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
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. Lütfi Kırdar 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 χ² 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-
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

<table>
<thead>
<tr>
<th>Anastomosis</th>
<th>No (%) of patients in the group</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>Linear staple</td>
<td>4 (16.7)</td>
<td>26 (9.4)</td>
</tr>
<tr>
<td>CRT</td>
<td>Yes 11 (45.8)</td>
<td>43 (15.5)</td>
</tr>
<tr>
<td>Neoadjuvant CRT</td>
<td>No 13 (54.2)</td>
<td>235 (84.5)</td>
</tr>
<tr>
<td></td>
<td>Yes 11 (45.8)</td>
<td>43 (15.5)</td>
</tr>
<tr>
<td>T stage</td>
<td>T1 0 (0)</td>
<td>26 (9.4)</td>
</tr>
<tr>
<td></td>
<td>T2 2 (8.3)</td>
<td>196 (70.5)</td>
</tr>
<tr>
<td></td>
<td>T3 18 (75)</td>
<td>6 (2.2)</td>
</tr>
<tr>
<td></td>
<td>T4 4 (16.7)</td>
<td>46 (16.5)</td>
</tr>
<tr>
<td></td>
<td>N0 7 (29.2)</td>
<td>133 (47.8)</td>
</tr>
<tr>
<td></td>
<td>N1 10 (41.7)</td>
<td>71 (25.5)</td>
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<tr>
<td></td>
<td>N3 7 (29.2)</td>
<td>74 (26.6)</td>
</tr>
<tr>
<td></td>
<td>N2 18 (75)</td>
<td>151 (54.2)</td>
</tr>
<tr>
<td></td>
<td>N3 ≥ 3</td>
<td>127 (45.7)</td>
</tr>
<tr>
<td></td>
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<td>151 (54.2)</td>
</tr>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>No (%) of patients in the group</th>
<th>p*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td>T stage</td>
<td>T0 0 (0)</td>
<td>4 (1.4)</td>
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<tr>
<td></td>
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Table 4. Multivariate analysis and logistic regression analysis

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DISCUSSION

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

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Standard deviation</th>
<th>Wald</th>
<th>p</th>
<th>Exp (B)</th>
<th>95% CI for Exp (B)</th>
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</thead>
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<td>Emergency/Elective</td>
<td>-19.737</td>
<td>4019.935</td>
<td>0.000</td>
<td>1.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Intestine preparation</td>
<td>-15.986</td>
<td>4019.935</td>
<td>0.000</td>
<td>1.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>COPD</td>
<td>-1.583</td>
<td>0.873</td>
<td>3.291</td>
<td>0.070</td>
<td>0.205</td>
<td>0.037 1.136</td>
</tr>
<tr>
<td>CAD</td>
<td>-4.272</td>
<td>1.067</td>
<td>16.038</td>
<td>0.000</td>
<td>0.014</td>
<td>0.002 0.113</td>
</tr>
<tr>
<td>Perioperative blood transfusion</td>
<td>-1.524</td>
<td>0.841</td>
<td>3.287</td>
<td>0.070</td>
<td>0.218</td>
<td>0.042 1.132</td>
</tr>
<tr>
<td>ASA</td>
<td>1.042</td>
<td>1.156</td>
<td>0.812</td>
<td>0.368</td>
<td>2.834</td>
<td>0.294 27.305</td>
</tr>
<tr>
<td>T stage</td>
<td>5.159</td>
<td>0.397</td>
<td>5.159</td>
<td>0.000</td>
<td>0.054</td>
<td>0.007 0.386</td>
</tr>
<tr>
<td>Neoadjuvant CRT</td>
<td>-2.928</td>
<td>1.008</td>
<td>8.433</td>
<td>0.004</td>
<td>0.054</td>
<td>0.007 0.386</td>
</tr>
<tr>
<td>Constant</td>
<td>7.931</td>
<td>86207.841</td>
<td>0.000</td>
<td>1.000</td>
<td>2781.003</td>
<td>0.000</td>
</tr>
</tbody>
</table>

B, Beta; Wald, confidence interval; Exp (B), exponentiated logistic coefficients; 95% CI for Exp (B), confidence interval; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; ASA, American Society of Anesthesiologists; CRT, Chemo-radiotherapy
bidity (23). In their 8442-case study, Kiran et al.
observed that AL and postoperative complications
were less common in the group with intestine pre-
paration 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 tra-
uma, and lower inflammatory response indica-
tors (26). Despite these advantages of laparos-
copy, 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 sur-
gery in terms of AL.

In the analysis of a study with 13 randomized con-
trols 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 anas-
tomosis (30). In another study performed on co-
lorectal 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 mor-
tality rates. Thus, early diagnosis should be made
and treatment should start immediately for pa-
ients with AL. The International Study Group of
Rectal Cancer classifies leakages detected in im-
aging 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 tre-
attment and follow up; and as grade C if 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 under-
go surgery. It has been proven that late surgical
decisions are the most important factor for mor-
tality (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 he-
aling 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 draina-
ge 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, ca-
es 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 tre-
atment 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 de-
crease AL development. However, in this study it
was detected that protective ostomy was not appli-
ced 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 inde-
pendent 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.

REFERENCES


FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.


