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Risk factors for anastomotic leakage after colorectal resection in ovarian cancer surgery: A multi-centre study

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HIGHLIGHTS

- 695 patients with colorectal anastomosis were included. The anastomotic leak (AL) rate was 6.6%
- Twelve pre-/intra-operative variables were analysed as potential independent risk factors for AL.
- Age, albumin, additional bowel resection, manual anastomosis and distance from the anal verge were associated with AL.
- A predictive model was created to stablish the risk of anastomotic leak for a given patient.

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ABSTRACT

Objective. To determine pre-/intraoperative risk factors for anastomotic leak after modified posterior pelvic exenteration (MPE) or colorectal resection in ovarian cancer and to create a practical instrument for predicting anastomotic leak risk.

Background. In advanced ovarian cancer surgery, there is rather limited published evidence, drawn from a small sample, providing information about risk factors for anastomotic leak.

Methods. Eight hospitals participated in this retrospective study. Data on 695 patients operated for ovarian cancer with primary anastomosis were included (January 2010–June 2018). Twelve pre-/intraoperative variables were analysed as potential independent risk factors for anastomotic leak. A predictive model was created to stablish the risk of anastomotic leak for a given patient.

Results. The anastomotic leak rate was 6.6% (46/695; range 1.7%–12.5%). A total of 457 patients were included in the final multivariate analysis. The following variables were found to be independently associated with anastomotic leakage: age at surgery (OR 1.046, 95% CI 1.013–1.080, $p = 0.005$), serum albumin level (OR 0.621, 95% CI 0.407–0.948, $p = 0.027$), one or more additional small bowel resections (OR 3.544, 95% CI 1.228–10.23, $p = 0.019$), manual anastomosis (OR 8.356, 95% CI 1.777–39.301, $p = 0.007$) and distance of the anastomosis from the anal verge (OR 0.839, 95% CI 0.726–0.971, $p = 0.018$).

Conclusions. Due to the low incidence of AL in ovarian cancer patients, a restrictive stoma policy based on the presence of risk factors should be the actual recommendation. Hand-sewn anastomosis should be avoided.

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1. Introduction

Cytoreductive surgery is the cornerstone of advanced ovarian cancer treatment and often requires the performance of a modified posterior pelvic exenteration (MPE) or colorectal resection, ideally followed by an end-to-end colorectal anastomosis with the aim of optimal cytoreduction [1,2]. One of the most challenging complications of this procedure is anastomotic leak (AL), which is considered a life-threating situation. With a reported incidence between 1.24% and 9% in ovarian cancer patients [3–14], AL makes any adjuvant postoperative treatment challenging and thus has a negative impact on overall prognosis [15].

Diverting ileostomy (DI) has been proposed as a protective resource to reduce the incidence and consequences of AL, even though studies suggest that they do not reduce actual leak rates but only reduce the rates of complications such as sepsis, the need for re-laparotomy etc. [11]. Furthermore, DI is related to dehydration, malnutrition and renal impairment determined by a high outflow debit, as well as complications related to prolapse or stricture [14]. The reversal of the stoma is also associated with a potential range of surgical complications, but most importantly, the stoma cannot be reversed in all patients due to longer-term antiangiogenetic maintenance treatment etc. [16,17]. DI affects self-image and has been associated with serious psychological effects and a decrease in quality of life (QoL) [18]. The ghost ileostomy (GI) has been previously described in ovarian cancer [19], presenting the advantages of DI but without its drawbacks and minimizing the impact of faecal peritonitis in the case of leakage [19–24].

The use of DI has been based on the risk factors taken from the colorectal surgery literature: adverse medical condition (e.g. malnutrition, severe heart disease, steroid use), obesity (BMI > 30), intra-operative bleeding >1 L, difficult pelvic dissection, inadequate blood supply, a positive air leak test, incomplete doughnut rings and evidence of potential intraoperative adverse events related to the stapled colorectal anastomosis, such as excessive tautness, bleeding, hematoma or anastomosis close to the anal verge [25–27]. Nevertheless, to date, there is no clear indication regarding which cases would and would not benefit from DI [28].

In advanced ovarian cancer surgery, there is rather limited published evidence, drawn from a small sample, providing information about risk factors for anastomotic leak, such as serum albumin ≤3 g/dL, multiple bowel resections, distance to the anal verge and a long operating time [3,6,15], but in the end, an individual decision-making process determines whether a diverting ileostomy, a terminal colostomy or primary anastomosis will be performed. The present retrospective, multicentre study aims to assess the incidence, risk factors and outcome of anastomotic leaks after colorectal anastomosis in ovarian cytoreductive surgery procedures.

Table 1
Demographic, pathological and surgical details for the whole group of patients.

Variable	$n = 695$
	n (%)
Centre	
A	126 (18.1)
B	169 (24.3)
C	100 (14.4)
D	83 (11.9)
E	64 (9.2)
F	61 (8.8)
G	60 (8.7)
H	32 (4.6)
Disease status	
Initial diagnosis	561 (80.7)
Relapse	134 (19.3)
FIGO - stage	
II	29 (4.2)
III	418 (60.1)
IV	114 (16.4)
Unknown (relapse)	134 (19.3)
Binary histology	
High grade	634 (91.8)
Low grade	57 (8.2)
Histotype	
Serous	572 (82.4)
Endometrioid	49 (7)
Mucinous	15 (2.2)
Clear cells	22 (3.2)
Others[a]	36 (5.2)
Performance status ECOG	
0	414 (64.3)
1	212 (32.9)
2	14 (2.2)
3	4 (0.6)
Other procedures performed (apart from rectosigmoid resection)	
Appendicectomy	412 (59.3)
Omentectomy	507 (73)
Lymphadenectomy	392 (56.4)
Diaphragm stripping	329 (47.3)
Splenectomy	213 (30.7)
Bladder or ureteric resection	43 (6.2)
Cholecystectomy	70 (10.1)
Other[b]	83 (11.9)

FIGO: International Federation of Gynecology and Obstetrics; ECOG: The Eastern Cooperative Oncology Group.
[a] Including: mixed tumour, undifferentiated, germinal, granulosa, carcinosarcoma and germinal tumours.
[b] Including distal pancreatectomy, debulking of the porta hepatis, partial liver resection, stomach curvature, lateral extended endopelvic resection (LEER), abdominal wall and pleural resection.

2. Material & methods

This is a retrospective, multicentre cohort study that included eight cancer centres across three European countries. After approval was obtained from the local ethics committee, a retrospective review was conducted in all patients who underwent cytoreductive surgery for primary advanced or relapsed ovarian cancer with colorectal resection and anastomosis between January 2010 and June 2018. Those patients with end colostomy or end ileostomy, as well as those for whom relevant information was missing, were excluded from this analysis (Fig. 1).

The following demographic and pathological variables were recorded: newly diagnosed or relapsed disease, International Federation of Gynecology and Obstetrics (FIGO 2014) stage, histotype, tumour grade (binary classification) and performance status (ECOG). Furthermore, extended surgical procedures, such as omentectomy, lymphadenectomy, appendicectomy, diaphragmatic stripping, splenectomy, partial liver resection, bladder/ureteric resection or gall bladder removal, were evaluated and recorded.

The following preoperative risk factors for AL were analysed: age at surgery, Body Mass Index (BMI), diabetes, smoking status, steroid use (defined as chronic use of corticosteroids due to diseases such as severe asthma, sarcoidosis, ulcerative colitis or rheumatoid arthritis), previous whole pelvic radiotherapy, neoadjuvant chemotherapy, previous use of bevacizumab (defined as last course administration in the last 2 months before colorectal resection), preoperative serum albumin level and operative risk assessed according to the American Society of Anesthesiology (ASA) score.

Intraoperative risk factors for anastomosis leakage included surgical time, additional non-colorectal bowel resection, type of anastomosis (stapled, hand sewn), use of stomas, distance from the colorectal anastomosis to the anal verge, result of a leakage test (bubble test), estimated blood loss, red blood intraoperative transfusion and use of HIPEC (Intraperitoneal hyperthermic chemoperfusion).

2.1. Statistical analysis

Clinical data were summarized as means (SD) in the case of continuous variables and as relative and absolute frequencies in the case of categorical variables. Logistic regression was carried out to assess and identify risk factors. Finally, because patients from the same hospital

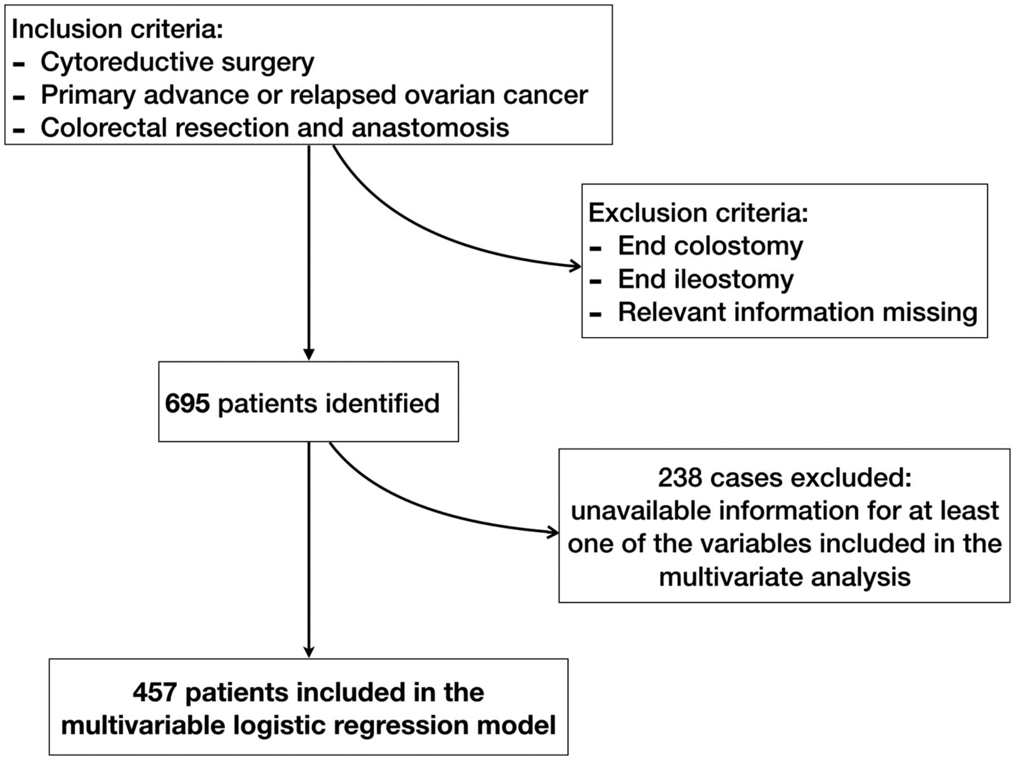

Fig. 1. Flow diagram.

are more likely to share risk factors with each other than with those from other hospitals, the logistic regression was extended with the "Hospital" variable as a random effect with a random intercept to correct for non-independence of the data. The discrimination power of the logistic regression model was summarized using the c-index, and the model was validated by employing bootstrapping (500 repetitions). $P < 0.05$ was considered to indicate statistical significance (2-tailed test). R software (version 3.5.1) and the packages rms (version 5.1-2), clickR (version 0.4.20) and lme4 (version 1.1-18-1) were used for the descriptive and inferential analyses. A risk model score based on the multivariate logistic regression analysis of preoperative and intraoperative risk factors to establish the risk of AL was created.

3. Results

3.1. Patient baseline characteristics (Table 1)

Between January 2010 and June 2018, a total of 695 patients were included. In 561 cases (80.7%) it was a first diagnosis of cancer, and in 134 cases (19.3%) the surgery was performed because of relapsed disease. The most common FIGO stage was III, with 481 patients (60.1%), followed by stage IV (16.4%). Most of the tumours were classified as high grade (91.8%) and of the serous histotype (82.4%). The vast majority of patients (97.2%) had a good performance status of ECOG 0–1. Additional surgical procedures included appendectomy (n 418; 59.3%), omentectomy (n 507; 73%), 73%), lymphadenectomy (n 392; 56.4%), diaphragm stripping (n 329; 47.3%), splenectomy (n 213; 30.7%), bladder or ureteric resection (n 43; 6.2%) and gall bladder resection (n 70; 10.1%). Note that most of the procedures were previously performed in patients with relapsed ovarian cancer. Patient- and tumour-related characteristics are presented in Table 1.

3.2. Anastomotic leak-related risk factors (Table 2)

The average incidence of AL was 6.6% (46/695; range 1.7%–12.5%). The preoperative risk factors of those patients who experienced an AL and those who did not were as follows: age at surgery (57.8 years vs 61.4 years), BMI (25.1 kg/m^2 vs 25.6 kg/m^2); diabetes (5.6% vs 6.3%); smoking status (15.3% vs 11.1%); chronic use of corticosteroids (5.7% vs 4.4%); previous history of radiotherapy (0.7% vs 2.2%); previous neoadjuvant chemotherapy (26.4% vs 21.7%); previous treatment with bevacizumab (7.2% vs 2.2%); serum albumin level (3.8 g/dl vs 3.7 g/dl) and ASA score (I 5.1% vs 4.4%; II 70.2% vs 63%; III 24.4% vs 28.2%; IV 0.3% vs 4.4%).

Regarding the description of intraoperative risk factors between AL and no-AL patients, they were the following: operating time (349.2 min vs 395.5 min); additional bowel resection (large bowel: 19.9% vs 19.6%; large and small bowel: 9.1% vs 13%; small bowel ≥1 8.4% vs 15.2%); type of anastomosis (stapled anastomosis + reinforcing suture: 34.3% vs 19.6%; stapled: 62.1% vs 71.7%; hand sewn: 3.6% vs 8.7%); positive leakage test (1.6% vs 4.8%); distance from the anastomosis to the anal verge (8.8 cm vs 8.5 cm); use of a stoma (ghost ileostomy 7.2% vs 4.4%; ileostomy 15.9% vs 32.6%); estimated blood loss (564.4 mL vs 637.1 mL); intraoperative red blood transfusion (1.7 units vs 1.4 units) and HIPEC use (8.9% vs 13%).

3.3. Multivariate analysis (Table 3)

A total of 238 cases were excluded because of unavailable information for at least one of the variables included in the multivariable logistic regression model, so that only 457 patients were finally included in the multivariate analysis (Fig. 1). The following variables were found to be independently associated with anastomotic leakage: age at surgery (OR 1.046, 95% CI 1.013–1.080, $p = 0.005$), serum albumin level (OR 0.621, 95% CI 0.407–0.948, $p = 0.027$), one or more additional small bowel resections (OR 3.544, 95% CI 1.228–10.23, $p = 0.019$), manual anastomosis (OR 8.356, 95% CI 1.777–39.301, $p = 0.007$), and distance of the anastomosis from the anal verge (OR 0.839, 95% CI 0.726–0.971, $p = 0.018$). Regarding discrimination power, the model showed a raw c-index of 0.73 and a cross-validated c-index of 0.64. A risk model score APP based on an Excel sheet was created to determine the risk

Table 2
AL related risk factors.

Variable	Total n = 695	No leak *n* = 649	Anastomotic leak *n* = 46
Centre, n (%)			
A	126	119	7 (5.6)
B	169	163	6 (3.5)
C	100	92	8 (8)
D	83	76	7 (8.4)
E	64	56	8 (12.5)
F	61	55	6 (9.8)
G	60	59	1 (1.7)
H	32	29	3 (9.4)
Pre-operative			
Age at surgery (years), mean (SD)		57.8 (11.9)	61.4 (11.5)
BMI (kg/m^2), mean (SD)		25.1 (4.9)	25.6 (4.9)
Diabetes, n (%)		36 (5.6)	3 (6.3)
Smoking, n (%)		85 (15.3)	4 (11.1)
Steroid use, n (%)		28 (5.7)	2 (4.4)
Previous pelvic radiotherapy, n (%)		4 (0.7)	1 (2.2)
Neoadjuvant chemotherapy, n (%)		171 (26.4)	10 (21.7)
Use of bevacizumab, n (%)		47 (7.2)	1 (2.2)
Albumin serum level (g/dL), n (%)		3.8 (0.8)	3.7 (0.8)
ASA score, n (%)			
I		33 (5.1)	2 (4.4)
II		455 (70.2)	29 (63)
III		158 (24.4)	13 (28.2)
IV		2 (0.3)	2 (4.4)
Intra-operative			
Operating time (min), mean (SD)		349.2 (130.3)	395.5 (145.4)
Additional bowel resection, n (%)			
No		406 (62.6%)	24 (52.2%)
Large bowel		129 (19.9%)	9 (19.6%)
Large and Small bowel		59 (9.1%)	6 (13%)
Small bowel (≥1)		55 (8.4%)	7 (15.2%)
Type of anastomosis, n (%)			
Stapled anastomosis + reinforcing suture		222 (34.3%)	9 (19.6%)
Stapled		402 (62.1%)	33 (71.7%)
Hand sewn		23 (3.6%)	4 (8.7%)
Leakage test, n (%)			
Negative		564 (98.4%)	40 (95.2%)
Positive		9 (1.6%)	2 (4.8%)
Distance from anastomosis to anal verge (cm), mean (SD)		8.8 (3.3)	8.5 (2.4)
Stomas, n (%)			
No		499 (76.9%)	29 (63%)
Ghost ileostomy		47 (7.2%)	2 (4.4%)
Ileostomy		103 (15.9%)	15 (32.6%)
Estimated blood loss (cc), mean (SD)		564.4 (323.3)	637.1 (438.1)
IOP transfusion (Red blood units), mean (SD)		1.7 (1.7)	1.4 (1.6)
HIPEC, n (%)		58 (8.9%)	6 (13%)

BMI: Body Mass Index; ASA: American Society of Anesthesiologists; IOP: Intra-operative.

Table 3
Multivariable logistic regression model.

C-Index 0.73 Validated C-Index 0.64	Estimate	Odds Ratio	Confidence Interval 95%	P-value
(Intercept)	-6.563	0.001	[0, 1.091]	0.053
Age at surgery (years)	0.045	1.046	[1.013, 1.080]	**0.005**
BMI (Kg/m^2)	-0.002	0.998	[0.930, 1.071]	0.95
Diabetes	-0.050	0.951	[0.263, 3.443]	0.94
Neoadjuvant chemotherapy	-0.632	0.532	[0.235, 1.204]	0.13
Albumin serum level (g/dl)	-0.476	0.621	[0.407, 0.948]	0.027
Additional bowel resection				
No		1	-	
Large bowel	-0.294	0.745	[0.303, 1.832]	0.52
Large and Small bowel	0.379	1.461	[0.469, 4.553]	0.51
Small bowel (≥1)	1.265	3.544	[1.228, 10.23]	**0.019**
Operating time (min, log)	0.827	2.288	[0.844, 6.20]	0.10
Type of anastomosis				
Stapled anastomosis + reinforcing suture		1	-	
Hand sewn	2.123	8.356	[1.777, 39.301]	**0.007**
Stapled	0.691	1.996	[0.841, 4.740]	0.12
Stomas				
No		1	-	
Ghost ileostomy	-1.275	0.279	[0.060, 1.298]	0.10
Ileostomy	-0.059	0.943	[0.413, 2.153]	0.89
Use of HIPEC	-0.095	0.909	[0.322, 2.565]	0.86
Distance of the anastomosis to the anal verge (cm)	-0.175	0.839	[0.726, 0.971]	**0.018**
IOP transfusion (additional Red blood unit)	-0.141	0.868	[0.697, 1.081]	0.21

BMI: Body Mass Index; ASA: American Society of Anesthesiologists; IOP: Intra-operative. In bold means that the variable has been found statistically significant ($p < 0.05$).

of AL in individual patients by applying the logistic regression formula (Annex I, available at https://oaa.app.link/LrSzCkpZoT).

4. Discussion

AL represents a challenging scenario after colorectal anastomosis and has been associated with high morbidity and mortality rates, worsening the outcome in ovarian cancer patients [15]. The reported incidence of AL is lower in ovarian cancer patients than in colorectal cancer patients. This scenario limits a proper analysis of risk factors. The restrictions of previously published evidence are probably justified by the size of the sample, its heterogeneity and/or the small number of events in some of the cohorts, which may restrict the detection of risk factors.

In order to bridge the gap, with regard to the sample size, we carried out a retrospective study involving several centres dedicated to advanced ovarian cancer surgery to improve the statistical power and perform a multivariate analysis. As the surgical technique may vary between centres, the hospital of origin was considered a random effect with a random intercept to correct for the non-independence of the data in the multivariate analysis. The reason for this design is given by the low incidence of leakage in ovarian cancer. Finally, 695 patients were included, which represents the largest published sample to date. Only pre- and intraoperative factors were evaluated because they may influence the decision to perform DI; in contrast, postoperative risk factors are not considered in this decision. Several variables which have been previously reported to increase the risk of anastomotic leak and some additional factors which differ between colorectal and ovarian cancer patients were included. For an accurate analysis, 457 patients were included in the final multivariable logistic regression model. The other patients were excluded because of unavailable information for at least one of the variables included in the model. Some factors, such as chronic use of corticosteroids, previous pelvic radiotherapy or use of bevacizumab, were also excluded from the multivariate model because of their low incidence or because of unavailable information in other cases.

Age at surgery, serum albumin level, multiple small bowel resection, hand sewn anastomosis and distance to the anal verge were identified as independent factors associated with AL in the multivariate analysis. Note that the older the patient was, the higher the risk of leak found (OR 1.046, 95% CI 1.013–1.080, $p = 0.005$): an increase in age of 1 year was associated with an increase of 1.046 in the odds of anastomotic leakage. Elderly patients have a theoretical deficit in the healing process and usually present multiple comorbidities that may condition a leak. Serum albumin indicates the patient's nutritional status and is reduced after inflammatory episodes such as surgery or acute stress events. A relation between albumin serum level and AL was also found. As the serum albumin level increases (better nutritional status), the risk of AL decreases (OR 0.621, 95% CI 0.407–0.948, $p = 0.027$): an increase of one unit of serum albumin levels was associated with a decrease of 0.62 in the odds of anastomotic leakage. Additional small bowel resection (≥1) was related to AL (OR 3.544, 95% CI 1.228–10.23, $p = 0.019$): small bowel resection was associated with an increase of 3.54 in the odds of anastomotic leakage compared with not having had any additional bowel resection. No statistical association was found between AL and additional large bowel resection or additional large and small bowel resection. From our point of view, this could be explained by the heterogeneity of this variable. Given the fact that hand-sewn anastomosis increases AL rates approximately 8-fold (OR 8.356, 95% CI 1.777–39.301, $p = 0.007$): manual anastomosis was associated with an increase of 8.36 in the odds of anastomotic leakage compared with using both anastomosis techniques. According to these results, stapled anastomosis seems to be justified as an elective technique to prevent AL. Regarding the distance of anastomosis from the anal verge, as it increases, the risk of AL decreases (OR 0.839, 95% CI 0.726–0.971, $p = 0.018$): an increase in 1 cm in the distance from the anal verge was associated with a decrease of 0.84 in the odds of anastomotic leakage, this being one of the factors to be considered for protective measures such as GI or DI. In addition to BMI, diabetes, neoadjuvant chemotherapy, operating time and intraoperative transfusion, neither the use of DI (OR 0.943; CI 95% 0.413–2.153) nor that of GI (OR 0.279; CI 95% 0.06–1.298) were associated with AL. In consequence, the use of a stoma cannot be recommended by itself in order to diminish the incidence of leakage. With an intraoperative use of 9.22%, HIPEC was not identified as an independent risk factor related to AL (OR 0.909; CI 95% 0.322–2.565). To present our results from a practical point of view, we created a predictive model based on the multivariate analysis to determine the risk of AL at the end of the surgery (Annex I). Notwithstanding, a prospective validation of this predictive model is needed for its clinical application.

In previous studies, a serum albumin level ≤ 3 g/dL and multiple bowel resections were reported as potential risk factors associated with AL in ovarian cancer patients [3,5]. Additional risk factors, such as prior pelvic radiation, anastomosis ≤5 cm from the anal verge, a failed leak test or contamination of the pelvis with stool, have also been identified in patients who underwent colorectal resection. Nevertheless, this analysis was performed in a heterogeneous cohort of patients including only up to 70% of ovarian cancer patients [27]. Regarding the use of DI, based on the presence of risk factors, extended operating time and increased length of rectosigmoid resection have been associated with the decision to perform a DI in ovarian cancer [11]. Nonetheless, in this study the authors reported that some major risk factors, such as the distance of the anastomosis from the anal verge, could not be correctly evaluated owing to unavailable data. In the most recent publications about this topic, the same group of authors reported that no AL risk factor could be identified (except for a weak higher AL rate in the case of multiple bowel resections without a statistically significant increase) [6]; on the other hand, the presence of additional large bowel resection was found to be related to a higher risk of AL (OR 7.23: CI 95% 1.04–50.39; $p = 0.046$) [15]. In recent studies, the use of HIPEC has been a major concern regarding a possible AL, and this fact has led to a high rate of stoma use [37]. HIPEC was not identified as an independent risk factor related to AL. This should be borne in mind in order not to exceed the use of stomas for this reason and considering that some positive evidence from a clinical trial has been published recently [37].

Regarding the use of DI, it has been traditionally recommended in patients with a “high risk” of leak, although its use is not standardized in the management of advanced ovarian cancer. From previously published studies, there is not enough evidence to establish a clear indication for DI use based on the presence of risk factors [3–14]. The performance of DI has been supported by its theoretical decrease of the AL rate. To date, DI has demonstrated a reduction in the severity of AL consequences but not a decrease in the incidence of AL in ovarian cancer [11]. DI is related to a higher morbidity and to a decrease in QoL [18]. GI has been proposed as an alternative to DI, presenting the advantages of DI without its potential drawbacks [19]. Despite all previously exposed, there is no clear indication about which cases would and which would not benefit from DI or GI [29–36].

Concerning the limitations of the study, the retrospective nature of the study might have led to variance in interpretation of the data collected from multiple centres, as well as patients with missing variables. We want to highlight that the key to avoiding AL is to practice a good surgical technique at the moment of anastomosis. One of the major limitations of the previous and present studies consists of the “not possible to measure” factors: achieve a good arterial vascularization, poor venous blood return and free-tension-free anastomosis. Lastly, even though the patients' characteristics are homogeneous, the sample size might still be too small to reach strong results, and conclusions should therefore be interpreted with caution.

In conclusion, due to the low incidence of AL in ovarian cancer patients, a restrictive stoma policy based on the presence of risk factors should be the actual recommendation. Hand sewn anastomosis should be avoided. In the absence of risk factors, conservative management or the use of GI should be recommended. For patients with any of the identified risk factors, the most reasonable option would be to perform a GI as it presents the advantages of DI without its drawbacks, minimizing the impact of faecal peritonitis in the case of a leak and avoiding a stoma in those patients without AL. In case of a combination of risk factors, such as elderly patients after multiple bowel resection associated with low albumin serum levels and/or a short distance from the anastomosis to the anal verge, DI should be considered according to the surgeon's criteria. However, a prospective, multicentre study is needed to corroborate these results.

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Authorship contribution

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References

[1] R.E. Bristow, M.G. Del Carmen, H.S. Kaufman, F.J. Montz, Radical oophorectomy with primary stapled colorectal anastomosis for resection of locally advanced epithelial ovarian cancer, J. Am. Coll. Surg. 197 (2003) 565–573.

[2] G. Houvenaeghel, M. Gutowski, M. Buttarelli, J. Cuisenier, F. Narducci, C. Dalle, et al., Modified posterior pelvic exenteration for ovarian cancer, Int. J. Gynecol. Cancer 19 (5) (2009) 968–973 Jul.

[3] D.L. Richardson, A. Mariani, W.A. Cliby, Risk factors for anastomotic leak after rectosigmoid resection for ovarian cancer, Gynecol. Oncol. 103 (2) (2006) 667–672 Nov.

[4] M. Peiretti, R.E. Bristow, I. Zapardiel, M. Gerardi, V. Zanagnolo, R. Biffi, 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. 126 (2) (2012) 220–223 Aug.

[5] E. Kalogera, S.C. Dowdy, A. Mariani, A.L. Weaver, G. Aletti, J.N. Bakkum-Gamez, et al., Multiple large bowel resections: potential risk factor for anastomotic leak, Gynecol. Oncol. 130 (1) (2013 Jul) 213–218.

[6] C. Grimm, P. Harter, P.F. Alesina, S. Prader, S. Schneider, B. Ataseven, et al., The impact of type and number of bowel resections on anastomotic leakage risk in advanced ovarian cancer surgery, Gynecol. Oncol. 146 (3) (2017) 498–503 Sep.

[7] D.S. Chi, O. Zivanovic, K.L. Levinson, V. Kolev, J. Huh, J. Dottino, 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. 119 (2010) 38–42.

[8] M. Peiretti, V. Zanagnolo, G.D. Aletti, L. Bocciolone, N. Colombo, F. Landoni, 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. 119 (2010) 259–264.

[9] E.I. Braicu, J. Sehouli, R. Richter, K. Pietzner, C. Denkert, C. Fotopoulou, 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 105 (2011) 1818–1824.

[10] C. Fotopoulou, R. Zang, M. Gultekin, D. Cibula, A. Ayhan, D. Liu, et al., Value of tertiary cytoreductive surgery in epithelial ovarian cancer: an international multicenter evaluation, Ann. Surg. Oncol. 20 (2013) 1348–1354.

[11] Tseng JH, Suidan RS, Zivanovic O, Gardner GJ, Sonoda Y, Levine DA, et al. Diverting ileostomy during primary debulking surgery for ovarian cancer: associated factors and postoperative outcomes. Gynecol. Oncol.. 2016 Aug;142(2):217–24.

[12] R.D. Clayton, A. Obermair, I.G. Hammond, Y.C. Leung, A.J. McCartney, The Western Australian experience of the use of en bloc resection of ovarian cancer with concomitant rectosigmoid colectomy, Gynecol. Oncol. 84 (2002) 53–57.

[13] Mourton SM, Temple LK, Abu-Rustum NR, Gemignani ML, Sonoda Y, Bochner BH, et al. Morbidity of rectosigmoid resection and primary anastomosis in patients undergoing primary cytoreductive surgery for advanced epithelial ovarian cancer. Gynecol. Oncol. 2005;99:608–14.

[14] A. Obermair, S. Hagenauer, D. Tamandl, R.D. Clayton, J.L. Nicklin, L.C. Perrin, et al., Safety and efficacy of low anterior en bloc resection as part of cytoreductive surgery for patients with ovarian cancer, Gynecol. Oncol. 83 (2001) 115–120.

[15] T. Bartl, R. Schwameis, A. Stift, T. Bachleitner-Hofmann, A. Reinthaller, C. Grimm, et al., Predictive and prognostic implication of bowel resections during primary cytoreductive surgery in advanced epithelial ovarian cancer, Int. J. Gynecol. Cancer 28 (9) (2018) 1664–1671 Nov.

[16] M.A. Glasgow, K. Shields, R.I. Vogel, D. Teoh, P.A. Argenta, Postoperative readmissions following ileostomy formation among patients with a gynecologic malignancy, Gynecol. Oncol. 134 (3) (2014) 561–565 Sep.

[17] Phatak U.R; Kao L.S; You Y.N; Rodriguez-Bigas M.A; Skibber J.M; Feig B.W. et al. Impact of ileostomy-related complications on the multidisciplinary treatment of rectal cancer, Ann. Surg. Oncol. 2014 Feb;21(2): 507–512.

[18] S.M. Vonk-Klaassen, H.M. De Vocht, M.E. Den Ouden, E.H. Eddes, M.J. Schuurmans, Ostomy-related problems and their impact on quality of life of colorectal cancer ostomates: a systematic review, Qual. Life Res. 25 (1) (2016) 125–133 Jan.

[19] V. Lago, B. Flor, L. Matute, P. Padilla-Iserte, A. García-Granero, M. Bustamante, et al., Ghost ileostomy in advanced ovarian cancer: a reliable option, Int. J. Gynecol. Cancer 28 (7) (2018) 1418–1426 Sep.

[20] M. Sacchi, P.D. Legge, P. Picozzi, F. Papa, C.L. Giovanni, L. Greco, Virtual ileostomy following TME and primary sphincter-saving reconstruction for rectal cancer, Hepatogastroenterology 54 (2007) 1676–1678.

[21] M. Sacchi, P. Picozzi, P. Di Legge, M. Gasparrini, G. Berardi, G. Laracca, et al., Virtual ileostomy following rectal cancer surgery: a good tool to avoid un-useful stomas? Hepatogastroenterology 58 (2011) 1479–1481.

[22] N. Gullà, S. Trastulli, C. Boselli, R. Cirocchi, D. Cavaliere, G.M. Verdecchia, et al., Ghost ileostomy after anterior resection for rectal cancer: a preliminary experience, Langenbeck's Arch. Surg. 396 (2011) 997–1007.

[23] M. Miccini, S.A. Bonapasta, M. Gregori, P. Barillari, A. Tocchi, Ghost ileostomy: real and potential advantages, Am. J. Surg. 200 (2010) e55–e57.

[24] L. Mori, M. Vita, F. Razzetta, P. Meinero, G. D'Ambrosio, Ghost ileostomy in anterior resection for rectal carcinoma: is it worthwhile? Dis. Colon Rectum 56 (1) (2013) 29–34 Jan.

[25] P. Suding, E. Jensen, M.A. Abramson, K. Itani, S.E. Wilson, Definitive risk factors for anastomotic leaks in elective open colorectal resection, Arch. Surg. 143 (2008) 907.

[26] T. Konishi, T. Watanabe, J. Kishimoto, H. Nagawa, Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance, J. Am. Coll. Surg. 202 (2006) 439.

[27] E. Kalogera, C.C. Nitschmann, S.C. Dowdy, W.A. Cliby, C.L. Langstraat, A prospective algorithm to reduce anastomotic leaks after rectosigmoid resection for gynecologic malignancies, Gynecol. Oncol. 144 (2) (2017) 343–347 Feb.

[28] R. Tozzi, J. Casarin, R. Garruto-Campanile, H.S. Majd, M. Morotti, Morbidity and reversal rate of ileostomy after bowel resection during Visceral-Peritoneal Debulking (VPD) in patients with stage IIIC–IV ovarian cancer, Gynecol. Oncol. 148 (1) (2018) 74–78 Jan.

[29] P. Jestin, L. Pahlman, U. Gunnarsson, Risk factors for anastomotic leakage after rectal cancer surgery: a case-control study, Color. Dis. 10 (2008) 715.

[30] L. Morgenstern, T. Yamakawa, M. Ben-Shosham, H. Lippman, Anastomotic leakage after low colonic anastomosis, Am. J. Surg. 123 (1972) 104–109.

[31] N.Y. Wong, K.W. Eu, A defunctioning ileostomy does not prevent clinical anastomotic leak after a low anterior resection: a prospective, comparative study, Dis. Colon Rectum 48 (2005) 2076–2079.

[32] B.A.I. Leester, C. Polynib, Septic complications after low anterior rectal resection—is diverting stoma still justified? Acta Chir. Iugosl. 49 (2002) 67–71.

[33] I. Gastinger, F. Marusch, R. Steinert, S. Wolff, F. Koeckerling, H. Lippert, Protective defunctioning stoma in low anterior resection for rectal carcinoma, Br. J. Surg. 92 (2005) 1137–1142.

[34] E.B.A. Carlsen, Loop ileostomy: technical aspects and complications, Eur. J. Surg. 165 (1999) 140–143.

[35] S.N.M.M. Amin, N.C. Armitage, J.H. Scholefield, Defunctioning loop ileostomy and stapled side-to-side closure has low morbidity, Ann. R. Coll. Surg. Engl. 83 (2001) 246–249.

[36] P.T.H.J. Phang, J.J. Perez-Ramirez, R.D. Madoff, B.T. Gemlo, Techniques and complications of ileostomy takedown, Am. J. Surg. 177 (1999) 463–466.

[37] W.J. Van Driel, S.N. Koole, K. Sikorska, J.H. Schagen van Leeuwen, H.W.R. Schreuder, et al., Hyperthermic intraperitoneal chemotherapy in ovarian cancer, N. Engl. J. Med. 378 (3) (2018) 230–240 Jan 18.