Original Article

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Risk Factors for Anastomotic Leakage after Rectal Surgery in Locally Advanced Rectal Cancer

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Abstract:

Objective: To identify the risk factors for anastomosis leakage (AL) after rectal resection for locally advanced rectal cancers (LARCs) treated with neoadjuvant chemoradiation (nCRT).

Material and Methods: A retrospective risk factor study was conducted in LARC patients who received nCRT in Hatyai Hospital from September 2014 to September 2023. The patients were classified into two groups, AL and no anastomotic leak (No-AL) groups. The variables analyzed included age, gender, body mass index (BMI), American Society of Anesthesiologists classification score (ASA), history of significant weight loss, tumor level, time interval between nCRT and surgery, the number of staples, surgical approach, estimated blood loss (EBL), packed red cell (PRC) transfusions, operative time, diverting ostomy, and type of surgery. These predictive factors were analyzed by univariable and multivariable logistic regression.

Results: One hundred and seventeen patients were included in the study. The AL rate was 8.5% and the 30-day mortality rate was zero. The study found that BMI, time interval, EBL, and PRC transfusions were associated with a significantly increased AL risk under univariable analysis. In the multivariable analysis, four factors were identified as independent risk factors for AL: BMI less than 18 kg/m^2, time interval more than 11 weeks, needing packed red cells blood transfusion, and operative time more than 400 minutes.

Conclusion: Diverting stoma can reduce AL consequences but does not reduce its incidence. Diverting stoma should be considered in locally advanced rectal cancer treated with neoadjuvant chemoradiation patients with the risk factors noted above-BMI less than 18 kg/m^2, time interval longer than 11 weeks, needing PRC transfusion, or operative time more than 400 minutes.

Keywords: anastomosis leakage, locally advanced rectal cancer, neoadjuvant chemoradiation, risk factors

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Introduction

Although advanced treatment of rectal cancer including neoadjuvant chemoradiation (nCRT) and total mesorectal excision (TME) has further increased sphincter preservation, anastomotic leakage (AL) is still a serious complication of colorectal surgery causing higher reoperation rates, increased mortality, longer hospital stay, and increased local recurrence rates[1].

Several risk factors for anastomotic leak have been identified. These factors can help prevent and diagnose AL in high-risk patients. One study reported that the incidence of AL was reported as 2-19% and ranging from 2-7% when surgery was performed by an experienced team[2]. In another study, the anastomotic leak rate was 20.2% in patients receiving preoperative radiation and 5-fluorouracil[3]. AL harmed the overall survival in a meta-analysis[4]. Studies on the association between nCRT and the incidence of AL have shown conflicting results.

Diverting stoma at the time of rectal surgery does not appear to reduce the AL rate. Still, it may reduce its consequences[2,5] and the need for re-operation or intervention if anastomotic leakage does occur. The permanent stoma rate following rectal anastomotic leak was 27% and 57.1% from colonic leak in one study[6]. Most patients have a protective diverting ostomy in rectal surgery, especially post-chemoradiation treatment. The construction of an ostomy in low-risk patients causes unnecessary complications of a diverting ostomy. Improved knowledge of AL risk factors in nCRT patients could change pre-operative preparation and operative planning. The study aimed to identify AL risk factors after colorectal surgery in locally advanced rectal cancers (LARC) patients treated with nCRT.

Material and Methods

The study was conducted through retrospective data collection from September 2014 to September 2023 in Hatyai Hospital, a tertiary referral center hospital in southern Thailand. The study and statistical analysis were approved by the Human Research Ethics Committee, Hatyai Hospital, Songkhla province: document ID number HYH EC 048-66-01. Patients over 18 years old diagnosed as LARC who had completed nCRT treatment were enrolled. Abdominal perineal resection patients were excluded.

The study enrolled patients diagnosed as LARC with its lower border tumor located up to 15 centimeters from the anal verge. The study included all patients treated by elective or emergent surgery with local curative intention, in whom primary anastomosis was performed, who had a peritoneal drain placed before the closure of the abdominal wall, and whose nCRT course was long-term and based on 5-fluorouracil or capecitabine. The data were collected for 60 days postoperatively.

The patients were categorized into 2 groups, the anastomotic leakage group (AL group) and the no anastomotic leakage group (No-AL group). Fourteen variables were analyzed under univariable logistic regression: age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) classification score, history of significant weight loss, tumor level, time interval between nCRT and surgery, the number of staples, surgical approach, estimated blood loss (EBL), packed red cells (PRC) transfusions, operative time, diverting ostomy, and type of surgery. Before multivariate logistic regression analysis, these variables were categorized into binary data based on clinical differences.

Tumor level defined the distance of the tumor from the anal verge. The time interval between nCRT and surgery was defined as the number of weeks between completion of chemoradiotherapy and rectal surgery. A history of significant weight loss meant the persistent, unintentional loss of >10% of body weight over 6 months. The number of staples in the laparoscopic approach or the number of linear cutters staples in the open approach for the divided lower border of rectal cancer. The surgical approach meant a laparoscopic or open technique. The types of surgery

were categorized as low anterior resection (LAR), ultralow anterior resection (ULAR) or intersphincteric resection (ISR).

The International Study Group of Rectal Cancer (ISREC) defines AL after anterior resection as a defect of continuity localized at the surgical site of the anastomosis, creating communication between intra-luminal and extra-luminal compartments[7]. The severity of AL is graded based on the impact on clinical management. Grade A leakage results in no change in a patient's management, grade B leakage requires active therapeutic intervention without re-laparotomy, and Grade C leakage requires re-laparotomy. Clinical leakage signs are defined as prolonged bowel ileus, rectal bleeding, abdominal pain, fever, pus, or fecal discharge from the pelvic drain, peritonitis, and pelvic abscess. All clinically suspicious patients were confirmed by digital rectal examination, colonoscopy or abdominal computed tomography.

Statistical analysis

All data are presented as mean±standard deviation for continuous variables with normal distribution and as counts for discrete variables. The Student's t-test was used to compare continuous variables with normal distribution. The Non-normal distribution of continuous variables is presented with median and interquartile range and was analyzed with the Mann-Whitney U test. The chi-square test or Fisher's exact test were used to compare and analyze categorical variables. All analyses were two-sided, and a p-value<0.05 was considered statistically significant. The factors associated with AL after univariable and multivariable analysis were measured. All statistical analyses were performed using the statistics data program (version 15).

Results

One hundred and sixty-two patients were enrolled in the study. Forty-five patients who underwent abdominoperineal resection were excluded (Figure 1). The remaining 117 patients were categorized into AL (10 patients) and No-AL (107 patients) groups. The majority of surgeries were performed using a laparoscopic approach (92.3%). Fifty percent of the patients had a history of weight loss of at least 10% over the previous 6 months. Fifteen patients (12.8%) had a complete pathological response while seven patients (6%) had tumor progression after completion of their nCRT. Two patients developed colonic obstruction and underwent emergency surgery 2 weeks after finishing their nCRT. Seventy-seven patients (65.8%) underwent a diverting ostomy (Table 1). In the ostomy subgroup analysis, the ULAR and ISR patients had significantly more diverting ostomies than the LAR patients (75.0% vs 53.1%, p-value=0.018). One-fourth of the patients underwent rectal surgery with other organ resection. EBL in rectal surgery alone was not different from EBL compared to rectal surgery with other organ resections (median 300 vs 200 milliliters, p-value=0.106).

The AL incidence rate was 8.5% (LAR 4 patients, ULAR or ISR 6 patients). Three cases of AL without intervention or re-laparotomy (grade A) were treated with antibiotics. There was one case of Grade B AL which was treated with an endoluminal sponge. Six patients had grade C AL requiring re-laparotomy. The 30-day mortality was zero and no patients died during the follow-up period.

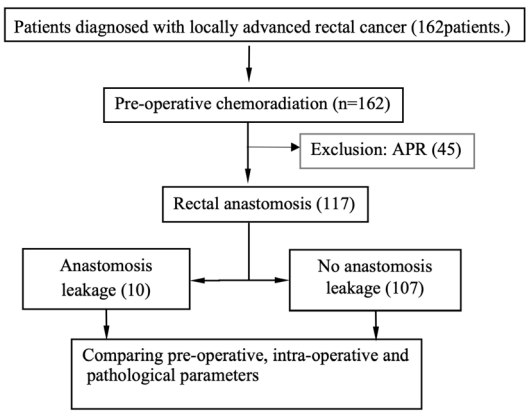

Figure 1 Patient selection

Table 1 Patient characteristics intra-operative and pathological data

Characteristic	n=117
Age, years (mean, range)	61.0 (29-84)
Male (n, %)	74 (63.2)
Body mass index, kg/m^2 (mean, range)	22.5 (15.1-39)
ASA (n, %)	
II	70 (59.8)
III	46 (39.3)
IV	1 (0.9)
Non-insulin dependent diabetes mellitus (n, %)	22 (18.8)
Ischemic heart disease (n, %)	6 (5.1)
History of smoking (n, %)	30 (25.6)
Significant weight loss (n, %)	62 (53.0)
Tumor level (n, %)	
Upper rectum	16 (13.7)
Middle rectum	66 (56.4)
Lower rectum	35 (29.9)
Tumor staging before nCRT (n, %)	
T2	3 (2.6)
T3	71 (60.7)
T4	43 (36.8)
Pre-operative albumin*, mg/dl (mean, range)	3.9 (2.6-4.8)
Pre-operative hemoglobin, mg/dl (mean, range)	11.7 (7.9-17.7)
Interval time (mean, range)	10.2 (3-23)
Pathological T staging, post nCRT (n, %)	
T0	15 (12.8)
T1	5 (4.3)
T2	26 (22.2)
T3	64 (54.7)
T4	7 (6.0)
Residual tumor classification (n, %)	
R0 (n, %)	114 (97.4)
R1 (n, %)	3 (2.6)
Differentiation of tumor, (n, %)	
Poor differentiation	3 (2.6)
Moderate differentiation	52 (44.4)
Well differentiated	62 (53.0)
Number of staples, pieces (n, %)	
0 (Hand sewn)	18 (15.4)
1	54 (46.2)
2	37 (31.6)
3	8 (6.8)
Surgical approach, laparoscopy (n, %)	108 (92.3)
EBL, milliliters (mean, range)	305.1 (25-1600)
PRC transfusion, units (mean, range)	0.3 (0-4)
Operative time, minutes (mean, range)	301.6 (110-515)

Table 1 (Countinued)

Characteristic	n=117
Diverting ostomy (n, %)	77 (65.8)
Type of surgery (n, %)	
Low anterior resection	66 (56.4)
Ultralow anterior resection	33 (28.2)
Intersphincteric resection	18 (15.4)

n=number, ASA=American Society of Anesthesiologists, nCRT=neoadjuvant chemoradiation, T=tumor staging, R0=resection for cure or complete remission, R1=microscopic residual tumor, EBL=estimated blood loss, PRC=packed red cells, *=110 patients

Table 2 Clinical characteristics of the study patients

Characteristics	AL (n=10)	No-AL (n=107)	odds ratio 95% CI	p-value
Age, years (mean±S.D.)	61.0±3.2	60.9±1.1	1.0 (0.9-1.1)	0.992
Male (n, %)	7 (70.0)	67 (62.6)	1.4 (0.3-5.7)	0.744
BMI (kg/m^2)(mean±S.D.)	18.7±0.9	22.8±0.4	0.6 (0.4-0.8)	0.002
ASA score (n, %)			1.4 (0.4-4.9)	0.556
2	5 (50.0)	65 (60.8)		
3	5 (50.0)	41 (38.3)		
4	0 (0.0)	1 (0.9)		
Significant weight loss (n, %)	6 (60.0)	56 (52.3)	1.4 (0.4-5.1)	0.748
Tumor level (mean±S.D.)	6.0±0.8	7.1±0.3	0.8 (0.7-1.1)	0.239
Interval time (mean±S.D.)	12.2±0.9	10.0±0.3	1.2 (1.0-1.5)	0.019
Number of staples, (n, %)			1.4 (0.6-3.1)	0.800
0 piece (Hand sewn)	1 (10.0)	17 (15.9)		
1 piece	4 (40.0)	50 (46.7)		
2 pieces	4 (40.0)	33 (30.8)		
3 pieces	1 (10.0)	7 (6.6)		
Laparoscopy approach (n, %)	8 (80.0)	100 (93.5)	0.3 (0.1-1.6)	0.171
EBL, ml**	525 (400, 800)	200 (100, 350)	1.0 (1.0-1.0)	0.002
PRC transfusions, units**	1 (0, 1)	0 (0.0)	1.6 (0.9-2.8)	0.002
Operative time, min**	302 (250, 480)	300 (245, 340)	1.0 (0.9-1.0)	0.415
Diverting ostomy (n, %)	5 (50.0)	72 (67.3)	0.5 (0.1-1.8)	0.307
Type of surgery (n, %)			1.5 (0.6-3.3)	0.577
Low anterior resection	4 (40.0)	62 (57.9)		
Ultralow anterior resection	4 (40.0)	29 (27.1)		
Intersphincteric resection	2 (20.0)	16 (15.0)		

AL=anastomosis leakage group, No-AL=no anastomosis leakage group, BMI=body mass index, ASA=American Society of Anesthesiologists, EBL=estimated blood loss, CI=confidence interval, S.D.=standard deviation, **=presented with median, interquartile range 25 and 75

Table 3 Univariable and multivariable logistic regression analysis of AL predictors

Variable predictors	AL (n=10) (n, %)	No-AL (n=107) (n, %)	Univariable odds ratio, 95% CI	p-value	Multivariable odds ratio, 95% CI	p-value
Age (years)						
≤60	5 (50.0)	51 (47.7)				
>60	5 (50.0)	56 (52.3)	0.9 (0.2-3.3)	0.888	0.6 (0-13.9)	0.745
Gender						
Female	3 (30.0)	40 (37.4)				
Male	7 (70.0)	67 (62.6)	1.4 (0.3-5.7)	0.645	3.2 (0.1-141.8)	0.544
BMI						
>18 kg/ m^2	5 (50.0)	102 (95.3)				
≤18 kg/m^2	5 (50.0)	5 (4.7)	20.4 (4.4-94.2)	<0.001	53.2 (2.3-1248.5)	0.014
ASA score						
II	5 (50.0)	65 (60.8)				
III+IV	5 (50.0)	42 (39.2)	1.5 (0.4-5.7)	0.510	0.7 (0-38.8)	0.848
Weight loss						
No	4 (40.0)	51 (47.7)				
Yes	6 (60.0)	56 (52.3)	1.4 (0.4-5.1)	0.643	0.7 (0-11.9)	0.814
Tumor level						
>7 centimeters	2 (20.0)	34 (31.8)				
≤7 centimeters	8 (80.0)	73 (68.2)	2.9 (0.6-14.3)	0.191	8.2 (0-14060.4)	0.580
Interval time						
≤11 weeks	3 (30.0)	84 (78.5)				
>11 weeks	7 (70.0)	23 (21.5)	8.5 (2.0-35.6)	0.003	114.3 (1.1-12043.5)	0.046
Staplers						
No use	1 (10.0)	17 (15.9)				
Use	9 (90.0)	90 (84.1)	1.7 (0.2-14.3)	0.625	2.1 (0.1-87.1)	0.698
Approach						
Laparoscopy	8 (80.0)	100 (93.5)				
Open	2 (20.0)	7 (6.5)	3.5 (0.6-20.1)	0.149	1.4 (0-1159.3)	0.928
EBL						
<400 milliliters	6 (40.0)	99 (92.5)				
≥400 milliliters	4 (40.0)	8 (7.5)	7.9 (2.0-31.2)	0.003	2.9 (0.1-95.7)	0.551
PRC transfusion						
No	4 (40.0)	90 (84.1)				
Yes	6 (60.0)	17 (15.9)	7.9 (2.0-31.2)	0.003	35.0 (1.0-1207.7)	0.049
Operative time						
<400 minutes	5 (50.0)	61 (57.0)				
≥400 minutes	5 (50.0)	46 (42.9)	4.8 (1.2-19.4)	0.027	29.4 (1.3-660.4)	0.033
Diverting ostomy						
No	5 (50.0)	35 (32.7)				
Yes	5 (50.0)	72 (67.3)	0.5 (0.1-1.8)	0.278	0.6 (0-9.2)	0.680
Type surgery						
LAR	4 (40.0)	46 (42.9)				
Other	6 (60.0)	61 (57.0)	1.8 (0.4-7.2)	0.431	0.3 (90-158.5)	0.692

AL=anastomosis leakage group, No-AL=no anastomosis leakage group, BMI=body mass index, ASA=American Society of Anesthesiologists, T=histological tumor invasion, EBL=estimated blood loss, CI=confidence interval, LAR=low anterior resection, other=ultralow anterior resection or intersphincteric resection

In univariable logistic regression analysis, the 4 predictive variables associated with AL were lower BMI (18.7±0.9 vs 22.8±0.4 mg/m^2, p-value=0.002), longer time interval (12.2±0.9 vs 10.0±0.3 weeks, p-value=0.019), high EBL (median: 525 ml vs 200 ml, p-value=0.002), and requiring a PRC transfusion (median: 1 vs 0 unit, p-value=0.002) (Table 2). BMI had the highest predictive ability when measured by area under the receiver operating characteristic (0.81). In subgroup analysis, BMI ≤18 kg/m^2 was not associated with either serum albumin less than 3.5 mg/dl (p-value=1.000) or a history of significant weight loss (p-value=0.748).

All AL patients had at least one risk factor of AL. The AL patients had suspected signs or symptoms of AL within 60 days (rectal bleeding in 3 patients, fever and abdominal pain in 3 patients, severe anal pain in 1 patient and anastomotic dehiscence from the rectal exam in 3 patients). The diagnosis of AL was confirmed by abdominal computer tomography or colonoscopy.

In the multivariable logistic regression analysis, all clinical predictors were categorized into binary data based on clinical differences (Table 3). Four independent risk factors were found: BMI ≤18 kg/m^2, time interval > 11 weeks, received PRC and operative time more than 400 minutes.

Discussion

nCRT has been demonstrated to reduce local recurrence and to downstage rectal tumors[8]. The optimal surgical timing after completion of nCRT is approximately 8-12 weeks to increase pathologic complete response rates[9]. An AL is still a serious complication for rectal surgery both with and without nCRT[2,4]. Research on AL following nCRT has had conflicting results. A randomized controlled trial on 318 patients with rectal cancer concluded that preoperative radiotherapy increased the risk of AL[3]. The AL rate was 20.2% in patients receiving preoperative radiation and 5-fluorouracil alone and 23.6% if this therapy was combined with oxaliplatin compared with 8.5% in patients with preoperative chemotherapy without radiation (p-value=0.007). A meta-analysis indicated that preoperative radiotherapy/chemoradiotherapy significantly increased the risk of postoperative wound complications but not AL and bowel obstruction[10], consistent with other research[11-13]. However, most surgeons consider that nCRT is a risk for anastomosis leakage, and most perform rectal surgery with a diverting ostomy to reduce the severity of leakage.

Earlier studies have found that a diverting stoma did not decrease the incidence rate of AL[15], mortality or infectious complications in rectal cancer patients undergoing rectal surgery after nCRT in a National Surgical Quality Improvement Program (NSQIP) analysis[14]. Moreover, the same study found that diverting stoma construction and closure was associated with increased morbidity and cost. Another study reported that the potential disadvantages of a protective stoma included increased surgical time, prolonged hospital stay and stoma-related complications, such as fluid and electrolyte imbalance, prolapse, stenosis, parastomal hernia, and skin irritation[2]. Therefore, the decision to construct a protective stoma should not be driven solely by previous nCRT. The identification of risk factors for AL in nCRT patients can help surgeons consider creating an ostomy in high-risk AL rectal cancer patients treated with nCRT and optimize any modifiable risk factors.

Lower BMI was a predictor associated with an increased incidence rate of AL. A lower BMI indicates a prolonged poor nutrition status that can affect wound healing in rectal anastomosis[16]. However, serum albumin and a history of significant weight loss were not significant risk factors for AL in this study. Earlier studies reported that a BMI >30 kg/m^2 was considered an independent risk factor for AL[2,14]. There were 5 patients with

BMI >30 kg/m^2 in this study and it was not associated with AL. BMI ≤18 kg/m^2 was a significant independent risk factor for AL in multivariable logistic regression analysis.

In an earlier randomized trial, patients who had surgery within 8 weeks after completion of chemoradiotherapy were found to have a higher leak rate of 10.8% compared with 4.5% in patients who had their operation 12 or more weeks after completion of neoadjuvant treatment[9]. This finding was suggested to be caused by tissue edema, pelvic fibrosis, and or vascular occlusion, which may negatively affect anastomotic healing. In another study the interval between nCRT and surgery from 8 to 12 weeks was associated with a 2-fold increase in pathological complete response rate without any significant difference in mortality and morbidity[9]. A time interval less than 8 weeks was not associated with an increased risk of AL in this study, however a time interval longer than 11 weeks was found to be a significant risk factor in multivariable analysis. Higher intra-operative blood loss and receiving a PRC transfusion were independent predictors of AL, which was consistent with the literature[2,19]. A systemic inflammatory response with changes in plasma concentrations of inflammatory mediators may explain this relationship[2,20]. An operative time longer than 3 hours has also been described in the literature as associated with an increased incidence of anastomotic dehiscence[2,14]. However, we found an operative time of more than 400 minutes was associated with AL by multivariable analysis. A long operative time indicates difficult or severe fibrosis, which lead to higher blood loss. Adjusted analysis in the present study indicated that treatment factors such as BMI ≤18 kg/m^2, time interval >11 weeks, needing a PRC transfusion and operative time longer than 400 minutes were independent risk factors for AL. We cannot offer any specific pathophysiological explanation for why each risk factor increased the AL rate, but it may be explained by the effect of multifactor.

Male gender has been reported in other studies as a significant risk factor for AL owing to the narrower pelvis of males, which may contribute to technical difficulties during a surgery[17,18]. A low rectal anastomosis or lower border of the tumor less than 5-7 centimeters from the anal verge were suggested in another study to possibly be associated with an increased leakage rate caused by possible insufficiency of the microvasculature and technical difficulties[18]. Patients with ASA-class≥ 3 were associated with an increased risk of AL in other studies[2,14] owing to increased comorbidities. Although increased age may increase the risk for comorbidities, one other study reported that the AL incidence was not correlated with the patient's age[14]. Another study found that using three or more staple firings was associated with a higher risk of AL in laparoscopic rectal resection[21]. Vertical rectal resection through a suprapubic port has been suggested as a useful technique for avoiding multiple stapler firings[21]. In our study 8 patients needed 3 staple firings. One-fourth of our patients underwent rectal surgery with other organ resection causing more surgical time than in other studies but the increased time was not associated with AL in our study.Any conclusions drawn from the findings of our study are limited to retrospective and small samples in single tertiary referral hospitals, even though the data were collected for a 9-year period. Further studies are needed with larger numbers of patients, from which a predictive scoring system could be developed to help the physician decide whether a diverting ostomy was indicated for patients after complete in nCRT.

Conclusion

Despite significant improvements in perioperative care, and advances in surgical techniques, anastomotic leak after rectal surgery can still have devastating consequences in both short and long-term outcomes. To reduce anastomosis leakage and such consequences,

early diagnosis, optimization of any modifiable risk factors, and or a diverting stoma can be constructed in locally advanced rectal cancer patients at high risk of AL.

Conflict of interest

The authors declare no conflicts of interest.

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