdominal pain or distension, leukocytosis, fever, presence of gas, pus, or feces in the drains, the abdominal incision, or vagina was confirmed by computed tomography (CT) scan with rectal contrast enema and/or immediate relaparotomy.

AL was defined as communication between the intra- and extraluminal compartments due to a defect in the integrity of the intestinal wall originating from the staple line of the neorectal reservoir between the colon and rectum. Pelvic abscess adjacent to the anastomosis were also categorized as anastomotic leakage even if no communication could be demonstrated with the colonic lumen at the anastomosis.21

The Common Terminology Criteria for Adverse Events v3.0 (CTCAE) was used to classify intraoperative complications (CTCAE 0–1 versus ≥ 2). The Extended Clavien–Dindo classification of surgical complications was used for the grading definition of early complications.22

OS was calculated from date of primary diagnosis to date of death or last follow-up.

Surgical Technique

All colorectal resections and anastomoses were performed by a dedicated team of general surgeon who routinely collaborate with our department. Regarding the resection technique, when possible, we tended to perform low ligation of the lower mesenteric artery, thus preserving the left colic artery. In some cases, selective ligation of the sigmoid arteries was performed, preserving the superior rectal artery to improve the vascularization of the rectal stump. In case of doubt regarding intestinal vascularity, we used a coarse evaluation of the pulsatile flow and/or a marginal artery section to the proximal colon.

The mobilization of the colon for the execution of tension-free anastomosis involved the following steps: The first surgical maneuver was mobilization of the splenic
flexure through the development of the avascular plane between the Gerota’s fascia and the left Toldt’s fascia. Second, the mobilization continued by dissecting the pancreatic–colic ligament. The ligation and section of the mesenteric vessels (first sacrificing the inferior mesenteric vein and/or the sigmoid vessels up to the ligation and sectioning of the inferior mesenteric artery) were maneuvers considered when the tension at the level of the anastomosis was still considered excessive by the surgeon. Colorectal anastomosis was performed using a circular stapling device for either end-to-end or side-to-end anastomosis. An air leakage test was performed immediately after completion of anastomosis. In case of intraoperative leakage, additional overstitches were placed.

In rare cases where the tissues were damaged or excessive leakage was found at the intraoperative air leakage test, the anastomosis was repackaged.

The level of the anastomosis was considered medium–low if the distance from the anal verge was less than 10 cm as measured by the rigid probe. The cutoff was set at 10 cm as this was considered and assumed to be the average length of the “extraperitoneal” rectum (medium–low rectum).

Diverting ostomy was performed based on the clinical status of the patient before surgery (compromised clinical condition, judged mainly by ASA and ECOG scores), the surgical procedures performed (multiple bowel resection), specific characteristics of the anastomotic complex (such as the level of anastomosis, the quality of the tissues, and their vascularization), and in general the surgical complexity (also judged by operative time and need for intraoperative transfusions).

**Statistical Analysis**

Considering that the leakage rate for OC ranges between 2.7% and 16.9%, a sample size of \( N = 515 \) patients was calculated to be appropriate to detect a 16.9% AL (conservative approach), with \( \alpha = 0.05 \) and a margin of error of 3.23%.

Descriptive statistics were used to describe the surgical procedures, patients, and pathological characteristics.

Absolute frequency and percentage were adopted for qualitative variables, or median and interquartile range (IQR) for continuous variables. The normality of data was verified via the Kolmogorov–Smirnov test. Groups were compared using the Mann–Whitney \( U \) test for continuous variables and the Pearson \( \chi^2 \) test or Fisher exact test for categorical variables.

Binomial logistic regression was performed to ascertain the effects of independent variables, judged as possible risk factors by clinicians, on the occurrence of AL and on the risk of diverting ostomy.

Multivariable logistic regression analysis was performed using a backward stepwise (likelihood ratio) model. Only the significant variables were included in the multivariable model. \( p \)-Value \( \leq 0.050 \) was considered statistically significant (two-tailed test).

Survival analysis was performed using the Kaplan–Meier method and the Cox regression models.

Statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, New York, NY) software for Windows.

**RESULTS**

**Patient and Surgical Data**

Five-hundred fifteen (515) patients [372 (72.2%) PDS and 143 (27.8%) IDS] were identified in the study period. Clinical features of the study population are presented in Table 1.

The study population was almost equally divided between women under the age of 60 years and (53.8%) and older women (46.2%). Of the study population, 12.6% was obese (BMI \( \geq 30 \) kg/m\(^2\)) while 4.9% was underweight (BMI < 18 kg/m\(^2\)). Forty-six patients (10.8%) had preoperative serum albumin values below 30 mg/dl, while 52 (10.1%) had preoperative hemoglobin values below 10.0 g/dl. Almost all patients had an American Society of Anesthesiologists (ASA) score of 2 or less (95.7%), and an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) equal to or less than 1 (96.1%).

Surgical characteristics of the studied population are presented in Table 2.

Optimal debulking was achieved in 95.9% of the enlisted population (CGR, 79.6%; RT (residual tumor) \( \leq 1 \), 16.3%) while RT > 1 cm was left in the remaining population (4.1%). The Surgical Complexity Score (SCS) was generally elevated, with 69.9% of patients belonging to group 3 (high complexity score group). Regarding the specific characteristics of the rectosigmoid resection, high resection was usually performed (75.1%), with left colic artery sparing in 75.1% of cases. Based on patients’ clinical characteristics, surgical complexity, and the surgeon’s decision, protective ostomy (ileostomy or colostomy) was performed in 230 patients (44.7% of cases). Twenty-one patients (4.1%) had intraoperative complications of grade 2–4. Estimated blood loss (EBL) above 500 ml was recorded in 61.4% of cases, while intraoperative transfusions were required in 24.9% of patients.

Postoperative features are described in Table 3.

The median hospital stay was 8 days, with 100 patients (19.4%) suffering severe postoperative complications.
grade III–V). Fourteen patients (2.7%) died within 90 days from surgery.

Median time to chemotherapy was 39 days, but 17 patients (3.3%) could not start or resume chemotherapy due to postoperative complications (deterioration of physical condition or death).

Of the 230 patients receiving protective ostomy, 153 (66.5%) underwent ostomy reversal, with a median time of 7 months. The remaining 77 had no reversal due to disease recurrence or refusal to undergo further surgery.

### Study Protocol Results

The registered AL rate was 2.9% (15 out of 515 patients) (Table 3).

Diagnosis of AL was generally made on postoperative day 5 (interquartile range (IQR): 4–10.5 days).

Seven of the 15 patients with AL (46.7%) had diverting ostomy during first surgery; 3 could be treated conservatively with drainage plus broad-spectrum antibiotic therapy, while the rest underwent reoperation with resection of the anastomotic complex and colostomy according to Hartmann procedures. All eight patients with AL and without diverting ostomy required surgical reintervention (six were treated with the Hartmann procedure, and two received ileostomy) (Supplementary Table S1). The following variables showed a statistical significant association with AL on univariate analysis (Table 4): age at surgery ≥ 60 years (odds ratio (OR): 3.307, 95% confidence interval (CI): 1.039–10.527, \( p = 0.043 \)), body mass index (BMI) < 18 kg/m² (OR: 16.461, 95% CI: 5.191–52.196, \( p < 0.001 \)), preoperative albumin value < 30 mg/dL (OR: 5.671, 95% CI: 1.772–18.143, \( p = 0.003 \)), pelvic lymph node resection (OR: 4.269, 95% CI: 1.297–14.051, \( p = 0.017 \)), section at

### Table 1

| Variable                | All n (%) |
|-------------------------|-----------|
| No. of cases            | 515       |
| Age (years)             |           |
| <60                     | 277 (53.8) |
| ≥60                     | 238 (46.2) |
| BMI (kg/m²)             |           |
| <18                     | 25 (4.9)   |
| 18–29.9                 | 425 (82.5) |
| ≥30                     | 65 (12.6)  |
| ASA                     |           |
| ≤2                      | 493 (95.7) |
| >2                      | 22 (4.3)   |
| ECOG-PS                 |           |
| 0–1                     | 495 (96.1) |
| 2                       | 20 (3.9)   |
| AACCI                   |           |
| 0–2                     | 337 (65.4) |
| >2                      | 178 (34.6) |
| Smokers                 |           |
| No                      | 386 (79.6) |
| Yes                     | 99 (20.4)  |
| NA                      | 30         |
| PIV at primary diagnosis|           |
| ≤6                      | 287 (62.3) |
| ≥8                      | 174 (37.7) |
| NA                      | 54         |
| Hb pre surgery          |           |
| <10.0 g/dL              | 52 (10.1)  |
| ≥10.0 g/dL              | 463 (89.9) |
| Preoperative albumin value (mg/dL) | |
| ≤30.0 mg/dL             | 46 (10.8)  |
| >30.0 mg/dL             | 380 (89.2) |
| NA                      | 89         |
| CA-125\(^b\)            |           |
| <1000 U/mL              | 254 (55.0) |
| ≥1000 U/mL              | 208 (45.0) |
| NA                      | 53         |
| Ascites                 |           |
| <500 cc                 | 286 (55.5) |
| ≥500 cc                 | 229 (44.5) |
| Surgical timing         |           |
| PDS                     | 372 (72.2) |
| IDS                     | 143 (27.8) |
| Number of cycles\(^c,d\) | 4.00 (3.00–5.00) |
| Time from CHT to surgery (days)\(^c,d\) | 40.00 (34.00–46.50) |
| Bevacizumab\(^d\)       |           |
| Yes                     | 40 (28.0)  |
the origin of the inferior mesenteric artery (IMA) (OR: 9.002, 95% CI: 2.814–28.801, *p* < 0.001), hypogastric vessels section (OR: 11.758, 95% CI: 3.354–41.220, *p* < 0.001), distance of the anastomosis from the anal verge > 10 cm (OR: 21.761, 95% CI: 4.840–97.838, *p* < 0.001), intraoperative transfusions (OR: 3.619, 95% CI: 1.286–10.187, *p* = 0.015), and postoperative anemia (OR: 5.132, 95% CI: 1.431–18.412, *p* = 0.012).

Among the variables included in multivariate logistic regression analysis, only the following were identified as independent predictors of AL: BMI < 18 kg/m² (OR: 19.621, 95% CI: 3.394–113.447, *p* = 0.001), preoperative albumin value < 30 mg/dL (OR: 20.639, 95% CI: 2.345–181.669, *p* = 0.006), section at the origin of the IMA (OR: 10.732, 95% CI: 1.862–61.846, *p* = 0.008), and distance of the anastomosis from the anal verge > 10 cm (OR: 14.673, 95% CI: 2.340–92.006, *p* = 0.004).

Among the variables included in multivariate logistic regression analysis, only the following were identified as independent predictors of AL: BMI < 18 kg/m² (OR: 19.621, 95% CI: 3.394–113.447, *p* = 0.001), preoperative albumin value < 30 mg/dL (OR: 20.639, 95% CI: 2.345–181.669, *p* = 0.006), section at the origin of the IMA (OR: 10.732, 95% CI: 1.862–61.846, *p* = 0.008), and distance of the anastomosis from the anal verge > 10 cm (OR: 14.673, 95% CI: 2.340–92.006, *p* = 0.004).

Supplementary Table S2 reports several pre- and intraoperative risk factors for diverting ostomy. Among all the analyzed variables, only the following showed increased risk on multivariate analysis: more than one bowel resection (OR: 5.412, 95% CI: 3.097–9.456, *p* < 0.001), medium–low anastomosis at less than 10 cm from the anal verge (OR: 2.414, 95% CI: 1.446–4.030, *p* = 0.001), operative time longer than 300 min (OR: 1.680, 95% CI: 1.023–2.758, *p* = 0.040), and need for intraoperative transfusions (OR: 1.688, 95% CI: 1.031–2.763, *p* = 0.037).
Table 5 compares risk factors for diverting ostomy and anastomotic leak.

**Postoperative Features and Survival Analysis**

Regarding the early postoperative course (Table 6), a significant difference among patients with and without AL was noted in length of hospital stay (8 versus 23.5 days, \( p = 0.001 \)) and time to chemotherapy (38 versus 49.5 days, \( p = 0.013 \)). Three patients with AL (20%) died from multiorgan failure (MOF) (Table 6) within 90 days versus 2.2% in women without AL (2.2% versus 20%, \( p = 0.001 \)).

Median OS was 28 months in the AL group versus 50 months in the no-AL group, although the difference was not statistically significant (HR 1.767, 95% CI 0.869–3.594, \( p = 0.116 \)) (Supplementary Fig. S1).

Supplementary Table S3 reports ostomy-related complications. We detected an overall rate of ostomy-related complications of 33.9% (78 out of 230 patients), of which only 16 were grade \( \geq 3 \) (7%).

The most frequently reported complication was dehydration (23.9%), with most patients requiring i.v. fluid therapy (22.2%), and four patients (1.7%) underwent early ostomy reversal.

Forty-five patients (19.6%) were admitted to the emergency department due to ostomy-related complications, but as many as 87 patients (37.8%) reported difficulties in ostomy management and impaired quality of life.

**DISCUSSION**

**Summary of Main Results**

AL was confirmed as a rare postoperative complication in OC surgery, with only 15 reported cases in the entire population of 515 patients (2.9%).

Of the ALs, 80% were classified as “severe” since they required reintervention, and three patients died during postoperative course, leading to a significant increase in early postoperative mortality rate. Generally, patients with AL had statistically longer hospital stay and prolonged time to start of chemotherapy.

Shorter median OS was observed in patients with AL versus no AL (hazard ratio (HR) 1.767, 95% CI 0.869–3.594, \( p = 0.116 \)) but the difference was not statistically significant. Therefore, AL could not be confirmed as a negative prognostic factor for OS.

Concerning variables that could increase the AL risk, the state of cachexia (demonstrated by low BMI and low preoperative albumin value) and specific characteristics of the colorectal anastomosis (ligation and section at the origin of the IMA and “mid–low level” anastomosis) resulted as relevant risk factors.

**Results in the Context of Published Literature**

Several studies have shown how the consequences of AL can have a profound and negative impact on patients’ postoperative course, resulting in prolonged hospital stay, reduced probability of starting chemotherapy, and increased time to start of chemotherapy. 7,10–15

Furthermore, some authors have recognized it as a significant negative prognostic factor in terms of 90-day mortality and OS, although these latter data did not reach statistical significance in our series. 15,24
| Variable                        | Univariate analysis | Multivariate analysis |
|--------------------------------|---------------------|-----------------------|
|                                | OR (95% CI)         | p-Value               | OR                  | p-Value               |
| Age (years)                    | Reference           | Reference             |
| <60                            | Reference           | 3.307 (1.039–10.527) | 0.043               | 5.773 (0.785–41.887) | 0.085               |
| ≥60                            | 5.773 (0.785–41.887)|                       |                      |                      |
| BMI (kg/m²)                    | Reference           | Reference             |
| 18–29.9                        | Reference           | 16.461 (5.191–52.196)| < 0.001             | 19.621 (3.394–113.447)| 0.001               |
| <18                            | 0.814 (0.100–6.621) | 0.848                 | 0.218 (0.004–10.735)| 0.444               |
| ≥30                            | 0.814 (0.100–6.621) | 0.848                 | 0.218 (0.004–10.735)| 0.444               |
| ECOG                           | Reference           | Reference             |
| 0–1                            | Reference           | 1.808 (0.226–14.473) | 0.557               |                      |
| 2                              | 2.218 (0.791–6.221) | 0.130                 |                      |                      |
| ACCI                           | Reference           | Reference             |
| 0–2                            | Reference           | 1.808 (0.226–14.473) | 0.557               |                      |
| >2                             | 2.218 (0.791–6.221) | 0.130                 |                      |                      |
| Preoperative albumin value (mg/dL) | Reference   | Reference             |
| ≥30.0                          | Reference           | 5.671 (1.772–18.143) | 0.003               | 20.639 (2.345–181.669)| 0.006               |
| <30.0                          | 5.671 (1.772–18.143)|                       |                      |                      |
| Type of surgery                | Reference           | Reference             |
| IDS                            | Reference           | Reference             |
| PDS                            | 5.553 (0.723–42.623)| 0.099                 |                      |                      |
| Ascites                        | Reference           | Reference             |
| <500                           | Reference           | 0.828 (0.290–2.362)  | 0.724               |                      |
| ≥500                           | 0.828 (0.290–2.362) | 0.724                 |                      |                      |
| PIV at first diagnosis         | Reference           | Reference             |
| <6                             | Reference           | 0.590 (0.185–1.884)  | 0.373               |                      |
| ≥8                             | 0.590 (0.185–1.884) | 0.373                 |                      |                      |
| SCS                            | Reference           | Reference             |
| 1–2                            | Reference           | 0.857 (0.288–2.550)  | 0.782               |                      |
| 3                              | 0.857 (0.288–2.550) | 0.782                 |                      |                      |
| No. of bowel resections        | Reference           | Reference             |
| 1                              | Reference           | 1.274 (0.398–4.080)  | 0.683               |                      |
| ≥2                             | 1.274 (0.398–4.080) | 0.683                 |                      |                      |
| Splenectomy                    | Reference           | Reference             |
| No                             | Reference           | 1.456 (0.510–4.163)  | 0.483               |                      |
| Yes                            | 1.456 (0.510–4.163) | 0.483                 |                      |                      |
| Hepatic resection              | Reference           | Reference             |
| No                             | Reference           | 3.426 (0.963–12.727) | 0.066               |                      |
| Yes                            | 3.426 (0.963–12.727)| 0.066                 |                      |                      |
| Lymph node resection           | Reference           | Reference             |
| None                           | Reference           | Reference             |
| Pelvic                         | 4.269 (1.297–14.051)| 0.017                 | 5.274 (0.878–31.700)| 0.069               |
| Lumbo-aortic                   | 4.269 (1.297–14.051)| 0.017                 | 5.274 (0.878–31.700)| 0.069               |
| Level of IMA section           | Reference           | Reference             |
| Preservation of the left colic artery | Reference | Reference             |
| Section at the origin          | 9.002 (2.814–28.801)| < 0.001               | 10.732 (1.862–61.846)| 0.008               |
| Hypogastric vessels section    | Reference           | Reference             |
| No                             | Reference           | Reference             |
| Yes                            | 11.758 (3.354–41.220)| < 0.001              | 6.412 (0.427–96.373)| 0.179               |
|                                |                     |                       |                      |                      |
However, the identification of the population at greatest risk for AL, and proven strategies to prevent it, are still lacking today. Patients with OC represent a particular population since they usually present with critical clinical conditions and malnourishment, due to abundant ascitic fluid and widespread carcinomatosis. Moreover, given the predominantly peritoneal spread of OC, resections are usually higher than those performed for rectal cancer, and as suggested by Richardson et al., this may explain the slightly lower rate of AL in OC patients.

When looking specifically at the OC literature, the studies appear inhomogeneous in assessing AL risk factors. This could be due both to its rarity and to the heterogeneity of the surgical technique used to perform the intestinal resection and anastomosis.

According to literature data, we confirmed the low preoperative albumin value (<30 mg/dL) and, in addition, identified low BMI (<18 kg/m²) as independent preoperative risk factors for AL.

### TABLE 4 (continued)

| Variable | Univariate analysis | Multivariate analysis |
|----------|---------------------|-----------------------|
| Distance of anastomosis from anal verge | | |
| ≥10 cm (high) | Reference | Reference |
| <10 cm (mid–low) | 21.761 (4.840–97.838) | <0.001 |
| Protective ostomy | | |
| None | Reference | |
| Ileostomy/colostomy | 1.087 (0.388–3.043) | 0.874 |
| HIPEC | | |
| No | Reference | |
| Yes | 0.844 (0.108–6.591) | 0.872 |
| Intraoperative complications | | |
| CTCAE 0–1 | Reference | |
| CTCAE ≥ 2 | 3.895 (0.820–18.492) | 0.087 |
| Operative time (min) | | |
| ≤300 | Reference | |
| >300 | 1.988 (0.533–7.141) | 0.292 |
| EBL | | |
| ≤500 mL | Reference | |
| >500 mL | 4.226 (0.943–18.930) | 0.060 |
| Intraoperative transfusions | | |
| No | Reference | Reference |
| Yes | 3.619 (1.286–10.187) | 0.015 |
| Postoperative anemia (Hb ≤ 8.0 g/dL) | | |
| No | Reference | Reference |
| Yes | 5.132 (1.431–18.412) | 0.012 |

Variables included in multivariate analysis: age, BMI, preoperative albumin value, lymph node resection, level of IMA section, hypogastric vessels section, distance of anastomosis from anal verge, intraoperative transfusions, and postoperative anemia.

OR odds ratio, CI confidence interval, BMI body mass index, ECOC-P Eastern Cooperative Oncology Group-Performance Status, AACC1 age-adjusted Charlson Comorbidity Index, PDS primary debulking surgery, IDS interval debulking surgery, PIV Predictive Index Value, SCS Surgical Complexity Score, IMA inferior mesenteric artery, HIPEC hyperthermic intraperitoneal chemotherapy, CTCAE Common Terminology Criteria for Adverse Events, EBL estimated blood loss, RT residual tumor, Hb hemoglobin.
Among intraoperative variables, in agreement with several other studies, we confirmed medium–low level of anastomosis as a relevant risk factor of AL.\textsuperscript{16,17,20,28} The hypotheses proposed to explain this association are various, such as the major surgical difficulty when performing an anastomosis in the narrower and deeper portion of the pelvis, with greater tissue trauma, increased tension, and lower blood flow.\textsuperscript{31} In this context, section of the IMA at its origin was another important negative predictor identified, suggesting that a reduced blood supply could hinder correct healing of the anastomosis. This hypothesis was also suggested by Son et al.,\textsuperscript{32} who demonstrated reduced incidence of AL in patients with preservation of superior rectal artery.

As anticipated, conflicting data are reported on the efficacy of ostomy as a strategy to prevent AL,\textsuperscript{33–44} although a broad consensus exists on its role in preventing the catastrophic consequences of AL, with a reduction in morbidity and mortality.\textsuperscript{34,36–38,40,45–48}

In our series, diverting ostomy did not prove to be a protective factor for AL, but it allowed conservative treatment in three patients who received it, which means a number needed to treat of 91 (91 ostomy to conservatively treat 1 AL). Another key to understanding these results could be that we correctly identify only 46.7% (7/15) of high-risk AL patients, in which we performed a protective ileostomy. Nevertheless, 57.1% (4/7) of these patients required a Hartmann procedure because of complete or nearly complete detachment of the anastomosis. These findings may indicate that there is a very small group of patients with an extremely increased risk of AL, where probably the best choice should be to perform a Hartmann procedure directly.

### Strengths and Weaknesses

The greatest bias in this study certainly lies in its retrospective nature, and we are aware that the limited number of AL events makes the risk factor analysis less reliable. Furthermore, this prevented an evaluation of interesting surgical maneuvers for the reduction of AL, such as techniques for mobilization of the descending colon to obtain an anastomosis as vascularized and tension free as possible. However, this is currently the largest monocentric study to specifically report the rate of AL and its main risk factors for patients with advanced OC.

---

**TABLE 5** Comparison of risk factors for diverting ostomy and anastomotic leak

| Variable                                      | OR     | IC       | p-Value | Variable                                      | OR     | IC       | p-Value |
|-----------------------------------------------|--------|----------|---------|-----------------------------------------------|--------|----------|---------|
| No. of bowel resection ≥ 2                   | 5.412  | 3.097–9.456 | <0.001  | BMI < 18 kg/m\(^2\)                           | 19.621 | 3.394–113.447 | 0.001  |
| Distance of anastomosis from anal verge < 10 cm | 2.414  | 1.446–4.030 | 0.001  | Preoperative albumin level < 30 mg/dL         | 20.639 | 2.345–181.669 | 0.006  |
| Operative time > 300 min                      | 1.680  | 1.023–2.758 | 0.040  | Section at origin of IMA                      | 10.732 | 1.862–61.846 | 0.008  |
| Intraoperative transfusions                   | 1.688  | 1.031–2.763 | 0.037  | Distance of anastomosis from anal verge < 10 cm | 14.673 | 2.340–92.006 | 0.004  |

AL anastomotic leak, BMI body mass index, IMA inferior mesenteric artery

**TABLE 6** Postoperative characteristics of patients with and without anastomotic leakage

| Variable                                | No AL n (%) | AL n (%) | p-Value |
|-----------------------------------------|-------------|----------|---------|
| No. of cases                            | 500         | 15       |         |
| Hospital stay (days)                    | 8 (5–13)\(^\ddagger\) | 23.5 (11.5–34.5)\(^\ddagger\) | 0.001* |
| Severe early postoperative complication | 87 (17.4)   | 13 (86.7) | 0.001\(^\ddagger\) |
| Time to chemotherapy (days)             | 38 (32.25–46)\(^\ddagger\) | 49.5 (41–62.75)\(^\ddagger\) | 0.013\(^\ddagger\) |
| Patients who could not start chemotherapy | 14 (2.8%)  | 3 (20%)  | 0.002\(^\ddagger\) |
| Early postoperative mortality rate (90 days) | 11 (2.2%) | 3 (20%) | 0.001\(^\ddagger\) |

\(^\ddagger\) Median (I–III interquartile)  
\(*\) Mann–Whitney U-test  
\(^\ddagger\) Pearson chi-squared test  
AL anastomotic leakage
undergoing PDS or IDS. Moreover, all the resections and anastomoses were performed by a dedicated team of general surgeons who routinely collaborate with gynecologic oncologists, and all the procedures were performed using the same surgical technique, further reducing the inherent limitations of a retrospective surgical study.

Implications for Practice and Future Research

The findings of our study totally support the hypothesis that cancer cachexia, malnutrition, and chronic inflammatory activity (documented by low serum albumin value)\textsuperscript{10,49} are the most predictive preoperative factors of surgical morbidity, and strongly influence the postoperative course of OC patients\textsuperscript{50,51} also increasing the incidence of AL. Therefore, increasing attention must be paid to preoperative optimization of the patient by developing programs that include physical exercise, and nutritional counseling with possible protein integration.\textsuperscript{51,53} Recently, in fact, a protocol was adopted in our department for preoperative optimization of the patient, providing both the association between mechanical bowel preparation and antibiotics, and careful nutritional assessment of the patient, protocols that were not active in the years considered in this study. Regarding the intraoperative details, data on the best colorectal resection and anastomosis in patients with advanced OC are lacking and the exact amount of blood flow needed to heal the intestinal wall remains to be determined.\textsuperscript{31} For this, it would be advisable to accurately tailor surgery according to tumor dissemination, to ensure maximal vascular supply to the anastomosis through preservation of the left colonic artery or, when possible, the upper rectal artery.\textsuperscript{31,54,55} For this purpose, intraoperative evaluation of anastomosis perfusion using indocyanine green could be an interesting topic for future studies.

Another currently open question is the usefulness of ostomy for AL prevention. We are aware of the high rate of ostomies performed, which we could explain with the high rate of optimal cytoreduction achieved (95.9\% of cases, with 79.6\% of CGR) and the high surgical complexity of the operations performed. In fact, in these cases, the surgeon, in an attempt to minimize the incidence and severity of postoperative complications, could be reassured by the diverting ostomy, although our results show that this did not prevent the onset of AL and allowed conservative treatment in a relatively low number of cases (NNT 91). In support of this, with the exception of the distance of the anastomosis from the anal verge, risk factors for ostomy and those for AL differed for the most part (Table 5). This means that the decision-making process that leads the surgeon to perform a protective ostomy is quite heterogeneous and based on personal experience and surgeon’s feelings, rather than actual risk factors for AL. However, considering the nonnegligible complication rate directly related to the ostomy itself, the nonreversal rate of 33.5\%, and its negative psychological consequences,\textsuperscript{56,57} further studies are needed to better define the population that could really benefit from it and to make intraoperative decision-making as objective as possible.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1245/s10434-022-11686-y.

ACKNOWLEDGEMENT None.

FUNDING Open access funding provided by Università Cattolica del Sacro Cuore within the CRUI-CARE Agreement.

DISCLOSURES The authors have no conflicts of interest to declare.

OPEN ACCESS This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program (SEER), Cancer Stat Facts: Ovarian Cancer. Available at https://seer.cancer.gov/statfacts/html/ovary.html. Accessed 26 August 2020.

2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70(1):7–30. https://doi.org/10.3322/caac.21590.

3. Du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfitzner J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d’Investigateurs Nationaux Pour les Etudes des Cancers de l’Ovaire (GINECO). Cancer. 2009;115(6):1234–44. https://doi.org/10.1002/cncr.21419.

4. Timmermans M, van der Hel O, Sonke GS, Van de Vijver KK, van der Aa MA, Kruitwagen RF. The prognostic value of residual disease after neoadjuvant chemotherapy in advanced ovarian cancer. A systematic review Gynecol Oncol 2019;153(2):445–51. https://doi.org/10.1016/j.ygyno.2019.02.019.

5. Ghirardi V, Moruzzi MC, Bizzarri N, Varginu V, D’indinoSante M, Garganese G, Pasciuto T, Loverro M, Scambia G, Fagotti A. Minimal residual disease at primary debulking surgery versus complete tumor resection at interval debulking surgery in
advanced epithelial ovarian cancer: a survival analysis. *Gynecol Oncol* 2020;157(1):209–13. https://doi.org/10.1016/j.ygyno.2020.01.010.

6. Fagotti A, Ferrandina G, Vizzielli G, Fanfani F, Gallotta V, Chiantera V, Costantini B, Margariti PA, Gueli Alletti S, Cosentino F, Tortorella L, Scambia G. Phase III randomised clinical trial comparing primary surgery versus neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPIAN trial): Final analysis of peri-operative outcome. *Eur J Cancer*. 2016;59:22–33. https://doi.org/10.1016/j.ejca.2016.01.017.

7. Grimm C, Harter P, Alesina PF, Prader S, Schneider S, Ataseven B, Meier B, Brunkhorst V, Hinrichs J, Kurrzeder C, Heitz F, Kahl A, Traut A, Groehm HT, Walz M, du Bois A. The impact of type and number of bowel resections on anastomotic leakage risk in advanced ovarian cancer surgery. *Gynecol Oncol*. 2017;146(3):498–503. https://doi.org/10.1016/j.ygyno.2017.06.007.

8. Sozzi G, Petrillo M, Berretta R, Capozzi VA, Paci G, Musico G, Di Donna MC, Vargiu V, Bernardini F, Lago V, Domingo S, Fagotti A, Scambia G, Chiantera V. Incidence, predictors and clinical outcome of pancreatic fistula in patients receiving splenectomy for advanced or recurrent ovarian cancer: a large multicentric experience. *Arch Gynecol Obstet*. 2020;302(3):707–14. https://doi.org/10.1007/s00404-020-05684-2.

9. Scaletta G, Quagliozzi L, Cianci S, Vargiu V, Mele MC, Scambia G, Fagotti A. Management of postoperative chylous ascites after surgery for ovarian cancer: a single-institution experience. *Updates Surg*. 2019;71(4):279–34. https://doi.org/10.4086/4-019-00656-x.

10. Chi DS, Zivanovic O, Levinson KL, et al. The incidence of major complications after the performance of extensive upper abdominal surgical procedures during primary cytoreduction of advanced ovarian, tubal, and peritoneal carcinomas. *Gynecol Oncol*. 2010;119(1):38–42. https://doi.org/10.1016/j.ygyno.2010.05.031.

11. Peiretti M, Zivanovic G, Zanagnolo V, Aletti GD, et al. Role of maximal primary cytoreductive surgery in patients with advanced epithelial ovarian and tubal cancer: Surgical and oncological outcomes. Single institution experience. *Gynecol Oncol*. 2010;119(2):259–64. https://doi.org/10.1016/j.ygyno.2010.07.032.

12. Tseng JH, Suidan RS, Zivanovic O, et al. Diverting ileostomy during primary debulking surgery for ovarian cancer: Associated factors and postoperative outcomes. *Gynecol Oncol*. 2016;142(2):217–24. https://doi.org/10.1016/j.ygyno.2016.05.035.

13. Braicu EI, Sehouli J, Richter R, Pietzner K, Denkert C, Fotopoulou C. Role of histological type on surgical outcome and survival following radical primary tumour debulking of epithelial ovarian, fallopian tube and peritoneal cancers. *Br J Cancer*. 2011;105(12):1818–24. https://doi.org/10.1038/bjc.2011.455.

14. Peiretti M, Bristow RE, Zapardiel I, et al. Rectosigmoid resection at the time of primary cytoreduction for advanced ovarian cancer. A multi-center analysis of surgical and oncological outcomes. *Gynecol Oncol*. 2012;126(2):220–3. https://doi.org/10.1016/j.ygyno.2012.04.030.

15. Kalogera E, Dowdy SC, Mariani A, et al. Multiple large bowel resections: potential risk factor for anastomotic leak. *Gynecol Oncol*. 2013;130(1):213–8. https://doi.org/10.1016/j.ygyno.2013.04.002.

16. Obermair A, Hagenauer S, Tamandl D, et al. Safety and efficacy of low anterior en bloc resection as part of cytoreductive surgery for patients with ovarian cancer. *Gynecol Oncol*. 2001;83(1):115–20. https://doi.org/10.1006/gyno.2001.6353.

17. Richardson DL, Mariani A, Cliby WA. Risk factors for anastomotic leak after recto-sigmoid resection for ovarian cancer. *Gynecol Oncol*. 2006;103(2):667–72. https://doi.org/10.1016/j.ygyno.2006.05.003.

18. Fotopoulou C, Zang R, Gultekin M, Cibula D, Ayhan A, Liu D, et al. Value of tertiary cytoreductive surgery in epithelial ovarian cancer: an international multicenter evaluation. *Ann Surg Oncol*. 2013;20:1348–54.

19. Koscielny A, Ko A, Egger EK, Kuhn W, Kalff JC, Keyyer-Paik MD. Prevention of anastomotic leakage in ovarian cancer debulking surgery and its impact on overall survival. *Anticancer Res*. 2019;39(9):5209–18. https://doi.org/10.21873/anticancer.13718.

20. Lago V, Fotopoulou C, Chiantera V, Minig L, Gil-Moreno A, Cascales-Campos PA, Jurado M, Tejerizo A, Padilla-Iserte P, Malune ME, Di Donna MC, Marina T, Sánchez-Iglesias JL, Olloqui A, García-Granero Á, Matute L, Fornes V, Domingo S. Risk factors for anastomotic leakage after colorectal resection in ovarian cancer surgery: a multi-centre study. *Gynecol Oncol*. 2019;153(3):549–54. https://doi.org/10.1016/j.ygyno.2019.03.241.

21. Rahbari NN, Weitz J, Hohenberger W, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. *Surgery*. 2010;147(3):339–51. https://doi.org/10.1016/j.surg.2009.10.012.

22. Katayama H, Kurokawa Y, Nakamura K, et al. Extended Clavien-Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. *Surg Today*. 2016;46(6):668–85. https://doi.org/10.1007/s00595-015-1236-x.

23. Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. *Am J Obstet Gynecol*. 2007;197(6):676.e1-7. https://doi.org/10.1016/j.ajog.2007.10.495.

24. Mirnezami A, Mirnezami R, Chandrakumaran K, Sasapu K, Sagar P, Finan P. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. *Ann Surg*. 2011;253(5):890–9. https://doi.org/10.1097/SLA.0b013e3182128929.

25. Laky B, Janda M, Cleghorn G, Obermair A. Comparison of different nutritional assessments and body-composition measurements in detecting malnutrition among gynecologic cancer patients. *Am J Clin Nutr*. 2008;87(6):1678–85. https://doi.org/10.1093/jcnu/87.6.1678.

26. Cianci S, Rumolo V, Rosati A, et al. Sarcomenia in ovarian cancer patients, oncologic outcomes revealing the importance of clinical nutrition: review of literature. *Curr Pharm Des*. 2019;25(22):2480–90. https://doi.org/10.2174/138161282566190722112808.

27. Yim GW, Eoh KJ, Kim SW, Nam EJ, Kim YT. Malnutrition identified by the nutritional risk index and poor prognosis in advanced epithelial ovarian carcinoma. *Nutr Cancer*. 2016;68(5):772–9. https://doi.org/10.1080/01635381.2016.1159702.

28. Mourton SM, Temple LK, Abu-Rustum NR, et al. Morbidity of the rectum: a proposal by the International Study Group of Rectal Cancer. *Ann Surg*. 2007;246(6):1348–54. https://doi.org/10.1093/ajcn/87.6.1678.

29. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg*. 2005;242(3):326–43. https://doi.org/10.1097/01.sla.0000179621.33268.83.

30. Khuri SF, Daley J, Henderson W, Kur H, Demakis J, Aust JB, Chong V, Fabri PJ, Gibbs JO, Grover F, Hammermeister K, Irvin G 3rd, McDonald G, Passaro E Jr, Phillips L, Scamman F, Spencer J, Strempel JF. The Department of Veterans Affairs’ NSQIP: the first national, validated, outcome-based, risk-adjusted, and peer-
controlled program for the measurement and enhancement of the quality of surgical care. National VA Surgical Quality Improvement Program. Ann Surg. 1998;228(4):491–507. https://doi.org/10.1097/00000658-199810000-00006.

31. Shogan BD, Carlisle EM, Alverdy JC, Umanskiy K. Do we really know why colorectal anastomoses leak? J Gastrointest Surg. 2013;17(9):1698–707. https://doi.org/10.1007/s11605-013-2227-0.

32. Son JH, Kim J, Shim J, et al. Comparison of posterior rectal dissection techniques during rectosigmoid colon resection as part of cytoreductive surgery in patients with epithelial ovarian cancer: close rectal dissection versus total mesorectal excision. Gynecol Oncol. 2019;153(2):362–7. https://doi.org/10.1016/j.ygyno.2019.02.029.

33. Karanjia ND, Corder AP, Bearn P, Heald RJ. Leakage from stapled low anastomosis after total mesorectal excision for carcinoma of the rectum. Br J Surg. 1994;81(8):1224–6. https://doi.org/10.1002/bjs.1800810580.

34. Matthiessen P, Hallböök O, Andersson M, Rutegård J, Sjödahl R. Defunctioning stoma in low anterior resection with total mesorectal excision: questions of safety. Br J Surg. 2005;92(9):1137–42. https://doi.org/10.1002/bjs.5045.

35. Kalogera E, Nitschmann CC, Dowdy SC, Cliby WA, Langstraat BF02562579. Guidelines for rectosigmoid resection in advanced ovarian cancer surgery [published online ahead of print, 2021 Feb 14]. Ann Surg Oncol. 2021. https://doi.org/10.1245/s10434-021-09651-2.

36. Marbach A, Vargiu V, Santullo F, et al. Rectosigmoid mesorectal sparing resection in advanced ovarian cancer surgery [published online ahead of print, 2021 Feb 11]. Ann Surg Oncol. 2021. https://doi.org/10.1245/s10434-021-09665-w.

37. Fielding LP, Stewart-Brown S, Hittinger R, Blesovsky L. Protective colostomy in low anterior resection of the rectum. Br J Surg. 2001;88(9):1216–20. https://doi.org/10.1046/j.0007-1323.2001.01862.x.

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.