Turkish Journal of Geriatrics
DOI: 10.31086/tjgeri.2019.107
2019; 22(3): 315-323

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RESEARCH

EFFECT OF AGE ON ANASTOMOTIC LEAKAGE AND RELATED MORTALITY FOLLOWING COLORECTAL CANCER SURGERY

Abstract

Purpose: The present study aimed to investigate the correlation between age and anastomotic leakage and leak-related mortality following colorectal cancer surgery.

Material and Method: Data of patients who underwent elective resection and anastomosis for colorectal cancer between January 2013 and December 2018 were retrospectively evaluated. Patients were divided into two groups: patients aged <65 years (Group 1) and those aged ≥65 years (Group 2). Demographic characteristics, perioperative risks, diseased colonic segment, neoadjuvant chemoradiotherapy and surgical procedure (laparoscopic/open) were evaluated between both groups. The primary endpoint of the study was the development of anastomotic leakage within 30 days postoperatively. The secondary endpoint was the leak-related mortality within 30 days postoperatively.

Results: The study included 358 patients; 60.6% of these were male and 39.4% were female, and mean age was 65.9 ± 12.33 years. The rate of anastomotic leakage was 5.6% (n = 9) in Group 1 and 5.1% (n = 10) in Group 2 (p = 0.283). Overall leak-related mortality was 1.95%. The leak-related mortality was 0.6% in Group 1 and 3.06% in Group 2 (p = 0.043).

Conclusion: Our results demonstrate that age is not a risk factor for anastomotic leakage following colorectal cancer surgery; however, there is an increased mortality following anastomotic leakage in elderly patients.

Keywords: Anastomotic leakage; Aged; Colorectal cancer; Mortality

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Received: 17/05/2019
Accepted: 08/08/2019

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ARAŞTIRMA

YAŞIN KOLOREKTAL KANSER CERRAHİSİ SONRASI ANASTOMOZ KAÇAĞI VE BUNA BAĞLI GELİŞEN MORTALİTE ÜZERİNE ETKİSİ

Öz

Amaç: Kolorektal kanser cerrahisi sonrası oluşan anastomoz kaçağının ve buna bağlı gelişen mortalitenin yaş ile ilişkisini araştırmaktır.

Materyal ve Metod: Ocak 2013-Aralık 2018 tarihleri arasında kolorektal kanser nedeniyle elektif şartlarda rezeksiyon ve anastomoz yapılan hastaların verileri retrospektif olarak değerlendirildi. Hastalar, <65 yaş (Grup 1), ≥65 yaş (Grup 2) olmak üzere iki gruba ayrıldı. Hastaların demografik özellikleri, perioperatif riskler, hastalıklı kolon segmenti, neoadjuvan kemoradyoterapi alıp almaması ve uygulanan cerrahi prosedür (laparoskopik/açık) iki grup arasında irdelendi. Çalışmanın birinci sonuç ölçütü ameliyattan sonra 30 gün içerisinde gelişen anastomoz kaçağı idi. İkinci çalışma ölçütümüz ise postoperatif 30 gün içerisinde anastomoz kaçağına bağlı gelişen mortalite idi.

Bulgular: Çalışmaya 358 hasta dahil edildi. Hastaların %60.6'sı erkek, %39.4'ü kadın idi ve yaş ortalamaları 65.9±12.33 idi. Anastomoz kaçağı oranı Grup 1'de %5.6 (n=9), Grup 2'de %5.1 (n=10) olarak saptandı (p=0.283). Anastomoz kaçağına bağlı gelişen toplam mortalite %1.95 idi. Grup 1'de anastomoz kaçağına bağlı mortalite %0.6 iken Grup 2'de %3.06 idi (p=0.043).

Sonuç: Kolorektal kanser cerrahisi sonrası yaşın anastomoz kaçağı için risk faktörü olmadığını ancak anastomoz kaçağı sonrası mortalitenin ileri yaşlı hastalarda arttığını göstermektedir.

Anahtar sözcükler: Anastomoz kaçağı; Yaşlı; Kolorektal kanser; Mortalite

INTRODUCTION

Colorectal cancer ranks third among all cancers (1). The elderly population has significantly increased in recent years, and advanced age is a risk factor for the development of colorectal cancer (2). This increase is expected to continue owing to the initiatives toward increasing life expectancy and early diagnosis (3,4). Of the patients diagnosed with colorectal cancer, 50% are aged ≥60 years and postoperative mortality and morbidity is high in elderly patients owing to the presence of comorbid diseases (5). However, curative resection is the main treatment for colorectal cancer. Studies have shown that advanced age is not a contraindication for colorectal cancer surgery (CCS) and that CCS can be safely performed and overall survival is similar to life expectancy (6,7). Although the cause remains unclear, anastomotic leakage (AL) that develops following colorectal surgery is one of the major complications that is worrisome because of the increased morbidity and mortality as well as of their negative impact on the duration of hospital stay and functional and oncologic outcomes. However, studies investigating this subject in elderly patients are limited in literature. Whether age plays a role in AL remains a matter of debate. Gessler B et al. have reported that AL does not correlate with age (8). Ureyen O et al. have reported that the risk of AL is higher in the elderly population (9). In contrast, Park JS et al. have reported that AL is more common in the young population (10). Following colorectal surgery, AL is observed in 3%–28% of cases and is responsible for one-third of postoperative mortality (11). However, AL-related mortality is higher in elderly patients (12). Unfortunately, there is a paucity of data on this subject in literature. The present study aimed to investigate the relationship between age and AL and AL-related mortality following CCS.

MATERIALS AND METHOD

Study design

Data of patients who underwent elective resection and anastomosis for colorectal cancer in our clinic between January 2013 and December 2018 were retrospectively evaluated by reviewing the hospital database system and patient files. The present study was approved by the ethics committee of our hospital (2019/514/148/13).

Patients who did not undergo curative resection for colorectal cancer, those treated with Hartmann procedure or transanal local resection, those treated only with deflective stoma, those with missing data, and those who were operated under emergency conditions were excluded from the study. According to the American Joint Commission on Cancer (AJCC) TNM staging (13), patients with middle and lower rectal carcinoma other than T1 received neoadjuvant chemoradiotherapy (CRT) and total mesorectal excision was performed 8–10 weeks after CRT. A protective ileostomy was routinely performed following anastomosis below the peritoneal reflection in patients with rectal tumor who received neoadjuvant CRT. The decisions were made on a case-by-case basis for the remaining patients with upper rectal and colonic tumors considering their general condition and depending on technical issues encountered both during anastomosis and during the perioperative period. In our study, all patients who underwent surgery for colorectal cancer under elective conditions underwent resection and anastomosis with or without stoma.

Outcome measure and other variables

Patients included in the study were divided into two groups: patients aged <65 years (Group 1) and those aged ≥65 (Group 2). Demographic characteristics, perioperative risks, diseased colonic segment, neoadjuvant CRT, and surgical procedure (laparoscopic/open) were evaluated between both groups. The primary endpoint of the study was AL that developed within 30 days postoperatively. The secondary endpoint was AL-related mortality within 30 days postoperatively.

Statistical analysis

SPSS 22.0 (IBM Corporation, Armonk, New



York, United States) software was used for the analysis of variables. Descriptive data were presented as percentages, mean ± standard deviation. Normality testing (Kolmogorov Sminov) was performed to determine whether the data followed a Gaussian distribution or not. Continuous variables in two independent groups were compared with Student t test or the Mann-Whitney U test. Categorical variables were compare by Pearson's chi-square test or Fisher's exact test. A binary logistic regression analysis was performed to identify potentially risk factors for age groups. A p value < 0.05 was considered as statistically significant.

RESULTS

Study population

The study included 358 patients who underwent elective resection and anastomosis for colorectal cancer. Of these patients, 60.6% were male, 39.4% were female, and mean age was 65.9 ± 12.33. Tumors were most commonly localized in the rectum (23.7%) and sigmoid colon (23.7%).

Anastomotic leakage

Overall incidence of AL in the study group was 5.3% (n = 19). The rate of AL was 5.6% (n = 9) in Group 1 and 5.1% (n = 10) in Group 2 (p = 0.283). Age was not found to have a significant influence on the development of AL. Of the 19 patients that developed AL, 9 had stoma and 10 had no stoma (p = 0.78).

When patient files and database were reviewed for the treatment and management of the patients with AL, of 9 patients with protective stoma that developed AL, 3 were detected, on an average, on the 5th day of the postoperative follow-up period (4-7) and 6 were detected when they presented to the General Surgery outpatient clinic with symptoms of abdominal pain and fever on average on the 11th day after discharge from the hospital (7-19). Conversely, in all patients without protective stoma that developed AL, diagnosis was made by means of clinical observation and imaging methods on the 4th day (3-7) of their postoperative follow-up period. Only two patients with protective stoma who developed AL required relaparotomy after the first operation. Of these 9 patients, 3 died in the postoperative period, 4 underwent ileostomy closure without any problems after completion of oncological treatment, and in the remaining 2 patients with anastomotic stricture, ileostomy was not closed in 1 patient and the other patient underwent the Hartmann procedure after ileostomy closure owing to acute renal failure. It was observed that relaparotomy was required in 8 out of 10 patients without protective stoma that developed AL. Of these patients, 6 underwent Hartman procedure and 2 underwent ileostomy operation. Endoscopic clipping was performed in 2 patients who did not require relaparotomy and showed no evidence of peritonitis on physical examination.

Mortality

Overall mortality was 0.6% (n = 1) in Group 1 and 4.1% (n = 8) in Group 2 (p = 0.037). AL-related mortality occurred in only one patient in Group 1, whereas it occurred in 6 out of 8 patients in Group 2. Of these 6 patients, protective stomas were performed in 3 patients, whereas it was not performed in the remaining 3. The total AL-related mortality was 2%; AL-related mortality was 0.6% in Group 1 and 3.1% in Group 2 (p = 0.043).

According to age groups, in favor of advanced age group hypertension, congestive heart failure (CHF), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), high American Society of Anesthesiologists (ASA) score, and presence of protective stoma found statistically significant (Table 1). There was a significant difference between both groups in terms of tumor N stage, number of lymph nodes removed, and number of metastatic lymph nodes (Table 2). Binary logistic regression analysis showed that CHF, CAD, presence of protective stoma, high ASA score, and number of metastatic lymph nodes significantly correlated with age (Table 3).

Table 1. Clinical characteristic of patients according to age groups.

		Group 1 (<65 years) n(%)	Group 2 (≥65 years) n(%)	Total n(%)	p
Age (average ± sd.)		54.52 ± 6.03	75.11 ± 7.46	65.79 ± 12.33	0.001**
Sex	Female	55(34.0)	86(43.9)	141(39.4)	0.056*
	Male	107(66.0)	110(56.1)	217(60.6)	
ASA(average ± sd.)		2.29 ± 0.46	2.81 ± 0.40	2.57 ± 0.49	0.001**
Anastomotic leakage	No	153(94.4)	186(94.9)	339(94.7)	0.283*
	Yes	9(5.6)	10(5.1)	19(5.3)	
Tumor location	Ascending Colon	23(14.2)	31(15.8)	54(15.1)	0.849*
	Descending Co-lon	0(0.0)	9(4.6)	9(2.5)	
	Rectosigmoid	41(25.3)	35(17.9)	76(21.2)	
	Rectum	47(29)	38(19.4)	85(23.7)	
	Sigmoid	24(14.8)	53(27)	77(21.5)	
	Splenic Flexure	1(0.6)	0(0.0)	1(0.3)	
	Transverse Co-lon	26(16)	30(15.3)	56(15.6)	
Protective ileostomy	No	126(77.8)	171(87.2)	297(83.0)	0.018*
	Yes	36(22.2)	25(12.8)	61(17.0)	
Mortality	No	161(99.4)	188(95.9)	349(97.5)	0.037*
	Yes	1(0.6)	8(4.1)	9(2.5)	
Intestinal preparation	No	0(0.0)	2(1)	2(0.6)	0.197*
	Yes	162(100.0)	194(99.0)	356(99.4)	
Comorbidity	Diabetes	35(21.6)	53(27.0)	88(24.6)	0.234*
	Hypertension	31(19.1)	103(52.6)	134(37.4)	0.001*
	Heart Failure	3(1.9)	31(15.8)	34(9.5)	0.001*
	MI	3(1.9)	0(0.0)	3(0.8)	0.056*
	COPD	6(3.7)	20(10.2)	26(7.3)	0.018*
	CAD	2(1.2)	17(8.7)	19(5.3)	0.002*
	CKF	4(2.5)	9(4.6)	13(3.6)	0.285*
Blood Transfusion	No	133(82.1)	148(75.5)	281(78.5)	0.131*
	Yes	29(17.9)	48(24.5)	77(21.5)	
Operation technique	Laparoscopic	46(28.4)	40(20.4)	86(24.0)	0.078*
	Open	116(71.6)	156(79.6)	272(76.0)	

*Chi-square test (Fisher's exact test). ** Mann–Whitney U analysis.Sd: Standard deviation.

ASA: American Society of Anesthesiologists, MI: Myocardial infarction, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, CKF: Chronic kidney failure.



DISCUSSION

The number of people aged ≥60 and is estimated to exceed 2 billion by 2050 (14). There is no consensus on the age limit in the definition of the elderly (15). The threshold of 65 years used in our study was in accordance with the elderly definition of the World Health Organization, although it would not completely reflect the physical decline associated with advanced age (16). Advanced age is a risk factor for the development of colorectal cancer, in addition to being the most important risk factor for postoperative mortality and morbidity (5). With increasing elderly population, there is an emerging need of recognizing specific risks associated with surgery (17). However, studies conducted to date have not adequately addressed the relationship between age and AL, which is one of the most serious complications of colorectal surgery, and AL-related morbidity and mortality. In the present study, we aimed to investigate the relationship between age and AL, as well as AL-related mortality, following CCS performed under elective conditions.

It has been reported that 50% of the patients diagnosed with colorectal cancer are aged ≥60 years (5). In our study, elderly patients constituted 54.7% of the study sample. In literature, male sex, high ASA score, CAD, COPD, steroid use, and diabetes mellitus have been reported as independent risk factors for AL (15,18). In our

Table 2. TNM stage, number of lymph nodes excised and neoadjuvant CRT in the groups.

		Group 1 n(%)	Group 2 n(%)	Total n(%)	p
T stage	T0	3(1.9)	3(1.5)	6(1.7)	0.512*
	T1	22(13.6)	20(10.2)	42(11.7)	
	T2	106(65.4)	143(73.0)	249(69.6)	
	T3	6(3.7)	3(1.5)	9(2.5)	
	T4	25(15.4)	27(13.8)	52(14.5)	
N stage	N0	74(45.7)	109(55.6)	183(51.1)	0.048*
	N1	41(25.3)	51(26)	92(25.7)	
	N2	47(29)	36(18.4)	83(23.2)	
TNM stage	<3	72(44.4)	105(53.6)	177(49.4)	0.359*
	≥3	90(55.6)	91(46.4)	181(50.6)	
Neoadjuvant therapy	No	120(74.1)	160(81.6)	280(78.2)	0.085*
	Yes	42(25.9)	36(18.4)	78(21.8)	
Number of lymph nodes removed(average ± sd.)		19.77± 8.99	17.56 ± 9.30	18.56 ± 9.21	0.024**
Number of metastatic lymph nodes(average ± sd.)		3.45 ± 5.90	1.79 ± 2.90	2.54 ± 4.58	0.001**

* Chi-square test (Fisher's exact test)** Mann–Whitney U analysis.
CRT: Chemoradiotherapy, TNM;T: Tumor, N: Node, M: Metastasis.

Table 3. Binary logistic regression analysis of according to the ages groups.

Variables	Odds ratio	95% CI	p value
Preventive ileostomy	5.893	2.631 to 13.199	0.001
ASA	9.439	4.639 to 19.206	0.001
CAD	0.229	0.043 to 1.210	0.043
Heart failure	0.082	0.021 to 0.326	0.001
Number of metastatic lymph node	0.875	0.777 to 0.985	0.028
Mortalite	0.153	0.0002 to 0.111	0.006

CI: Confidence Interval.Compared to general and spinal Anesthetic Technique (p = 0.0017), Compared to spinal and combined spinal-epidural Anesthetic Technique (p = 0.016), c. Compared to general and spinal Anesthetic Technique(p = 0.004)

study, binary logistic regression analysis showed that CHF, CAD, high ASA score, and number of metastatic lymph nodes significantly correlated with advanced age. Although these predictive factors related to AL are more significant in elderly patients, it is a matter of debate whether age plays a role in AL development. In the study by the Danish Colorectal Cancer Group and the American College of Surgeons National Surgical Quality Improvement Program, increasing age has been reported to correlate with a decrease in the rate of AL (19). They attributed this finding to both more meticulous preoperative preparation and surgical intervention in the elderly patients. In contrast to these findings, another study has reported an increasing incidence of AL with increasing age (20). In a meta-analysis of 16 studies involving a total of 4,479 cases, no significant difference was reported between the elderly and young patients in terms of the risk of developing AL (21).

The rate of AL following colon resection due to benign and malignant causes is 3.0%–6.4% (22,23). Rencuzogulları et al. have studied a cohort of 10,392 cases aged >65 years that underwent colon resection due to benign and malignant causes and reported that the rate of AL was 3.2% (15). In 45,488 patients who underwent surgery for colorectal cancer, Zaimi et al. have reported an incidence of 6.4% for AL in patients aged <60 years, 5.5% in patients aged 60–69 years, 5.4% in patients aged 70–80 years, and 4.9% in patients aged ≥80years (12).

In our study, the overall AL incidence was 5.3% (n = 19) in patients who underwent elective surgery for colorectal malignancy. The rate of AL was found to be 5.6% (n = 9) in patients aged <65 years and 5.1% (n = 10) in those aged ≥65 years. Age was not a significant factor for the development of AL. Of the 19 patients that developed AL, stoma was performed in 9 and it was not performed in 10 (p = 0.780). In the present study, we found that stoma had no protective effect against AL. This result was consistent with that observed previously (24).

Effective treatment is essential when AL is diagnosed. Early decision of surgery is the most important factor that reduces mortality. Especially AL, which develops in patients with protective stoma, is mostly asymptomatic, and medical supportive therapy is often sufficient. In patients with extraperitoneal anastomosis who do not have signs of peritonitis during examination, special drains inserted into the fistula tract following endoscopic debridement and negative-pressure



aspiration facilitate healing in AL and reduce the need for a second surgical intervention (8). In cases without protective stoma, proximal fecal diversion can be performed, and in cases with extensive peritonitis and those in which anastomosis is fully separated, the Hartmann procedure is essential (8). Of 9 patients with protective stoma included in this study, 2 were followed up with an endosponge, 4 with percutaneous drainage, 1 with stent, and 2 with only medical therapy. Of 10 patients without protective stoma that developed AL, relaparotomy was performed in 8 patients, 6 of whom underwent the Hartman procedure and 2 underwent ileostomy construction. Endoscopic clips were placed in the other 2 patients.

AL following colorectal surgery is responsible for one-third of postoperative mortality (11). However, AL-related mortality is higher in elderly patients (12). A multicenter study has reported four times higher mortality following AL in elderly patients compared with young patients (25). In the study by Zaimi et al., mortality following AL in patients who underwent surgery for colorectal cancer was reported to be 1.3% in patients aged <60 years, 4.8% in patients aged 60–69 years, 12.3% in patients aged 70–80 years, and 27.0% in patients aged ≥80 years (12).

In our study, the overall AL-related mortality was 1.95%. AL-related mortality was 0.6% in patients aged <65 years and 3.06% in patients aged ≥65 years ($p = 0.043$). In our study, patients aged ≥65 years exhibited higher number of comorbidities. This was related to the high ASA score of the elderly patients ($p = 0.001$). The significant difference between mortality of the two groups can be attributed to comorbidities in elderly patients; moreover, not consenting to a second surgery following AL is a possible reason. In our study, protective stoma was more common among the patients aged <60 years. This is attributable to the higher number of patients with rectal and rectosigmoid localization in this group compared with that in the group of patients ≥60 years.

In our clinic, post-anastomosis protective ileostomy below the peritoneal reflection is routinely performed in patients with rectal tumor receiving neoadjuvant CRT. The decision is made on a case-by-case basis for the remaining patients with upper rectal and colonic tumors considering their general condition and depending on technical issues encountered both during anastomosis and during the perioperative period. Protective stomas do not reduce the occurrence of AL; however, they reduce the severity of AL-related septic findings and facilitate the treatment of leakages using palliative methods (24).

The reason for low mortality in our study compared with that reported in literature is that the studies in the literature are heterogeneous studies including patients operated under both emergency and elective conditions. However, our study consisted of patients who were operated under elective conditions involving preoperative preparation. We believe that this difference allowed us to obtain more significant results compared to other studies.

In our study, higher ASA score was observed in elderly patients, and AL-related mortality was significantly higher in these patients. It has been shown that laparoscopic surgery for colorectal cancer is as safe in elderly patients as it is in younger patients (21). Our results are consistent with those in the literature. In our study, right hemicolectomy due to right-sided colon-localized tumor exhibited the lowest rate of AL in both groups. The incidence of AL was mostly observed in surgeries related to rectum-localized tumors.

In conclusion, the present study shows that age is not a risk factor for AL following CCS; however, there is an increase in AL-related mortality in elderly patients.

CONFLICT OF INTEREST

All authors declare that there is not any conflict of interest.

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