

## ORIGINAL ARTICLE

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# Anastomotic leak after colorectal cancer surgery - risk factors in 21<sup>st</sup> century

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### Summary

**Purpose:** The purpose of our study was to investigate pre-operative and intraoperative risk factors for anastomotic leak (AL) after elective colorectal resections performed for malignancies. In addition, we studied some features of post-operative recovery and their influence on AL occurrence.

**Methods:** We retrospectively reviewed the records of patients that underwent colorectal surgical procedures for malignancies between January 2013 and December 2017 in a single institution. Only procedures with primary anastomosis were included.

**Results:** Of the 153 patients, 56.2% were male. The mean age was 67.5 years. AL occurred in 15 patients (9.8%). In univariate analysis, multiorgan resection, delayed postop-

erative bowel movement and delayed onset of per oral intake were significantly correlated with AL. Gender, preoperative albumin level, primary cancer site and surgery duration did not have significant correlation with AL.

**Conclusions:** Risk factors described in the literature of the 20th century are no longer current. The main findings that feature postoperative recovery were associated with increased risk of AL and should be more carefully investigated in further studies which could lead towards the development of new specific post-operative protocols.

**Key words:** colorectal cancer, anastomotic leak, risk factors, rectal cancer, colon cancer

### Introduction

Despite many surgical and technological advances, anastomotic leak (AL) remains one of the most severe complications of colorectal surgery, directly influencing postoperative morbidity and mortality [1,2]. Additionally, AL after colorectal cancer surgery is linked with increased risk for local and distant cancer recurrence [3]. Different studies report its overall prevalence in wide range from 1 to 39%, but clinically significant AL occurs in 3-6% of the cases [4,5].

Currently, there is no reliable clinical tool for predicting the risk of AL occurrence. Numerous studies on the topic have been published, but their results are inconsistent and somewhat conflicting [1,2,6]. The most commonly identified predisposing factors are gender, age, preoperative serum

protein levels and intraoperative complications [1,2,4,6,7], but even for those factors, consensus is not achieved, probably due to the methodological issues and the vast diversity of the studied populations. Based on large dataset and multivariate analysis of this data, a predictive nomogram was constructed that includes six variables: gender, obesity, serum total protein level, number of hospital beds, and intraoperative complication [8]. Although, this nomogram was highly predictive of AL in that group, external validation is required before this nomogram could be implemented in routine clinical practice.

Knowledge about predisposing factors for AL is crucial for including individualized risk assessments in everyday practice. Such practice would

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bring enormous benefit in the decision-making process regarding the best treatment options, including decision about surgical technique, type of anastomosis, need for protective stoma and timing of surgery in order to correct correctable risk factors. Therefore, the purpose of our study was to investigate preoperative and intraoperative risk factors for AL after elective colorectal resections performed for malignancies. In addition, we studied some features of postoperative recovery and their influence on AL occurrence.

## Methods

This study was carried out in accordance with the Helsinki Declaration of 1975, as revised in 2000. The Ethical Committee of Belgrade School of Medicine approved the study.

We retrospectively reviewed the records of patients that underwent colorectal surgical procedures for malignancies between January 2013 and December 2017. We included colorectal procedures with primary anastomosis and excluded patients younger than 18 years and patients with American Society of Anesthesiologists (ASA) score 5 or 6. Finally, 153 patients were included in the study.

All operations were performed by four senior colorectal surgeons. At least one of four senior surgeons was always present to ensure the same operation technique.

All patients underwent standard preoperative protocol - thrombotic and antibiotic prophylaxis and bowel preparation. Postoperatively, all patients received metronidazole i.v. (500 mg three times daily for 3 days), third generation of cephalosporins i.v. (for 5 days) and low molecular heparin (until successful verticalization of the patient).

Depending on the localization of the process, we have done the following types of operation: right hemicolectomy, left hemicolectomy, low anterior resection and ultra-low resection of rectum. All the operating procedures were performed respecting oncological principles. For right hemicolectomy the vessels are taken very near to the origin of the superior mesenteric artery with clearance of lymph nodes. All anastomoses after right hemicolectomy were hand-sewn. For left hemicolectomy the vessels are taken very near to the origin of the inferior mesenteric artery with clearance of lymph nodes. All anastomoses after left hemicolectomy were hand-sewn. For rectal surgery, the rectal dissection was conducted in an areolar plane between the visceral fascia that envelops the rectum and mesorectum and the parietal fascia overlying the pelvic wall structures. Rectal resection with total mesorectal excision (TME) or partial mesorectal excision (PME) followed by stapled colorectal anastomosis was done in all patients with rectal carcinoma. After the resection, the rectal anastomosis was checked by hydropneumatic testing. Doughnuts were inspected for integrity after retrieval of the stapler.

Anastomotic leak was defined as luminal contents leaking from the surgical anastomosis between two hol-

low viscera, both of the stapler or hand-sewn method. Anastomotic leak was diagnosed radiologically and clinically. Patients who were diagnosed with anastomotic leakage within 30 days after initial surgery were identified.

## Statistics

All calculations were performed using IBM SPSS statistical package, version 22. Normality of data distribution was assessed with Shapiro-Wilk test. Data are presented as mean  $\pm$  standard deviation and percentage, as appropriate.

Continuous variables with normal distribution were analyzed by Student's t-test, and for variables with non-normal distribution by Mann-Whitney U test. Pearson's chi-square was used for comparison of the categorical variables. Differences were considered to be statistically significant when  $p < 0.05$ .

## Results

During the study period a total of 153 patients (67 female, mean age 67.5 years) were surgically treated for colon malignancy. The most common comorbidity was cardiovascular diseases (predominantly hypertension). Preoperative characteristics are presented in Table 1.

Clinically significant anastomotic leak was diagnosed in 9.8% patients in our study population.

**Table 1.** Baseline characteristics of the patients

Characteristics	n (%)
Gender	
Male	86 (56.2)
Female	67 (43.8)
Age (years), mean $\pm$ SD	67.5 $\pm$ 11.0
Comorbidity	
Cardiovascular disease	106 (69.3)
Cerebrovascular disease	10 (6.5)
Endocrine disorders	36 (23.5)
Renal disorders	3 (2)
ASA	
I and II	41 (26.8)
III and IV	112 (73.2)
Preoperative albuminemia, mean $\pm$ SD	36.5 $\pm$ 8.7
Preoperative HT and/or RT	5 (3.3)
Primary tumor site	
Caecum	17 (11.1)
Appendix	2 (1.3)
Ascending colon	10 (6.5)
Transverse colon	19 (12.4)
Descending colon	1 (0.7)
Sigmoid colon	33 (21.6)
Rectum	59 (38.6)
Rectosigmoid colon	12 (7.8)

There was no statistically significant difference in preoperative characteristics between patients with and without AL (Table 2). AL was slightly more frequent in men than in women. Likewise, AL was more common when rectum and rectosigmoid region were the primary cancer site but without reaching statistical significance.

Compared to the patients who did not have anastomotic leak, AL group had multiple organ resections more frequently and had more blood loss during surgery as indicated with more intraoperative blood transfusions (Table 3). In the cases where manual anastomosis was done and where ileostomy was formed, AL was less common (Table 3). The patients with no AL had regular bowel

movement sooner and also more often had oral intake during the first postoperative day (Table 3). The patients with no AL had slightly smaller tumor volume, but there were no significant differences in other tumor characteristics (Table 4).

## Discussion

The present study found clinically significant leak in 9.8% the patients. This rate is comparable, yet a bit higher than reported by other authors [4,5,7,9,10]. Generally, the incidence of AL is wide-ranged depending on the definition of AL, methods of diagnosis and features of particular study samples.

**Table 2.** Baseline characteristics of the patients with and without anastomotic leak

Characteristics	AL	No AL	<i>p</i> value
Age (years), mean±SD	70.3±7.2	67.1±11.3	0.288
Gender, n (%)			0.059
Male	12 (80)	74 (53.6)	
Female	3 (20)	64 (46.4)	
ASA score, median (range)	3 (1-3)	3 (1-4)	0.689
Preoperative albuminemia, mean±SD	37.1±5.4	36.5±9.0	0.805
Preoperative hemoglobin, mean±SD	122.8±18.2	118.7±23.4	0.511
Invasion of nearby organs, n (%)	6 (40)	31 (22.5)	0.199
Preoperative radiotherapy-chemotherapy, n (%)	0 (0)	6 (4.3)	1.000
Preoperative blood transfusion, n (%)			0.294
No transfusion	13 (86.7)	129 (93.5)	
Transfusion	2 (13.3)	9 (6.5)	
Primary cancer site, n (%)			0.098
Rectum and rectosigmoid colon	10 (66.7)	61 (44.2)	
Other	5 (33.3)	77 (55.8)	

AL: anastomotic leak

**Table 3.** Intraoperative features and postoperative recovery

Features	AL	No AL	<i>p</i> value
Surgery duration (min), mean±SD	122.5±27.2	132.4±39.2	0.356
Intraoperative transfusion, n (%)			0.730
No transfusion	12 (80)	114 (82.6)	
1-3 units of blood	3 (20)	24 (17.4)	
Ileostoma, n (%)	1 (6.7)	20 (14.5)	0.695
Anastomosis type, n (%)			0.601
Stapler	11 (10.7)	92 (89.3)	
Manual	4 (8.0)	46 (92.0)	
Multiorgan resection, n (%)	6 (40.0)	19 (13.8)	0.009
Time to bowel movement, median (range) (days after surgery)	3 (1-5)	2 (1-6)	0.019
Time to pass stool, median (range) (days after surgery)	4 (0-10)	4 (0-9)	0.930
Time to per oral intake, n (%) (days after surgery)			0.002
Day 1	8 (53.3)	118 (85.5)	
Day 2	7 (46.7)	20 (14.5)	
Hospitalization duration (days), mean±SD	20.3±7.1	11.3±4.6	0.001

AL: anastomotic leak

**Table 4.** Tumor characteristics in patients with and without anastomosis leak

Characteristics	AL	No AL	p value
Tumor volume (cm <sup>3</sup> ), median (range)	80 (2-498)	70 (2-337)	0.971
TNM classification			
T, n (%)			0.139
1	1 (6.7)	18 (13.0)	
2	1 (6.7)	23 (16.7)	
3	9 (60.0)	85 (61.6)	
4	4 (26.7)	12 (8.7)	
N, n (%)			0.387
0	9 (60.0)	79 (57.2)	
1	2 (13.3)	37 (26.8)	
2	4 (26.7)	22 (15.9)	
M, n (%)			0.347
0	13 (86.7)	130 (94.2)	
1	1 (6.7)	6 (4.3)	
2	1 (6.7)	2 (1.4)	
Dukes staging, n (%)			0.801
A	2 (13.3)	22 (15.9)	
B	6 (40.0)	55 (39.9)	
C	5 (33.3)	52 (37.7)	
D	2 (13.3)	9 (6.5)	
Histological grade, n (%)			0.057
G1	3 (20)	48 (34.8)	
G2	8 (53.3)	79 (57.2)	
G3	4 (26.7)	11 (8)	

AL: anastomotic leak

Male sex has consistently been associated with increased risk for AL [2,10-12]. AL was more frequent in males than in females, even in studies where statistical significance was not reached [9,13], as was the case in our study. The gender risk has been linked mainly to low rectal procedures because these procedures are technically more demanding in male's narrow pelvis. But having in mind that even in studies that excluded rectal procedures, AL still was more frequent in males [10].

It is assumed that hormonal differences influence intestinal microcirculation and may contribute to increased risk for AL in males [14].

Preoperative malnourishment, indicated by low serum albumin level, has long been implicated in the occurrence of postoperative complications [15]. In contrast to the findings in previous studies [8,12,16], we found no significant association of preoperative serum albumin level and risk for AL. A probable reason for this is that the incidence of hypoalbuminemia in our sample was very low (mean albuminemia in both groups was above the established threshold of 35 g/L). Our study group included only elective operations, so hypoalbuminemia was corrected preoperatively as part of standard protocol in our institution.

The question of the association of AL and the primary tumor site was examined in several studies with inconsistent conclusions. Telem et al [13] and Boccola et al [17] reported higher AL rates after rectal resections, while Suding et al [12] did not find association between the level of anastomosis and risk for AL. Several authors reported high AL rate with low anastomoses (<8 cm from anal verge) [18]. The proposed explanation for this is anatomical differences in arterial collaterals in the rectal region so unrecognized disruption of small arteries during resection can lead to compromised perfusion and consequently to AL [19]. In our study sample AL occurred more often when the primary cancer site was the rectum or rectosigmoid colon than other localization, but the difference was not statistically significant, probably due to the relatively small sample size. Additionally, our data did not record the precise distance of anastomosis from the anal verge and maybe for that reason we failed to capture this association.

Some previous studies investigated the influence of operating time on the occurrence of AL and reported that prolonged surgery significantly increased the incidence of AL [9,13,20]. Our results did not show such connection. In the study of Talem

et al [13] the mean operating time in AL group was 203 min, while other authors considered operating time as a dichotomous variable using various cut off points. Konishi et al [9] used 4 hours and Buchs et al [20] 3 hours as a cut off. Both values are much longer than the mean operation time in our study. It can be argued that the operation time reflects the complexity of the operation, as well as the experience of the surgeon and operational protocols of the institution. The latter can vary significantly in cases of large and multicentric studies, while our study included operations performed by four senior surgeons experienced in colorectal surgery, so the operating time is quite uniform across our sample. At the same time multiorgan resection was more frequent in the AL group indicating more advanced disease and more complex operating procedures, which confirms the thesis that the duration of the operation primarily reflects the surgeon's experience.

The most prominent differences in our study concerned factors of postoperative recovery. Patients without AL had earlier bowel movement and started earlier oral intake, with the oral intake having a stronger correlation with the occurrence of AL. Early oral administration has several positive effects: it enhances regular bowel movement which increases the microcirculation and improves the perfusion of the anastomosis site, and also prevents bowel bacterial overgrowth.

Our study has several strengths: the study sample was quite uniform including only patients who were operated due to colon malignancies by

four experienced surgeons following the same operating protocol, which eliminated the effects specific to the other diseases and personal preferences of the surgeon. On the other hand, limitation is that the sample was relatively small preventing us from applying more robust statistical methods with greater power. It is necessary to implement larger, methodologically well-designed studies in order to reach more concrete conclusions.

Our study implies that even though AL is definitely multicausal with the development of diagnostic and surgical procedures, as well as the possibilities of good preoperative preparation, risk factors described in the literature of the 20th century are no longer current, and attention should be directed to the examination of other factors, such as the development of new specific postoperative protocols.

### Authors' contributions

D. Jasarovic was responsible for the acquisition of data and designing and writing the article. D. Stojanovic was responsible for the acquisition of data, analysis and interpretation of data and revision of the article contents. N. Mitrovic was responsible for the acquisition of data and revision of the article contents. D. Stevanovic was responsible for the acquisition of data and revision of the article contents.

### Conflict of interests

The authors declare no conflict of interests.

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