ORIGINAL ARTICLE

Risk factors associated with anastomotic leakage in patients operated due to colorectal tumour

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ABSTRACT

Aim To evaluate risk factors that may cause anastomotic leakage (AL) in patients who underwent resection and anastomosis due to colorectal cancer.

Methods Patients who underwent resection and anastomosis due to colorectal cancer between January 2014 and July 2018 in our clinic were included into the study. The patients were divided into two groups as ones with AL being Group 1, ones without AL being Group 2. Parameters related to the clinical characteristics, surgical and pathologic results in both groups were evaluated with univariate and multivariate analyses.

Results A total of 302 patients were included in the study. The AL was observed in 24 (7.9%) patients. Mortality was observed in five (20.8%) and six (2.2%) patients in Group 1 and Group 2, respectively (p=0.001). Significant risk factors for AL in the univariate analysis were coronary artery disease (CAD), chronic obstructive pulmonary disease, high American Society of Anesthesiologists (ASA) score, emergency surgical intervention, absence of preoperative intestine preparation, performed perioperative blood transfusion, tumour T stage, and neoadjuvant chemo-radiotherapy application. Only CAD and neoadjuvant CRT were determined as the independent risk factors for AL in the multivariate analysis.

Conclusion The AL developing after colorectal surgery continues to be an important problem thereby increasing mortality and morbidity along with its negative effect on hospitalization time and functional and oncologic results. Despite several studies on the topic, it is still very difficult to estimate the AL possibility in advance. Therefore, avoiding anastomosis in high risk patients may perhaps be the best option.

Keywords: cancer, morbidity, mortality

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INTRODUCTION

Anastomotic leakage (AL) after colorectal surgery is at the top of the most feared complications thereby increasing mortality and morbidity along with its negative effect on hospitalization time and functional and oncologic results. The AL rate after colorectal surgery has been reported to be between 1% and 30% (1,2). Moreover, AL related mortality changes between 6% and 22% (3,4). The AL is the cause of approximately one third of all deaths after colorectal surgery (5). There have been several risk factors reported for AL, such as malnutrition, corticosteroid application, intraoperative septic conditions, male gender, smoking, high ASA score, neoadjuvant chemo-radiotherapy (CRT), old age, obesity, anastomosis methods, and emergency surgical intervention (6,7). One of the most studied risk factors is diversion ostomies, which do not decrease AL rates, but decrease the severity of ALs and provide the possibility to treat the leakages with palliative methods (8).

The aim of this study was to evaluate the risk factors that may cause AL in our patients who underwent resection and anastomosis due to colorectal cancer.

PATIENTS AND METHOD

Patients and study design

Data of patients who were operated and underwent anastomosis due to colorectal cancer between January 2014 and July 2018 in the Department of General Surgery, Kartal Training and Research Hospital, Istanbul, Turkey, were retrospectively evaluated with the help of the hospital's automation system and patient files.

The patients included in the study were separated into two groups as Group 1, those with AL, and Group 2, those without AL. Between the two groups, comparisons were made with regard to patients' demographic characteristics, accompanying diseases, perioperative blood transfusions, performance of the operation under emergency or elective conditions, protective ostomy status, American Society Anesthesiologists (ASA) score (9), whether prior intestine preparation was performed, type of anastomosis (end to end, end to side, and side to side), anastomosis technique (circular stapler, linear cutter and manual), TNM stage (evaluated stage < 3 and stage ≥ 3) (10), and whether neoadjuvant CRT was administered.

An approval was obtained from the University of Health Sciences, Kartal Dr. LütfiKırdar Training and Research Hospital Ethics Committee to conduct the study.

According to the TNM classification (T describes the size of the tumour and any spread of cancer into nearby tissue; N describes spread of cancer to nearby lymph nodes; M describes metastasis, e. g. spread of cancer to other parts of the body) (10), neoadjuvant CRT was performed on all T2 and above upper and mid rectal tumours, and total mesorectal excision was performed 8–10 weeks after the treatment.

Methods

Following the anastomosis performed 10 cm and below from the anal verge on the rectum tumours, which had neoadjuvant CRT, protective ileostomy was performed on all patients. The decision was based for the remaining upper rectum and colon tumours depending on reasons, such as the clinical state of the cases, technical difficulties encountered during anastomosis, etc. resection and anastomosis with or without ostomy was performed on all patients.

Statistical analysis

Independent Samples t-test and Mann–Whitney U tests were used for the comparison of two independent groups. Pearson $\chi 2$ and Fisher exact tests were used with the comparison of categorical variables among themselves. The variables were analysed with 95% confidence interval and $p<0.05$ was considered as significant.

RESULTS

A total of 302 patients were included in the study, of which 181 (59.9%) and 121 (40.1%) were males and females, respectively. The average age of the both group patients was 65.1±12.75 years, 65.9 ±10.82 and 65.1±12.75 years, respectively, in group 1 and group 2 ($p<0.772$). There was significant statistical differences according to ASA score between group 1 and group 2 ($p<0.000$).

Tumour location was mostly observed in the sigmoid and rectosigmoid colon, AK were observed in five (20.8%) and three (12.5%) patients respectively. In this study, although the frequ-

ency of the tumour location in rectum was seen as the third, most of the anastomotic leakages (37.5%, n=9) were observed in this level. The AL was observed in 24 (7.9%) patients. Mortality was observed in five (20.8%) patients in Group 1 and six (2.2%) patients in Group 2 (p=0.001). In the univariate analysis all the presence of coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), high ASA score, emergency surgical intervention, no preoperative intestine preparation performed, and perioperative blood transfusion performed was observed significant in terms of AL development. AL rates were lower when oral and rectal laxatives without antibiotics were given to the cases with intestine preparation . There were no significant differences between laparoscopic and open surgery in terms of AL. In addition to this, age also was not significant in terms of AL (Table 1).

Table 1.Univariate logistic regression model analysis of anastomotic leakage in patients with colorectal cancer

Variable		No (%) of patients in the group			p*
		Group 1	Group 2	Total	
Gender	Female	9 (37.5)	112 (40.3)	121 (40.1)	0.789
	Male	15 (62.5)	166 (59.7)	181 (59.9)	
Age	< 65	10 (41.7)	128 (46)	138 (45.7)	0.68
	≥ 65	14 (58.3)	150 (54)	164 (54.3)	
Emergency/ Elective	Emergency	11(45.8)	39 (14)	50 (16.6)	0
	Elective	13 (54.2)	239 (86)	252 (83.4)	
Related colon segment	Ascending	2 (8.3)	42 (15.1)	44 (14.6)	0.07
	Descending	3 (12.5)	10 (3.6)	13 (4.3)	
	Rectosigmoid	3 (12.5)	60 (21.6)	63 (20.9)	
	Rectum	9 (37.5)	49 (17.6)	58 (19.2)	
	Sigmoid	5 (20.8)	64 (23)	69 (22.8)	
	Splenic flexure	0 (0)	1 (0.4)	1 (0.3)	
	Transverse colon	2 (8.3)	52 (18.7)	54 (17.9)	
Protective ostomy	No	18 (75)	224 (80.6)	242 (80.1)	0.511
	Yes	6 (25)	54 (19.4)	60 (19.9)	
Mortality	No	19 (79.2)	272 (97.8)	291 (96.4)	0.001
	Yes	5 (20.8)	6 (2.2)	11 (3.6)	
Intestine preparation	No	11 (45.8)	40 (14.4)	51 (16.9)	0.001
	Yes	13 (54.2)	238 (85.6)	251 (83.1)	
Accompanying diseases	Diabetes	3 (12.5)	66 (23.7)	69 (22.8)	0.208
	Hypertension	13 (54.2)	100 (36)	113 (37.4)	0.077
	Heart failure	1 (4.2)	30 (10.8)	31 (10.3)	0.305
	COPD	6 (25)	20 (7.2)	26 (8.6)	0.003
	CAD	13 (54.2)	9 (3.2)	22 (7.3)	0
	CKF	2 (8.3)	8 (2.9)	10 (3.3)	0.152
Perioperative blood transfusion	No	13 (54.2)	224 (80.6)	237 (78.5)	0.003
	Yes	11 (45.8)	54 (19.4)	65 (21.5)	
Laparoscopic / open surgery	Laparoscopic	5 (20.8)	40 (14.4)	45 (14.9)	0.395
	Open	19 (79.2)	238 (85.6)	257 (85.1)	

*Fisher's exact test; COPD, chronic obstructive pulmonary disease, CAD, coronary artery disease, CKF, chronic kidney failure

There was no significant difference detected between the two groups in terms of the anastomosis shape, anastomosis technique (end to end, end to side or side to side), and anastomosis ends being colocolic, ileocolic, or colorectal (Table 2).

Table 2. Distribution of data regarding anastomosis depending on the existence of anastomotic leakage in the patients

Anastomosis		No (%) of patients in the group			p*
		Group 1	Group 2	Total	
Anastomosis ends	Ileotransverso-stomy	2 (8.3)	44 (15.8)	46 (15.2)	0.31
	Colocolic Anastomosis	3 (12.5)	57(20.5)	60 (19.9)	
	Colorectal Anastomosis	19 (79.2)	177 (63.7)	196 (64.9)	
Anastomosis connection type	End to end	20 (83.3)	191(68.7)	211 (69.9)	0.132
	End to side	4 (16.7)	39 (14)	39 (12.9)	
	Side to side	24 (100)	48 (17.3)	52 (17.2)	
Anastomosis technique	Linear cutter	3 (12.5)	49 (17.6)	52 (17.2)	0.463
	Manual	4 (16.7)	26 (9.4)	30 (9.9)	
	Circular stapler	17 (70.8)	203 (73)	220 (72.8)	

*Fisher's exact test

The TNM stage was significant at the limit (p=0.05) while tumour T stage and neoadjuvant CRT application was significant in AL development with p=0.002 and p=0.001, respectively (Table 3).

Table 3. Oncologic characteristics of the patients according to the existence of anastomotic leakage

Variable		No (%) of patients in the group			p*
		Group 1	Group 2	Total	
T stage	T0	0 (0)	4 (1.4)	4 (1.3)	0.002
	T1	0 (0)	26 (9.4)	28 (9.3)	
	T2	2 (8.3)	196 (70.5)	214 (70.9)	
	T3	18 (75)	6 (2.2)	10 (3.3)	
	T4	4 (16.7)	46 (16.5)	46 (15.2)	
N stage	N0	7 (29.2)	133 (47.8)	140 (46.4)	0.145
	N1	10 (41.7)	71(25.5)	81 (26.8)	
	N2	7 (29.2)	74 (26.6)	81 (26.8)	
TNM stage	< 3	6 (25)	127 (45.7)	133 (44)	0.05
	≥ 3	18 (75)	151 (54.2)	169 (56)	
Neoadjuvant CRT	No	13 (54.2)	235 (84.5)	248 (82.1)	0.001
	Yes	11(45.8)	43 (15.5)	54 (17.9)	

* Fisher's exact test; TNM; tumour, node, metastasis; CRT, Chemo-radiotherapy

Multivariate analysis and logistic regression analysis were performed on the parameters observed to be significant in the univariate analysis. The CAD and neoadjuvant CRT applications were observed to be significantly related to AL in the multi regression analysis (Table 4).

DISCUSSION

The most feared complication after colorectal surgery is AL, and it ranks among the top causes of

Table 4. Multiple logistic regression model analysis of anastomotic leakage in patients with colorectal cancer

	B	Standard deviation	Wald	p	Exp (B)	%95 CA for Exp (B)	
						Lower	Upper
Emergency/Elective	-19.737	40191.935	0.000	1.000	0.000	0.000	
Intestine preparation	-15.986	40191.935	0.000	1.000	0.000	0.000	
COPD	-1.583	0.873	3.291	0.070	0.205	0.037	1.136
CAD	-4.272	1.067	16.038	0.000	0.014	0.002	0.113
Perioperative blood transfusion	-1.524	0.841	3.287	0.070	0.218	0.042	1.132
ASA	1.042	1.156	0.812	0.368	2.834	0.294	27.305
T stage			5.159	0.397			
Neoadjuvant CRT	-2.928	1.008	8.433	0.004	0.054	0.007	0.386
Constant	7.931	86207.841	0.000	1.000	2781.003		

B, Beta; Wald, confidence interval; Exp (B), exponentiated logistic coefficients; %95 CA for Exp (B), confidence interval, COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; ASA, American Society of Anesthesiologists; CRT, Chemo-radiotherapy

severe mortality and morbidity. AL rate after colorectal surgery is reported to be between 1% and 30% (1,2). Moreover, mortality due to peritonitis and septicemia developing after AL varies between 6% and 22% (3,4). In our study, AL rate was 7.9%, and AL related mortality rate was 20.8%. Many risk factors such as malnutrition, corticosteroid application, intraoperative septic conditions, male gender, smoking, ASA score, preoperative chemo-radiotherapy, old age, obesity, anastomosis techniques, and emergency surgical intervention have been reported for AL (6,7).

It has been reported that AL is more prevalent among men than women, especially due to the technical difficulties which are encountered because of narrow pelvis (11). Since only 19.2% of the patients in our study had rectal tumour, there was no significant difference found with respect to gender.

The role of age in AL is still a topic of discussion. Different studies have reported that AL is not related to age (12,13). Moreover, it has also been reported that AL is more common among the younger population (2), despite the assumption that the risk would be higher in the older population (14). In the study performed by Ebubekir et al. it was reported that CAD out of accompanying diseases is related to AL (8). In our study, there was no significant difference identified in terms of AL between the patients under the age of 65 and those at or above the age of 65, while the accompanying diseases of CAD and COPD statistically affected AL rate significantly.

It has been reported that AL and postoperative mortality rates are higher in anastomoses performed due to emergency surgery (15,16). In our study, AL rate was significantly higher in the patients who were operated under emergent conditions. Moreover, 80% of the mortalities developed due to AL were associated with patients operated under emergency conditions.

Schrock et al. reported that AL is three times more common in patients who received neoadjuvant CRT compared to those who did not (17). In contrast, in a study in the Netherlands conducted on 1861 patients, it was concluded that short term radiotherapy did not create a risk for AL (18). In our study, it was determined that neoadjuvant CRT was an independent risk factor related to AL. Although radiotherapy is considered to be a risk factor for AL, neoadjuvant treatment should not be neglected in rectal cancer treatment due to its positive effects on local control, survival, and sphincter protection (19).

High TNM stage along with tumour diameter (>3 cm) were reported as independent risk factors in AL development (20). In our study, TNM stage was related to AL at the limit, while advanced T stage was found to be statistically significant in terms of AL development.

Tadros et al. reported that blood transfusion increases anastomosis abscess incidence and creates a negative effect in the healing of anastomosis (21). Buchs et al. showed that a high ASA score is an independent risk factor (3). In our study, preoperative blood transfusion and high ASA score were significant in terms of AL development.

It is still unclear whether intestine preparation should be performed before the operation and, if required, whether this preparation should be done with antibiotics or mechanically. Cao et al. observed that preoperative intestine preparation has no effect on AL (22). In contrast, in another study on advanced age colorectal cases, it was reported that intestine preparation decreases AL rates and mor-

bidity (23). In their 8442-case study, Kiran et al. observed that AL and postoperative complications were less common in the group with intestine preparation with antibiotics, compared to the one with intestine preparation without antibiotics, and they observed the worst results in the group without intestine preparation (24). In our study, oral and rectal laxatives without antibiotics were given to the cases with intestine preparation, and AL rates were observed to be lower in these cases.

Studies comparing the laparoscopic approach with open surgery for colorectal tumour report that the oncologic results are similar (25), and that laparoscopic approach has advantages, such as better view of the surgical field, less intraoperative blood loss, decreased tissue trauma, and lower inflammatory response indicators (26). Despite these advantages of laparoscopy, it was reported in many studies that its AL rates are similar to that of open surgery (27, 28). In our study, no significant relationship was found between laparoscopic and open surgery in terms of AL.

In the analysis of a study with 13 randomized controls that evaluated colon and rectal anastomoses performed by hand, by circular stapler, or by linear stapler, there was no significant difference found in terms of AL (29). Our results were compatible with the literature. In a study conducted on rectal tumour cases, which evaluated the effect of the type of end connection after the intestine segment is resected on leakage rates, it was reported that AL rates are lower in cases with end to side anastomosis (30). In another study performed on colorectal resection and anastomosis, there was no relationship observed between the type of intestine end connection and AL (31). In our cases, there was no significant difference identified in terms of AL between the anastomosis types performed as end to end, end to side, or side to side.

The later diagnosis in patients who develop AL is correlated with the higher morbidity and mortality rates. Thus, early diagnosis should be made and treatment should start immediately for patients with AL. The International Study Group of Rectal Cancer classifies leakages detected in imaging methods as grade A if they are asymptomatic and do not require treatment; as grade B if they are recommended to be treated with percutaneous or trans anal drainage and with antibiotic treatment and follow up; and as grade Cif the ALs require re-laparotomy, give septic findings, and negatively affect the oncologic results (32). In our study, 3, 5, and 15 patients were graded as A, Band C, respectively. The most important decision for these patients is whether they need to undergo surgery. It has been proven that late surgical decisions are the most important factor for mortality (8). For patients with grade B AL, who do not have peritoneum irritation findings and who have low anterior resection performed, the need for reoperation can be decreased by providing healing with special drainages placed on the fistula line or with the drainage of the surgical space (33). In our study we intervened on two out of the five operated rectum tumour patients with class B AL by placing an endo-sponge on the fistula line, and intervened on three other patients by using drainage procedures performed with imaging, achieving 80% success in these cases. Stoma can be opened in cases without protective stoma depending on the clinical condition of the patient; however, cases with more separation in the anastomosis may require Hartmann surgery. Hartmann procedure is a closure of the rectum following resection of the tumour and anastomosing the proximal part of the colon to the skin (end colostomy) in a patient with a rectosigmoid tumour first described in 1921 by French surgeon Henri (34).

Patients with protective stoma AL tend to be mostly asymptomatic, and medical support treatment is sufficient in most cases. Protective stoma does not decrease AL rates, but decreases the severity of the ALs and provides the possibility of leakage treatment with palliative methods (8). It was observed that protective ostomy did not decrease AL development. However, in this study it was detected that protective ostomy was not applied in 80% of the patients who developed mortality and we found that mortality rates were higher in patients who were not applied protective ostomy.

In the multiple regression analysis of our study, CAD and neoadjuvant CRT were detected as independent risk factors related to increased AL risk.

In conclusion, AL development after colorectal surgery continues to be an important problem with its increasing morbidity and mortality, along with its negative effect on the duration of hospitalization and the functional and oncologic results. Despite several studies conducted on

this topic, it is still difficult to estimate the possibility of AL in advance. Therefore, avoiding anastomosis in high risk patients could perhaps be the best approach.

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