

Anastomotic leak after colon cancer surgery. A retrospective, single-center analysis of 631 patients

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Abstract. Objective: Anastomotic leak continues to represent a fearsome complication in the surgical treatment of colon cancer patients despite the constant interest in reducing its incidence and identifying possible risk factors. Material and Method: Patients diagnosed with colon cancer that underwent curative surgery between January 2013 and December 2015, were included in the study. Patient demographics, comorbidities, preoperative biological parameters, tumor and surgery-related factors alongside with postoperative complications were analyzed in relation to anastomotic leak occurrence 30 days after surgery. Results: The anastomotic leak appeared in 24 (3.95%) of the 631 patients that met the inclusion criteria. Several factors were statistically significantly associated with the anastomotic complication: colon cancer stage ($p=0.034$), metastatic disease ($p=0.02$), tumor location ($p=0.05$), high urea levels ($>60\text{U/l}$) ($p=0.01$) and preoperative creatinine levels over 1.4 mg/dl ($p=0.05$). The type of surgical intervention (elective vs. emergency), the surgical approach (open vs. laparoscopic) and the technique of anastomosis (hand-sewn vs. mechanical, one-layered vs. double-layered) were not associated with anastomotic leak. The following factors were independently linked to anastomotic leak: stage IV disease ($p=0.02$, OR: 3.93, CI 95% 1.205 – 12.850), location of the tumor in the left colon ($p=0.049$, OR: 1.98, CI 95% 0.032 – 1.207) and preoperative creatinine levels $>1.4\text{ mg/dl}$ ($p=0.043$, OR: 3.4, CI 95% 1.038 – 11.130). Conclusions: The only independent risk factors associated with anastomotic leak after colon cancer surgery were stage IV colon cancer, left colon tumors and preoperative high creatinine levels. In our study group, we evaluated possible risk factors for anastomotic leak after colon cancer surgery exclusively.

Key Words: colon cancer, colon resections, anastomotic leak, risk factor, complications.

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Introduction

Anastomotic leak (AL), which can appear after colon cancer surgery, remains a frequent and undesirable complication that can increase short-term morbidity and mortality (Bakker et al 2014, Trencheva et al 2013, Daams et al 2013, Kube et al 2010). Despite the constant interest in the latest decades in diminishing its rate and the numerous conditions identified as predisposing factors, there is a lack of homogenous recommendations in relation to its prevention, diagnostic or management. Since the first definition proposed back in 1991 by Peel et al at the International Study Group for Surgical Infections that assigns AL as „the leak of enteral content from the union of two hollow viscera”, not less than 56 alternatives have been proposed (Bruce et al 2001) and hence the difficulty in getting consistent results and proper recommendations after literature analysis. Identifying factors (patient characteristics, tumor or surgical variables) that may have a role in AL appearance can be of significant clinical relevance from several points of view. Establishing a relationship between certain factors and the previously mentioned complication would allow either their complete removal or a preoperative correction. Moreover, identifying high-risk patients before surgery, allows the surgeon to apply a personalized treatment

and to consider either a reinforcement of the anastomosis or a stoma formation, if it would be more appropriate. Not least, patients who are predisposed to postoperative complications need to benefit from careful monitoring for rapid diagnosis and management of an eventual AL. Literature research has focused on factors that predispose to AL after colorectal cancer surgery but only a few studies analyze AL occurrence after colon cancer exclusively and results are contradictory. Various factors like: male gender (Bakker et al 2014, Jarbouï et al 2017, Parthasarathy et al 2017, McDermott et al 2015, Pommergaard et al 2014), comorbidities (diabetes mellitus (Trencheva et al 2013, Jarbouï et al 2017), cardiovascular (Kube et al 2010) and liver diseases (McDermott et al 2015), previous abdominal surgery (Bakker et al 2014)), alcohol abuse (McDermott et al 2015) and smoking (Pommergaard et al 2014), advanced TNM stage (Bakker et al 2014, Boccola et al 2011) or emergency surgery (Bakker et al 2014, Parthasarathy et al 2017, McDermott et al 2015) are associated with AL in some studies but not in others. The aim of this study was to identify possible risk-factors for AL exclusively in colon cancer patients undergoing surgery with curative intent in a single institutional center.

Material and Methods

Study population

This was a retrospective, longitudinal, observational, analytic cohort study. It included patients diagnosed with malignant tumors of the colon, who were admitted in a single-center specialized in abdominal surgery and underwent curative surgery with primary anastomosis, between January 2013 and December 2015. Patients with rectal cancer or with anastomosis below 15 cm from the anal verge were excluded. Patients with exploratory laparotomies, internal derivations, permanent stomas or with bowel restoration procedures were also excluded from the study. The study protocol was approved by the Ethics Committee of the Regional Institute of Gastroenterology and Hepatology. Open or laparoscopic interventions were performed for the treatment of colon cancer patients included in the study. In all cases, a primary anastomosis was performed. The anastomoses were either hand-sewn (in either one-layer or two-layer technique) or mechanical devices were used, according to the surgeon's preference. The interventions were performed electively or in emergency. Patients operated with left hemicolectomy or with segmental resection of the sigmoid colon were included in the left-sided group of colon cancer surgery due to the particular anatomical characteristics of this colonic segment.

Variables

Anastomotic leak (AL) was the variable of interest in the study and was defined as either (1) the extravasation of enteral content from the union of two bowel ends through the abdominal drains or through the surgical wound (Peel AL et al 1991, Choi HK et al 2006), or as (2) the presence of liquid or gas content in the proximity of the anastomosis diagnosed through CT, ultrasound or abdominal radiography (Fernandes R et al 2013, Volk A et al 2011). Patients with AL have been identified from the Institution's Database recordings as a postoperative complication. Independent variables that were studied in relationship with AL occurrence as potential risk-factors were: patient demographics (age, gender), medical history (diabetes mellitus, cardiovascular or liver disease, associated neoplasms, history of previous abdominal surgery), smoking and alcohol consumption, preoperative data (serum hemoglobin 14-18g/dl, serum total proteins 6-8 g/dl, serum creatinine 0.67-1.17 mg/dl and urea 18-48 mg/dl, serum liver transaminases GOT 5-45 U/l, GPT 5-45 U/l, and pancreatic amylases 30-100 U/l), tumor-related factors (tumor location, TNM stage, grade of differentiation), surgery-related factors (emergency or elective surgery, preoperative occlusion or perforation of the colon, open vs. laparoscopic approach, type of anastomosis, type of suture, the use of protective ileostomy, multi-organ resections), mechanical bowel preparation.

Statistics

Statistical analysis was performed using MedCalc Statistical Software version 17.9.7 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2017). Categorical variables were reported using frequency and percentage, while continuous ones were expressed as mean \pm SD and ranges. For categorical variables the Chi-square test was used to determine the differences between groups, and the Mann-Whitney test was applied for quantitative data. We used AUROC in order to calculate a cut-off value for the risk of AL. Variables that achieved

statistical significance in univariate analysis were further introduced in multivariate logistic regression. A p value <0.05 was considered statistically significant.

Results

Patient related data and AL

From a total of 990 patients registered in the database between January 2013 and December 2015, a number of 631 met the inclusion criteria and have been subjected to statistical analysis (Fig 1).

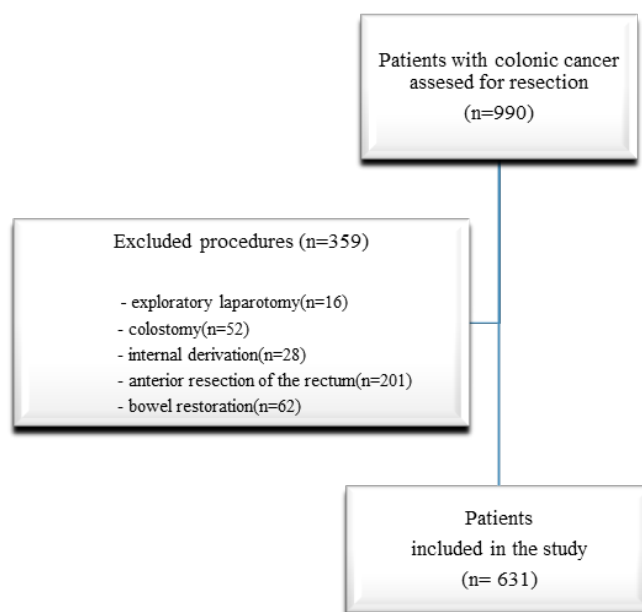


Fig.1 Inclusion criteria chart

The anastomotic leak (AL) rate in the present study was 3.95% (24 patients). Demographic data along with medical history of the 631 patients are presented in Table 1. None of the analyzed variables achieved statistical significance ($p<0.05$).

Tumor characteristics and surgery-related data are presented in Table 2.

Tumor-related variables that reached statistical significance ($p<0.05$) were colon cancer stage ($p=0.034$), metastatic disease ($p=0.02$) and tumor localization ($p=0.05$). None of the surgery-related variables were associated with a higher risk of AL in the present study.

From patient preoperative biological parameters, only urea ($p=0.01$) and creatinine levels ($p=0.05$) were associated with a higher risk of AL occurrence, while serum hemoglobin, total protein level, liver transaminases or pancreatic amylases did not have statistical significance ($p<0.05$) (Table 3).

We calculated for creatinine a cut-off value of 1.4 mg/dl, over which the risk of AL increased, with an AUC of 0.606, with a Se of 37.5% (CI 95% 18.8% - 59.4%) and a Sp of 90.9% (CI 95% 88.4% - 93.1%). Variables that achieved statistical significance in univariate analysis were further introduced in logistic

Table 1. Categorical Variables Related to the Patient and their Association with Anastomotic Leak (AL) in Univariate Analysis (X2 Test)

Variables	Patients without AL n=607/631 (96.05%)	Patients with AL n=24/631 (3.95)	p
Gender			
Male	345/363 (95.05%)	18/363 (4.95%)	0.1
Female	262/268 (97.77%)	6/268 (2.23%)	
Comorbidities			
No	85/89 (95.51%)	4/89 (4.49%)	0.71
Yes	522/542 (96.31%)	20/542 (3.69%)	
Cardiovascular diseases			
No	449/466 (96.36%)	17/466 (3.64%)	0.73
Yes	158/165 (95.76%)	7/165 (4.24%)	
Diabetes			
No	519/540 (96.12%)	21/540 (3.88%)	0.78
Yes	88/91 (96.71%)	3/91 (3.29%)	
Liver disease (Cirrhosis)			
No	600/624 (96.16%)	24/624 (3.84%)	0.59
Yes	7/9 (100%)	0/24 (0.0%)	
Previous neoplasia			
No	579/603 (96.02%)	24/603 (3.98%)	0.28
Yes	28/28 (100%)	0/28 (0.0%)	
Previous abdominal surgery			
No	518/541 (95.75%)	23/541 (4.25%)	0.14
Yes	89/90 (98.89%)	1/90 (1.11%)	
Smoking			
No	580/603 (96.2%)	23/603 (3.8%)	0.98
Yes	27/28 (96.4%)	1/28 (3.6%)	
Alcohol consumption			
No	509/527 (96.6%)	18/527 (3.4%)	
Yes	98/104 (94.3%)	6/104 (5.7%)	0.25

regression multivariate analysis. Multivariate analysis confirmed stage IV, tumor location in the left colon (including descending and sigmoid colon) and high creatinine levels (>1.4mg/dl) as independent risk factors for AL in colon cancer surgery (Table 4).

Discussion

Anastomotic leak (AL) after colorectal resection has been widely studied in the literature. However, only 6 papers have analysed its occurrence exclusively in colon cancer and they reported rates between 3-8.7% (Bakker et al 2014, Trencheva et al 2013, Kube et al 2010, Leichtle et al 2012, Krarup et al 2012, Frasson et al 2015). The highest incidence of AL (8.7%) was reported by Frasson M et al (2015) (The ANACO Study Group) in the only prospective, multi-centric study that analysed the impact of various factors on AL rate. In our paper, the incidence of AL after colon cancer resections was 3.95%, being within the previously mentioned range. None of the patient-related factors were associated with AL in the present study. One explanation could be their individual analysis with respect to AL. Recent studies (Trencheva et al 2013) have drawn attention to the fact that the

use of a Comorbidity Score (Charlson et al 1987) could be of great value when studying the impact of various conditions over the occurrence of a certain complication. This score quantifies both the number and the severity of most common diseases in patients (cardiovascular, pulmonary, liver and kidney disease, diabetes mellitus, associated neoplasms). According to Trencheva et al (2013), there is a cumulative effect of patient diseases over the occurrence of AL, and the risk of AL is higher when the score increases. Smoking and alcohol consumption were not risk factors for AL occurrence in this paper even if the number of AL in case of alcohol abuse was higher 6/104 (5.7%) than in the group that denied its use 18/527 (3.4%). Most studies in the literature report, however, the association between smoking (Parthasarathy et al 2017, McDermott et al 2015, Boccola et al 2011, Frasson et al 2015) or a history of smoking (Jarboui et al 2017, Baucom et al 2014) and the risk of developing AL, but also the association between alcohol consumption and anastomotic complications (Jarboui et al 2017, McDermott et al 2015). McDermott FD et al (2015) reported AL rates that were 7.18 times higher in case of alcohol consumption. An explanation for

Table 2. Categorical Variables Related to the Surgery and the Tumor and their Association with Anastomotic Leak in Univariate Analysis (X2 Test)

Variables	Patients without AL n=607/631 (96.05%)	Patients with AL n=24/631 (3.95)	p
Colon cancer stage			
I-II	307/317 (96.85%)	10/317 (3.15%)	0.034
III	259/268 (96.65%)	9/268 (3.35%)	
IV	41/46 (89.13%)	5/46 (10.87%)	
(T) Tumor extension in colonic wall			
T1	20/20 (100%)	0/20 (0%)	0.8
T2	75/78 (96.15%)	3/78 (3.85%)	
T3	314/326 (96.32%)	12/326 (3.68%)	
T4	198/207 (95.65%)	9/207 (4.35%)	
(N) Nodal Status			
N0	318/329 (96.66%)	11/329 (3.34%)	0.43
N1	176/182 (96.7%)	6/182 (3.3%)	
N2	113/120 (94.17%)	7/120 (5.83%)	
(M) Metastasis			
M0	568/587 (96.76%)	19/587 (3.23%)	0.02
M1	39/44 (88.64%)	5/44 (11.36%)	
Cancer Grades/Differentiation			
G1/Well	118/120 (98.34%)	2/120 (1.66%)	0.2
G2/Moderately	313/330 (95.45%)	15/330 (4.54%)	
G3/Poorly	86/92 (93.48%)	6/92 (6.52%)	
Tumor localization			
Right colon (including hepatic flexure)	232/238 (97.48%)	6/238 (2.52%)	0.05
Transverse colon	11/13 (84.62%)	2/13 (15.38%)	
Left colon (including sigmoid colon)	364/380 (95.79%)	16/380 (4.21%)	
Type of surgical intervention			
Elective	494/512 (96.49%)	18/512 (3.51%)	0.69
Emergency	113/119 (94.96%)	6/119 (5.04%)	
Preoperative complication (occlusion)			
No	534/553 (96.57%)	19/553 (3.43%)	0.19
Yes	73/78 (93.59%)	5/78 (6.41%)	
Preoperative complication (perforation)			
No	586/610 (96.06%)	24/610 (3.94%)	0.35
Yes	21/21 (100%)	0/21 (0.0%)	
Surgical approach			
Open	568/591(96.11%)	23/591 (3.89%)	0.6
Laparoscopic	39/40 (97.5%)	1/40 (2.5%)	
Anastomosis technique			
Manual	558/579 (96.38%)	21/579 (3.62%)	0.43
Mechanical	49/52 (94.24%)	3/52 (5.76%)	
Type of Manual Anastomosis			
Single-layer	298/306 (97.39%)	8/306 (2.61%)	0.63
Double-layer	312/325 (96%)	13/325 (4%)	
Protective ileostomy			
No	574/595 (96.47%)	21/595(3.53%)	0.55
Yes	33/36 (91.67%)	3/36 (8.33%)	
Multiorgan resection			
No	526/546 (96.34%)	20/546 (3.66%)	0.87
Yes	81/85 (95.3%)	4/85 (4.7%)	

Table 3. Continuous Variables and their Association with Anastomotic Leak in Univariate Analysis (X2 Test)

Variables	Patients without AL n=607/631 (96.05%)	Patients with AL n=24/631 (3.95)	p
Preoperative hemoglobin (g/dl)	11 (10; 13)	11.3 (10.3; 14.2)	0.1
Preoperative total protein (g/dl)	7.4 (6.8; 7.9)	7.5 (6.8; 8.2)	0.3
TGO (U/l)	24 (17; 37)	30 (17;55)	0.09
TGP (U/l)	14 (8; 30)	15 (8; 39)	0.75
Pancreatic amylases	48.5 (33; 66)	53 (33; 73)	0.5
Urea	39 (30; 50)	45 (37; 77)	0.01
Creatinine levels	0.93 (0.77; 1.12)	1.01 (0.75; 2.130)	0.05

Table 4. Evaluation of Independent Risk Factors for AL in Multivariate Analysis

Variables	p	OR	95% CI
Colon cancer stage			
I-II	0.06		
III	0.76	1.15	0.452 – 2.963
IV	0.02	3.93	1.205 – 12.850
Tumor localization			
Right colon (including hepatic flexure)	0.153		
Transverse colon	0.301	0.41	0.075 – 2.224
Left colon (including sigmoid colon)	0.049	1.98	0.032 – 1.207
Creatinine level >1.4 mg/dl	0.043	3.4	1.038 – 11.130

the results in our study could be a poorer acknowledgement of the use of both tobacco and alcohol by our patients.

Regarding tumor-related factors, advanced stage neoplastic disease was associated in the present study with a higher risk of developing anastomotic complications. Similar results were obtained by Boccola et al (2011). This could be explained by the fact that an advanced stage of colon cancer disease may need a more extensive resection, subject to difficulties, or it can be associated with late presentation, increased age and poor general condition (McDermott et al 2015). Even if no statistical significance was obtained in univariate analysis, a higher number of AL was seen in locally advanced T4 tumors, in advanced lymph node (N2) metastatic disease, and in the presence of a poor differentiation pattern of the tumor. Advanced metastatic disease was a risk factor for AL in univariate analysis, but the significance was lost in multivariate analysis.

Left colon cancer represents a risk factor for AL occurrence in colon resections. A particularity of left colon vascularization (including both left colon and the sigmoid one) is the presence of two critical points with poor vascularization in the paracolic arcade: Griffith's point - in the splenic flexure region, respectively Sudeck's point in the recto-sigmoid area (Meyers 1975, Sinkeet et al 2012). These situations could explain the greater risk of compromising an anastomosis in these areas with subsequent AL appearance, situation also encountered in our study. A greater risk of AL after left colon resection was previously mentioned by Krarup et al (2012).

Surgery-related factors have also been studied in the literature as possible risk factors for AL. The CLASSIC trial (Jayne et al 2010) set similar AL rates between open (3%) and laparoscopic (4%) approaches to colon cancer. Similar results have been obtained in further studies (Parthasarathy et al 2017, Leichtle et al 2012). In the present study, AL appeared more frequently

after open procedures, but their percentage was much higher than the one of minimally invasive procedures (93.7% vs. 6.3%). Emergency surgery did not influence the rate of postoperative anastomotic complications in the present study. Similar results were found by Parthasarathy et al (2017) and Leichtle et al (2012) while other research papers (Bakker et al 2014, McDermott et al 2015, Krarup et al 2012) reported increased AL rates after emergency surgery. Moreover, preoperative colon cancer complications like intestinal occlusion, bleeding or colonic perforation, increased AL rates (Bakker et al 2014, McDermott et al 2015). In our study, a higher percentage of AL 5/78 (6.6%) was observed following obstructive colon cancer vs. tumors without occlusion 19/553 (3.4%), but no statistical significance was found. None of the patients who developed AL presented tumor perforation.

Anastomotic technique (hand-sewn vs. mechanical) and suture type (single-layer vs. double-layer) were not risk factors for AL occurrence in the present study. Similar results were reported by Sliker et al (2012), who recommend mechanical anastomosis due to its reproducibility and simplicity of use or the single-layer technique in case of hand-sewn anastomosis to avoid excessive inflammation. Results in favour of mechanical anastomosis were reported by Choy et al (2011), who highlighted low AL rates after mechanical anastomoses (1.3%) compared to AL after hand-sewn anastomoses (6.7%), by Kube et al (2010) regarding colonic resections in general and by Singh et al (2014) in terms of ileocolic anastomosis performed after right colon cancer surgery. The anastomotic technique continues to be not a standardized procedure and that is performed according to the surgeon's preferences without having impact over the postoperative anastomotic complication.

The use of diverting stomas has no clear indications in the treatment of colorectal cancer and they are generally performed

according to the surgeon's assessment of each patient's risk. Their use offers contradictory results. Thus, they can reduce the severity of postoperative anastomotic complications, but do not reduce their incidence (McDermott et al 2015). The presence of a diverting stoma in case of AL occurrence could eliminate the need for emergency re-intervention (Montedori et al 2010). However, it should be noted that the rate of complications in reversal surgery is high, with values between 41.6 – 46.5% (Horesh et al 2017, Khan et al 2016). Some studies (Miccini et al 2010, Mori et al 2013) proposed "ghost ileostomy", which would only be opened if a postoperative complication occurs but the procedure is not widely accepted. In this study, the use of diverting stoma did not influence AL rates.

The patient's preoperative biological parameters like haemoglobin and serum protein levels are not risk factors for AL in this paper, while others (Leichtle et al 2012, Iancu et al 2008) found a statistically significant association. Both preoperative anaemia (defined as haemoglobin levels lower than 12g/dl) and hypoproteinemia (defined as serum protein levels lower than 6g/dl) were adjusted before surgery, according to the institution's protocol, and could thus explain the result. Impaired renal function significantly increased the risk of AL in the studied group. Some studies (Parthasarathy et al 2017) reported contradictory results, while others confirmed the association between impaired renal function and the risk of developing AL (McDermott et al 2015, Domencho Pina et al 2016), emphasizing the need to be corrected.

Risk factors for anastomotic leak (AL) after colorectal surgery have been widely studied in the literature but results are inconsistent. However, only few studies focus on its occurrence after colon cancer surgery exclusively, although there are anatomical, pathological and therapeutic differences between colon and rectal tumors. Our results give information regarding the risk of AL occurrence after colon cancer surgery alone. Thus, stage IV colon cancer and tumor localization in the left colon (descending and sigmoid colon) are independent risk factors for AL development, while no other patient, tumor or treatment-related factor was found to influence the risk of AL. Preoperative high creatinine levels (>1.4 mg/dl) represented the only biological parameter associated with a higher risk of AL and so it should be further considered and adjusted, together with hemoglobin and protein levels, in the preoperative management of patients with neoplastic disease.

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