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Original Article

Assessment of Risk Factors for Anastomotic Leakage After Resection for Rectal Cancers

Ahmed Allejy[1], Samir Kenaan[2], Mahmood Daberha[3]

[1,2,3]*Department of General Surgery, Tishreen University, Faculty of Medicine, Lattakia, Syria.*

[1]*Corresponding Author : rawanibraheeem0@gmail.com*

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Abstract *- Background: Anastomotic leakage(AL) after colorectal cancer surgery is encountered frequently, which is considered one of the most potentially lethal complications. It affects the quality of life and increases hospital costs, so detecting risk factors for leakage might have a beneficial effect on reducing the occurrence and improving the final outcome. Objective: This study aimed to investigate risk factors associated with the development of leakage. Patients and Methods: An analytic retrospective study was conducted in patients with a proven diagnosis of rectal cancer. They were selected from the Department of General Surgery, Tishreen University Hospital in Lattakia, Syria, between January 2017 and January 2021. Patients were divided into two groups: group 1 included patients who developed anastomotic leakage(11 patients), and group 2 included patients without leakage (67 patients). Risk factors for AL and mortality were compared between the two groups. Results: The population of 78 patients was predominantly males (61.5%), with a mean age of 61.12±7.3 years. The most frequent age group was older than 60 years (70.5%), with the presence of type 2 diabetes mellitus(T2DM) in 30.8%. Stage III represented the most frequent grade of the tumor (42.3%), followed by stage II and I (57.7%), with the presence of a history of chemotherapy in 15.4% of the patients. The rate of AL was 14.1%, which was divided into two groups: early in 9 cases(11.5%) and late in 2 cases(2.6%). Prevalence of AL was significantly higher in males(18.8% versus 6.7%,p:0.001), patients with BMI >30(30% versus 11.8%,p:0.008), presence of chemotherapy before surgery(25% versus 12.1%,p:0.02), decreased levels of albumin(30% versus 8.6%,p:0.0001), tumors with distance from anal verge<5 cm(31.8% versus 7.1%,p:0.0001), and in cases of blood transfusion(19.4% versus 9.5%,p:0.04). The mortality rate was higher in the presence of leakage(27.3% versus 4.5%,p:0.004), hypoalbuminemia (RR 3.9), longer duration of surgery (RR 2.4), male gender (RR 2.01) and presence of obesity (RR 3.1)were independent factors that associated significantly with the risk for progression of AL. Conclusion: The current study demonstrated an important prevalence of AL in our hospital, and the presence of hypoalbuminemia, longer duration of surgery, male gender, and obesity are all warning flags that may predispose to leakage after colorectal surgery.*

Keywords *- Anastomotic Leakage(AL), Cancer, Colorectal, factors, Mortality, Risk.*

1. Introduction

Colorectal cancer(CRC) represents the third most common cancer worldwide, with various rates of incidence around the world[1,2,3]. It poses a huge public health concern as it is the second leading cause of cancer-related deaths globally, so regular CRC screening has improved significantly the final outcome of patients[4,5,6,7,8].

It affects predominantly older individuals, with which the majority of cases occurring in persons older than 50 years[9,10,11]. CRC is a multifactorial disease process that includes genetic factors, environmental exposures, and inflammatory disease, so a better understanding of the biology of tumors, along with high efficiency of diagnostic and therapeutic methods, will improve the final outcome of CRC patients[12,13].

Surgery is considered the definitive treatment modality for rectal cancer, and surgical intervention is performed either by local or radical excision, depending on the clinical stage, size, and location of the primary tumor[13,14].

Anastomotic leakage (AL) remains one of the most severe complications following CRC surgery and is commonly associated with higher reoperation rates and increased morbidity and mortality risk following colorectal surgery[16,17,18]. It is defined as a defect of continuity localized at the surgical site of the anastomosis, creating communication between the intra-luminal and extra-luminal compartments [19,20]. Incidence of AL varies from 3 to 21%, with a high rate of mortality in spite of improvements in surgical techniques there are many risk factors have been identified to affect the incidence of anastomotic dehiscence, which can be classified into preoperative, intraoperative, and perioperative factors[21,22]. Therefore, the objective of the study was to 1- determine risk factors that are associated with the occurrence of AL. 2- to investigate the mortality rate in patients who developed AL.

2. Patients and Methods

This is an analytic retrospective study of a group of patients attending the Department of General Surgery at

Tishreen University Hospital in Lattakia, Syria, during a four-year period (January 2017 and January 2021). The inclusion criteria were patients with proven diagnoses of rectal cancer who underwent surgical resection by using the stapled technique in all cases.

The exclusion criteria were patients who underwent emergency surgery for the management of complicated rectal cancer(bleeding, perforation, obstruction), palliative surgery for advanced stages and in the presence of metastasis, and patients who didn't undergo anastomosis after surgery or stoma. Complete medical history together with the physical examination were done. Age, sex, body mass index(BMI), and comorbidities were recorded.

BMI was calculated as weight(kg) divided by height(m) squared(kg/m2), and patients were classified according to BMI to normal weight (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2) and obesity (≥30 kg/m2). Preparation of the bowel was performed before surgery with the administration of intravenous perioperative antibiotic prophylaxis.

The surgical procedure was performed by laparotomy, with resection of the rectum and mesorectum (TME) up to the level of the pelvic diaphragm, sparing the autonomic nerves. End-to-end anastomosis was performed with a stapler. Patients were assigned to Group 1 (11 patients) who developed anastomotic leakage, and Group 2 (67 patients) who didn't develop leakage. Patients were followed up at regular intervals, and outcomes were compared between the two groups.

2.1. Ethical Consideration

All patients were provided complete and clear informed consent after discussion about the study. This study was performed in accordance with the Declaration of Helsinki.

2.2. Statistical Analysis

Statistical analysis was performed by using IBM SPSS version 20. Basic Descriptive statistics included means, standard deviations(SD), frequency, and percentages. The chi-square test was used to examine the relationships and comparisons between the two groups. All the tests were considered significant at a 5% type I error rate($p<0.05$), β:20%, and power of the study:80%.

3. Results

The study included a group of 78 patients (48 male, 30 female) with a diagnosis of rectal cancer. Age ranged from 41 to 79 years with a mean age of 61.12±7.3, and patients were divided according to age into two groups: younger than 60 years(29.5%) and >60 years (70.5%). Body mass index(BMI) was greater than 30 in 12.8% of the patients, with the presence of type 2 diabetes mellitus(T2DM) in 30.8%.

Tumor grades ranged from I- II in 45 cases (57.7%) to III in 33 cases (42.3%), distance of cancer from the anal verge was < 5 cm in 28.2% and > 5 cm in 71.8% with presence of chemotherapy prior to surgery in 12 cases (15.4%).

Table 1. Demographic characteristics of the study population

Variable	Result
Age (years)	41-79(Mean: 61.12±7.2)
Age group(years)	
<60	23(29.5%)
>60	55(70.5%)
Sex	
Male	48(61.5%)
Female	30(48.4%)
BMI	
<30	68(87.2%)
>30	10(12.8%)
T2DM	
Present	24(30.8%)
Absent	54(69.2%)

According to laboratory findings, hemoglobin(Hb) was less than 10 g/dL in 60 cases(76.9%) and albumin was < 3.5 g/dL in 20 cases(25.6%).

Table 2. Characteristics of tumor and laboratory investigations

Variable	Result
Tumor stage	
I-II	45(57.7%)
III	33(42.3%)
Distal margin of tumor	
< 5 cm	22(28.2%)
>5 cm	56(71.8%)
Chemotherapy before surgery	
Present	12(15.4%)
Absent	66(84.6%)
Laboratory investigations	
✓ Hb(g/dL)	
<10	60(76.9%)
>10	18(23.1%)
✓ Albumin(g/dL)	
<3.5	20(25.6%)
>3.5	58(74.4%)

Table 3. Characteristics of surgery of the study population

Variable	Result
Duration of surgery(hours)	
< 3	16(20.5%)
>3	62(79.5%)
Blood transfusion	
Present	36(46.2%)
Absent	42(53.8%)
Anastomotic leakage	
Present	11(14.1%)
Absent	67(85.9%)

As shown in Table (3), the duration of surgery was longer than 3 hours in 62 cases(79.5%), with the need for blood transfusion in 36 cases(46.2%). The incidence rate of anastomotic leak after surgery was 14.1%, which was divided into two groups: early in 9 cases(11.5%) and late in 2 cases(2.6%).

The demographic characteristics were compared between the two groups as shown in Table 4. There were no significant differences between the two groups regarding age groups and the presence of T2DM. Age groups were compared between two groups (group 1 versus group 2); <60(13.1% versus 86.9%) and >60(14.5% versus 85.5%),p:0.2 . Presence versus absence of T2DM was as follows;(12.5% versus 14.8%) in group 1 and (87.5% versus 85.2%) in group 2,p:0.2. Anastomotic leakage tended to correlate significantly with male gender (18.8% versus 6.7%, p: 0.001) and with increasing BMI(30% in patients with BMI >30 versus 11.8% in the other group,p:0.008).

Table 4. Demographic characteristics of the study population according to presence of leakage

Variable	Leakage		P value
	Group 1 Present	Group 2 Absent	
Sex			
Male	9(18.8%)	39(81.2%)	**0.001**
Female	2(6.7%)	28(93.3%)	
Age groups(year)			
<60	3(13.1%)	20(86.9%)	**0.2**
>60	8(14.5%)	47(85.5%)	
BMI groups(kg/m2)			
<30	8(11.8%)	60(88.2%)	
>30	3(30%)	7(70%)	**0.008**
T2DM			
Present	3(12.5%)	21(87.5%)	
Absent	8(14.8%)	46(85.2%)	**0.3**

As shown in Table (5), patients receiving neoadjuvant chemotherapy for cancers tended to have increased incidence of leakage with the presence of a significant difference between groups (25% versus 12.1% in patients who did not receive chemotherapy, p:0.2). Anastomotic leakage tended to be significantly more frequent in tumors located less than 5 cm from the anal verge(31.8% versus 7.1%,p:0.0001) and in patients with levels of albumin <3.5(30% versus 8.6%,p:0.0001). There were no significant associations between the occurrence of leakage and grade of tumors(13.5% in grade I-II versus 15.1% in stage III.p:0.9) and with levels of Hb(13.3% in levels <10 and 16.7% with Hb >10,p:0.8)

Table 5. Characteristics of tumor and laboratory investigations by comparison of the two group

Variable	Leakage		P value
	Group 1 Present	**Group 2 Absent**	
Tumor stage			
I-II	6(13.3%)	39(86.7%)	0.9
III	5(15.1%)	28(84.9%)	
Chemotherapy before surgery			
Present	3(25%)	9(75%)	0.02
Absent	8(12.1%)	58(87.9%)	
Distal margin of tumor			
< 5 cm	7(31.8%)	15(68.2%)	0.0001
>5 cm	4(7.1%)	52(92.9%)	
Laboratory investigations			
✓ Hb			
<10	8(13.3%)	52(86.7%)	0.8
>10	3(16.7%)	15(83.3%)	
✓ Albumin			
<3.5	6(30%)	14(70%)	0.0001
>3.5	5(8.6%)	53(91.4%)	

Table 6. Characteristics of surgery and mortality by comparison of the two group

Variable	Leakage		P value
	Group 1 Present	Group 2 Absent	
Duration of surgery(hours)			
< 3	1(6.2%)	15(93.8%)	0.001
>3	10(16.1%)	52(83.9%)	
Blood transfusion			
Present	7(19.4%)	29(80.6%)	0.04
Absent	4(9.5%)	38(90.5%)	
Mortality			
Present	3(27.3%)	3(4.5%)	0.004
Absent	8(72.7%)	64(95.5%)	

Development of leakage was significantly higher with a duration of surgery longer than 3 hours (16.1% versus 6.1%,p:0.001) and in the presence of blood transfusion(19.4% versus 9.5%,p:0.04). The rate of mortality was significantly higher in the presence of leakage(27.3% versus 4.5%,p:0.004).

In the multivariate logistic regression analysis, hypoalbuminemia (RR 3.9,95% CI 1.2-11.2, p=0.0001), longer duration of surgery (RR 2.4,95% CI 1.1-9.6, p=0.0001), male gender (RR 2.01,95% CI 1.5-8.2, p=0.002), and presence of obesity (RR 3.1,95% CI 1.1-10.1, p=0.0001)were factors that associated with the risk of progression anastomotic leakage, Table (7).

Table 7. Multivariate logistic regression analysis of risk factors of anastomotic leakage

Variable	RR [CI 95%]	P value
Hypoalbuminemia	3.9[1.2-11.2]	0.0001
Duration of surgery	2.4[1.1-9.6]	0.0001
Males	2.01[1.5-8.2]	0.002
Presence of obesity	3.1[1.1-10.1]	0.0001

4. Discussion

This analytic study of surgical management of rectal cancer in 78 patients assessed the prevalence of anastomotic leakage occurring after surgery and the final outcome regarding quality of life. The result of the current study revealed that leakage was more frequent in males than females, who fall in the advanced age group. It might be related to the high frequency of adenomatous polyps in this group, which predisposes to rectal cancer. Approximately 50% of the patients were in an advanced stage of tumor, which might be explained by delay in diagnosis and the absence of screening programs. Anemia was present in the majority of the patients due to chronic blood loss and cancer-associated malnutrition. Anastomotic Leakage(AL) was developed in 14% of the cases, which was more frequent in males than females and in the presence of obesity. These findings might be attributed to anatomical differences in the pelvis between males and females and differences in intestinal microvascular that are associated with androgens. In addition, there were disproportionately large omentum, thickened mesentery, and increasing intraabdominal pressure that increased the technical operating difficulty in obese patients. The harmful effects of chemotherapy on intestinal tissue and the healing of anastomosis increased the incidence of AL.

AL was observed more frequently in extremely low rectal anastomosis because it may be related to the poor blood supply of the cut ends, the technical operating difficulty that leads to tissue injuries, and small artery vascular trauma during surgery. Additionally, AL was associated significantly with a longer duration of surgery and blood transfusion, which might be related to exposure to tissue injuries, the occurrence of inflammation, ischemia, and transfusion of blood cells, which may trigger immune suppression and increase infection. Finally, there are a number of risk factors that may predispose to the development of AL, which include hypoalbuminemia, longer duration of surgery, male gender, presence of obesity, and the rate of mortality was higher in the presence of AL, which might be related to delay in diagnosis, surgical intervention without performing protective stoma. These findings are comparable with the results of previous studies.

Jannasch et al. (2015) demonstrated in a study conducted in 17867 patients during the period of 10 years that the prevalence of AL was 11.9%, with a high prevalence of mortality in this group(7.55 versus 1.4%,p:0.0001). Risk factors associated with the risk of AL: male gender, smoking, blood transfusion, lower location of tumors, and without performing ileum stoma[23].

Qi et al. (2021) showed in a study conducted on 298 patients during 6 years that the prevalence of AL was 2.7%, which was observed in male gender(p:0.2), advanced age(p:0.04), in the presence of chemotherapy(37% versus 12%,p:0.09). Longer duration of surgery(>200 minutes) is an independent risk factor for leakage(OR:9, P:0.01) [24].

Wang et al. (2022) demonstrated in a study that included 1013 patients during three years that the prevalence of AL was 6.6% which was observed more frequently in males(p:0.007), advanced age(older than 60 years), grade II tumor, and in the absence of stoma(p:0.02). Risk factors associated significantly with male

gender(OR:2.5), duration of surgery(OR:2.3), and tumors located less than 5 cm from the anal verge(OR:5.3) [15].

In summary, AL remains a significant cause of both mortality and morbidity in patients who have undergone open surgical resection for rectal cancer, so it is essential to identify risk factors for AL and develop effective prevention strategies to reduce anastomotic leakage and improve final outcome.

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