



# DIFFERENCE IN PREDICTORS OF ANASTOMOTIC LEAKAGE DEPENDING ON THE LEVEL OF ANASTOMOSIS AFTER COLORECTAL CANCER SURGERY

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**SUMMARY** – Anastomotic leak (AL) after colorectal cancer surgery is one of the most serious postoperative complications which has major impact on outcomes. The aim of this study was to investigate preoperative and intraoperative risk factors for AL, as well as to examine whether there are differences in risk factors for AL depending on the primary tumor location. We retrospectively reviewed records of patients having undergone colorectal surgical procedures for malignancies between January 2013 and December 2017 in a single institution. Only procedures with primary anastomosis were included. Of the 153 patients, AL occurred in 10.6% of patients with primary tumor in the sigmoid colon and rectum, and in 8.2% of patients with primary tumor in the proximal sections of the colon. On univariate analysis, delayed oral intake and more advanced histologic stages of the tumor were significantly correlated with AL in patients with tumors in the sigmoid colon and rectum, and multiorgan resection and distant metastases in patients with tumors in the proximal sections of the colon. In conclusion, risk factors for the occurrence of AL vary depending on the primary tumor location and further investigation is needed to provide better insight into these differences.

**Key words:** *Colorectal cancer; Anastomotic leak; Risk factors; Rectal cancer; Colon cancer*

## Introduction

Colorectal cancer is the third most frequently diagnosed cancer, but second in terms of mortality, with over 1.8 million new cases and 881,000 deaths estimated to have occurred in 2018<sup>1</sup>. The vast majority of newly diagnosed patients undergo surgical treatment. Regardless of the significant advances in surgical techniques, diagnostics and postoperative monitoring, anastomotic leak (AL) remains a significant issue that substantially affects postoperative morbidity and mortality rates, as well as the overall cost of treatment<sup>2-6</sup>. Different studies report its overall prevalence in a wide range from 1% to 39%, but clinically significant AL occurs in 3%-6% of cases<sup>7-9</sup>. An accurate risk assess-

ment for AL is needed in order to implement an optimal treatment plan for each patient in colorectal surgery. Unfortunately, there is still no reliable clinical tool for predicting the occurrence of AL. Most studies designed to assess risk factors for AL investigated heterogeneous study populations that included both colic resections with intraperitoneal anastomosis and rectal resections with extraperitoneal anastomosis. The incidence of AL has been shown to be significantly higher after extraperitoneal anastomosis<sup>2,3,10</sup>, suggesting the possible different risk factors for AL depending on the level of anastomosis. Therefore, the aim of our study was to investigate independent risk factors for AL in a subpopulation of patients having undergone rectal and sigmoid colon resection for malignancy with primary rectal anastomosis, and to compare them with patients having undergone resection of the proximal parts of the colon. In addition, we studied some features of postoperative recovery and their impact on the occurrence of AL.

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## Patients and Methods

### *Study population*

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

This study was carried out in accordance with the Helsinki Declaration of 1975, as revised in 2000. Ethics Committee of the Belgrade School of Medicine approved the study. Informed consent was obtained from all subjects included in the study.

### *Surgery procedures*

All operations were performed by one of four senior colorectal surgeons to ensure the same operation technique. All patients underwent standard preoperative protocol with thrombotic and antibiotic prophylaxis and bowel preparation. Postoperatively, all patients received metronidazole (500 mg three times daily for 3 days), third generation cephalosporin (2 g daily for 5 days) and low molecular heparin until successful mobilization of the patient.

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

Anastomotic leak was defined as luminal contents leaking from the surgical anastomosis between two hollow viscera. AL was diagnosed clinically and/or radiologically. Patients diagnosed with AL within 30 days of the initial surgery were identified.

### *Statistics*

All calculations were performed using IBM SPSS Statistics version 22. The normality of data distribution was assessed with Shapiro-Wilk test. Data were expressed as mean  $\pm$  standard deviation, median and percentage, as appropriate. Continuous variables with normal distribution were analyzed by Student's t-test, and variables with non-normal distribution by Mann-Whitney U test. Pearson  $\chi^2$  and Fisher exact test were used for comparison of categorical variables. Differences were considered to be statistically significant when  $p < 0.05$ .

## Results

During the study period, a total of 153 patients (86 male, mean age 67.5 years) were surgically treated for colon malignancy. In 104 (68%) patients, the primary tumor localization was at the level of sigmoid colon or rectum. Patients with primary tumor located at this level of colon had better physical status, as documented by lower ASA score, and also had better nutritional status, as documented by preoperative albumin levels.

The most common comorbidity were cardiovascular diseases (predominantly hypertension). Preoperative characteristics of study patients are presented in Table 1. AL occurred more frequently in patients with primary tumor located on the sigmoid colon and rectum than in patients with other primary tumor localizations (10% *vs.* 8%), but without statistical significance. Comparing the baseline characteristics of patients with AL, the only significant difference was the higher incidence of low hemoglobin in patients with primary tumor in the proximal colon (Table 2).

When we analyzed the group of patients with primary tumor on the sigmoid colon and rectum, the surgery took for 5 minutes more on average in patients with AL, but this difference did not reach statistical significance. Also, in this group of patients, AL occurred less frequently when oral intake was initiated earlier. On the other hand, in the group of patients with primary tumor in the more proximal colon sec-

Table 1. Baseline characteristics of study patients

Variable	RS (n=104)	Other localization (n=49)	p
Gender, n (%):			
Male	63 (60.6)	23 (46.9)	0.113
Female	41 (39.4)	26 (53.1)	
Age (years), mean ± SD	66.4±12.04	69.9±7.95	0.074
Comorbidity, n (%):			
Cardiovascular disease	68 (65.4)	38 (77.6)	0.128
Cerebrovascular disease	9 (8.7)	1 (2.0)	0.123
Endocrine disorders	24 (23.1)	12 (24.5)	0.848
Nephrology disorders	1 (1.0)	2 (4.1)	0.194
ASA, n (%):			
I and II	33 (31.7)	8 (16.3)	0.045
III and IV	71 (68.3)	41 (83.7)	
Preoperative albuminemia, mean ± SD	38.5±5.82	35.2±6.87	0.003
Preoperative RT/CT, n (%)	3 (2.9)	3 (6.1)	0.336

RS = rectum and sigmoid colon; ASA = American Society of Anesthesiologists Score; RT/CT = radiotherapy/chemotherapy; SD = standard deviation

tions, AL was somewhat more common (without reaching statistical significance) when stapler anastomosis was performed. In this group of patients, AL occurred more frequently when multiorgan resection was performed (Table 3).

In the group of patients with primary tumor on the sigmoid colon and rectum, AL occurred more frequently in patients with higher histologic grade of tumor, whereas in patients with primary tumors in proximal sections of the colon AL occurred more often when distant metastases were present (Table 4).

## Discussion

The present study found a clinically significant leak in 10.6% of patients with primary tumor on the sigmoid colon and rectum, and in 8.2% of patients with

Table 2. Baseline characteristics of patients with anastomosis leak according to primary tumor localization

	RS (n=11)	Other localization (n=4)	p
Age (years), mean ± SD	70.6±8.25	69.5±4.04	0.799
Gender, n (%):			0.085
Male	9 (81.8)	3 (75.0)	
Female	2 (18.2)	1 (25.0)	
ASA, n (%):			0.218
I and II	2 (18.2)	2 (50.0)	
III and IV	9 (81.8)	2 (50.0)	
Preoperative albuminemia, mean ± SD	38.36±3.23	33.5±8.85	0.127
Preoperative low hemoglobin, n (%)	2 (18.2)	3 (75.0)	0.039
Invasion of adjacent organs, n (%)	4 (36.4)	2 (50.0)	0.634
Preoperative BT, n (%)	0 (0.0)	2 (50.0)	0.057

RS = rectum and sigmoid colon; ASA = American Society of Anesthesiologists Score; Low hemoglobin = hemoglobin <110 g/L; BT = blood transfusion; SD = standard deviation

primary tumor in the more proximal sections of the colon. These rates are comparable, even though they are slightly higher than those previously reported by other authors<sup>11,12</sup>. The results of previously published studies consistently report a higher incidence of AL in men than in women, especially when low resections are performed, which is most often explained by a technically more demanding intervention in the anatomically narrow area<sup>3,12-14</sup>. In our study, although statistical significance was not reached, a higher incidence of AL in men was evident, even more pronounced in the group of patients with primary tumor on the sigmoid colon and rectum.

Several studies examined the impact of the disease stage at the time of surgery on the occurrence of AL, with somewhat inconsistent results<sup>11,15-18</sup>. While Bakker *et al.*<sup>11</sup> showed no influence of the disease stage on the occurrence of AL, Ng *et al.*<sup>16</sup> report a threefold, and Kaser *et al.*<sup>17</sup> even fourfold increase in the likelihood of AL in patients with metastatic disease at the time of surgery. In our study, histologic grade of tumor

Table 3. Intraoperative features and postoperative recovery

	RS (n=104)			Other localization (n=49)		
	AL (n=11)	No AL (n=93)	p	AL (n=4)	No AL (n=45)	p
Surgery duration (min), mean ± SD	70.6±8.25	65.9±12.35	0.216	69.5±4.04	69.8±8.23	0.943
Intraoperative BT, n (%)	2 (18.2)	39 (41.9)	0.127	1 (25.0)	25 (55.6)	0.241
Anastomosis n (%):						
Stapler	2 (18.2)	31 (33.3)	0.307	2 (50.0)	6 (13.3)	0.057
Manual	9 (81.8)	62 (66.7)		2 (50.0)	39 (86.7)	
Multiorgan resection, n (%)	3 (27.3)	13 (14.0)	0.248	3 (75.0)	6 (13.3)	0.002
Time to bowel movement (days after surgery), median (range)	2 (4)	2 (5)	0.090	3 (3)	2 (3)	0.083
Time to pass stool (days after surgery), median (range)	4 (10)	3 (8)	0.368	3 (5)	4 (8)	0.217
Time to oral intake (days after surgery), median (range)	4 (10)	3 (7)	0.001	3 (5)	3 (3)	0.877

RS = rectum and sigmoid colon; BT = blood transfusion; SD = standard deviation

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

	RS (n=104)			Other localization (n=49)		
	AL (n=11)	No AL (n=93)	p	AL (n=4)	No AL (n=45)	p
Tumor volume (cm <sup>3</sup> ), median (range)	64 (337)	60 (496)	0.516	233.5 (286)	110 (440)	0.294
TNM classification:						
T, n (%)						
1	1 (9.1)	13 (14.0)	0.141	0 (0.0)	5 (11.1)	0.573
2	1 (9.1)	13 (14.0)		0 (0.0)	10 (22.2)	
3	6 (54.5)	61 (65.6)		3 (75.0)	24 (53.3)	
4	3 (27.3)	6 (6.5)		1 (25.0)	6 (13.3)	
N, n (%)						
0	5 (45.5)	55 (59.1)	0.209	4 (100.0)	24 (53.3)	0.195
1	2 (18.2)	24 (25.8)		0 (0.0)	13 (28.9)	
2	4 (36.4)	14 (15.1)		0 (0.0)	8 (17.8)	
M, n (%)						
0	10 (90.9)	86 (92.5)	0.327	3 (75.0)	44 (97.8)	0.027
1	0 (0.0)	5 (5.4)		1 (25.0)	1 (2.2)	
2	1 (9.1)	2 (2.2)		0 (0.0)	0 (0.0)	
Dukes staging, n (%):						
A	2 (18.2)	15 (16.1)	0.853	0 (0.0)	7 (15.6)	0.107
B	3 (27.3)	38 (40.9)		3 (75.0)	17 (37.8)	
C	5 (45.5)	33 (35.5)		0 (0.0)	19 (42.2)	
D	1 (9.1)	7 (7.5)		1 (25.0)	2 (4.4)	
Histologic grade, n (%):						
G1	2 (18.2)	34 (36.6)	0.006	1 (25.0)	14 (31.1)	0.714
G2	5 (45.5)	53 (57.0)		3 (75.0)	26 (57.8)	
G3	4 (36.4)	6 (6.5)		0 (0.0)	5 (11.1)	

RS = rectum and sigmoid colon; AL = anastomotic leak

was a significant predictor of AL occurrence only in the group of patients with primary tumor on the sigmoid colon and rectum, while distant metastases were predictive of AL occurrence in the group of patients with primary tumor located in the more proximal sections of the colon. Resections of the rectum involve interventions in an anatomically tight space, so a higher stage of the disease makes these interventions even more challenging. At the same time, distant metastases usually indicate worsened physical and nutritional status of the patient, which may be a contributing factor for AL<sup>19,20</sup>.

In the group of patients with primary tumor on the sigmoid colon and rectum, early administration of oral nutrition had a protective effect on the onset of AL. Early oral administration has several positive effects, i.e. it enhances regular bowel movement, which increases microcirculation and improves perfusion of the anastomosis site, and also prevents bowel bacterial overgrowth<sup>21</sup>.

It is well documented that AL not only compromises short-term prognosis, but is also associated with long-term outcomes and survival of cancer patients. Low resections are particularly demanding because of the anatomic relationships and specificity of the vascularization, so it is of great importance to identify risk factors in order to modify surgical strategy. Our study identified disease stage as indicated by histologic grade and TNM grading system and the necessity of multi-organ resection as risk factors for AL, whereas early administration of oral nutrition had a protective effect. Those risk factors for AL occurrence vary depending on the location of primary tumor and further investigation is needed to provide better insight into these differences.

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### Sažetak

## RAZLIKE U PREDIKTORIMA DEHISCENCIJA ANASTOMOZE NAKON OPERACIJE KOLOREKTALNOG KARCINOMA OVISNO O RAZINI ANASTOMOZE

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Dehiscencija anastomoze (DA) nakon operacija karcinoma kolorektuma je jedna od najozbiljnijih poslijeoperacijskih komplikacija koja ima velik utjecaj na ishod liječenja. Cilj ove studije bio je istražiti prijeoperacijske i intraoperacijske čimbenike rizika za DA, kao i ispitati postoje li razlike u čimbenicima rizika za DA ovisno o mjestu primarnog tumora. Retrospektivno smo analizirali podatke bolesnika podvrgnutih kirurškim zahvatima zbog kolorektalnog karcinoma na jednoj klinici u razdoblju od siječnja 2013. do prosinca 2017. Uključeni su samo postupci s primarnim anastomozama. Od 153 bolesnika, DA se pojavila u 10,6% bolesnika s tumorom rektuma i sigmoidnog kolona te u 8,2% bolesnika s tumorom proksimalne lokalizacije. Univarijatna analiza je pokazala da su odgođeni početak peroralnog unosa te viši histološki stadij tumora u značajnoj korelaciji s DA u bolesnika s tumorom rektuma i sigmoidnog kolona, dok su multiorganska resekcija te udaljene metastaze u značajnoj korelaciji s DA u bolesnika s tumorom proksimalne lokalizacije. Zaključeno je da se čimbenici rizika za pojavu DA razlikuju ovisno o mjestu primarnog tumora pa su potrebne daljnje studije koje bi pružile bolji uvid u te razlike.

**Ključne riječi:** *Karcinom kolorektuma; Propuštanje anastomoze; Rizični čimbenici; Karcinom rektuma; Karcinom kolona*