

Risk factors for anastomotic leakage after low anterior resection without diversional stomas*

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Abstract

Objective The most important complication after low anterior resection (LAR) for mid-low rectal cancer is symptomatic anastomotic leakage (AL). More than one-third of patients with rectal cancer who underwent LAR will have functional stomas during primary operation. The aim of this retrospective study was to evaluate the risk factors associated with clinical AL following LAR without diversional stomas.

Methods Between 2012 and 2017, information about 578 consecutive patients with rectal tumors less than 12 cm from the anal verge who underwent LAR without diversional stomas by the same surgical team was collected retrospectively. A standardized extraperitonealized anastomosis and pelvic drainage were conducted for all patients during primary operations, and the outcome of interest was clinical AL. The associations between AL and 14 patient-related and surgical variables were examined by both univariate chi-square test and multivariate logistic regression analysis.

Results The AL rate was 7.27% (42 of 578). Univariate and multivariate analyses showed that male sex ($P = 0.018$), mid-low rectal cancer (located 10 cm or less above the anal verge) ($P = 0.041$), presence of diabetes (odds ratio = 2.117), longer duration of operation (odds ratio = 1.890), and intraoperative contamination (odds ratio = 2.163) were risk factors of AL for LAR without diversional stoma and independently predictive of clinical AL. Nearly 83.3% (35 of 42) of leakage could be cured by persistent pelvic irrigation-suction-drainage without surgical intervention. Only 7 patients (16.7%) with severe complications, such as peritonitis, and fistula, required reoperation, and functional stoma was used as a salvage treatment.

Conclusion From the findings of this retrospective survey, we identified that mid-low rectal cancer and male sex were independent risk factors for developing clinical AL after LAR without diversional stomas, as well as longer duration of operation, presence of diabetes, and contamination of the operative field. Moreover, we deemed that LAR without diversional stomas for mid-low rectal cancers was safe, effective, and feasible. Extraperitonealized anastomosis and pelvic drainage obtained a relatively low rate of AL and avoided unnecessary functional stomas. Pelvic irrigation-suction-drainage was an effective procedure to resolve AL, and functional stoma was potentially used as a salvage modality for serious leakage.

Key words: anastomotic leakage (AL); low anterior resection (LAR); diversional stomas

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With the emergence of advanced stapling devices and their increasing use to create low-level anastomosis, low anterior resection (LAR) with total mesorectal excision (TME) has become the preferred surgical option for mid-low rectal cancer. However, high anastomotic leakage (AL) rate and increased rate of proximal diversion have been reported in numerous surgical institutions.

The rate of AL varies from 1% to 21% and is generally higher than 10% [1–6], depending on the anastomotic mode and inspection method. Clinical AL is a serious, sometimes disastrous, complication and a major cause of morbidity and mortality after anterior resection for rectal cancer. In particular, AL increases postoperative local recurrence and worsens long-term prognosis [7–8]. In

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fact, the function of routine defunctioning stoma in the prevention of AL has been widely debated. A few clinical surveys demonstrated that 32.3% to 57% of patients with rectal cancer undergoing LAR would need protective defunctioning stomas during the primary operation^[9-10]. Nevertheless, such prophylactic procedure is associated with a prominent reduction in the quality of life, including psychological health; in addition, 15% to 50% of initial temporary stomas would become permanent^[11-12]. Moreover, diversional stoma itself extends the hospital stay and raises treatment costs, and the closure operation increases length of stay and costs^[13]. With this associated controversy, defunctioning diversional stoma are considered cautiously.

Thus, a deep understanding of patients who are at a higher risk for developing AL in rectal cancer surgery is important for colorectal surgeons. To study the risk factors for clinical symptomatic AL following LAR without diversional stomas, we retrospectively collected data from 578 consecutive patients with mid-low rectal cancer in the Affiliated Hospital of Southwest Medical University, Luzhou, China, from January 2012 to December 2017. Moreover, the association between AL and perioperative variables was examined using univariate and multivariate analyses. It is worth mentioning that, during LAR without diversional stomas, extraperitonealized anastomoses, pelvic irrigation-suction-drainage, and/or functional colostomy, depending on the state, has been the standard treatment procedure for mid-low rectal cancer and AL after LAR in our hospital (The Affiliated Hospital, Southwest Medical University, Luzhou, China). Surely, we evaluated the efficacy and safety of this pelvic irrigation-suction-drainage modality to substitute the application of prophylactic functional stomas in this study.

Materials and methods

Patients and perioperative variables

From January 2012 to December 2017, 712 consecutive patients with tumors located less than 12 cm from the anal verge by preoperative colonoscopy or digital examination underwent rectum resection with curative intent for histologically proven adenocarcinoma in our department (Department of Gastrointestinal Surgery, The Affiliated Hospital, Southwest Medical University, Luzhou, China), including 578 LAR, 99 abdominoperineal resections, and 35 Hartmann's resections. LAR for mid-low rectal cancers was defined by the height of the anastomotic line below the level of peritoneal reflex, and the sphincter preservation rate was 81.2% (578 of 712). Patient characteristics, details of the surgical procedure, histopathologic parameters of tumors according to the criteria of the WHO and AJCC^[14], and postoperative

outcome and follow-up were documented prospectively, and all data were collected in a file and entered into our computer database. Due to the retrospective nature of this survey, approval by the ethics committee was not required.

In this study, a total of 578 patients undergoing LAR without primary functional stomas were included, and the outcome of interest was clinical AL. The seven patient-related variables were sex, age (< 65 years and ≥ 65 years), body mass index (BMI) in kg/m² (< 30 and ≥ 30), diabetes mellitus (defined as fasting plasma glucose level ≥ 7.0 mmol/L or with a glucose tolerance test, 2 h after the oral dose, a plasma glucose level ≥ 11.1 mmol/L), preoperative serum albumin level (< 3.0 g/dL and ≥ 3.0 g/dL), diameters of the tumor (≤ 3.0 cm and > 3.0 cm), and distance of the tumor from the anal verge (≤ 10 cm defined as mid-low rectal cancer). The seven surgical variables were blood transfusion, surgical procedures (open vs. laparoscopic techniques), duration of operation (≤ 210 min and > 210 min), intraoperative contamination (clean-contaminated vs. contaminated-dirty), resection of other organs simultaneously (such as invaded appendix, partial liver, or ovary for suspicious metastasis), tumor stage (quoted as a number I, II, III, and IV, derived from the TNM staging system of the AJCC), and resection type, curative or palliative (palliative resection defined as positive resection margin or intraoperatively diagnosed distal metastases that were not excised during this operation or local resection).

Surgical procedure and major management

All operations were performed by the same team of surgeons specializing in colorectal cancer surgery. We performed standardized TME procedure for mid-low rectal cancers as described by Heald^[14]. Following the completion of anastomosis, the pelvic peritoneum was rebuilt to extraperitonealize the anastomosis by suturing the parietal peritoneum over the pelvic cavity to the sigmoid colon on the left and to the mesocolon on the right. Then, in the absence of leakage indication identified by transanal air insufflation, a double-catheterization cannula was cautiously placed just below the anastomotic line in the true pelvis and laterally diverted retroperitoneally passing through the left abdominal wall. Normally, if without any sign of suspected leakage, the drain tubes were completely extracted within 7 postoperative days. Irrigation-suction-drainage was conducted, if any sign of leakage is suspected.

The definition of AL in the present study was clinical: gas, pus, or fecal discharge from the drain, peritonitis, signs of rectovaginal fistula, pelvic abscess close to the anastomosis, or discharge of pus per rectum. Radiologically demonstrated leakage without clinical symptoms was excluded. In patients with AL, absolute diet, together

with empirical antibiotics, total parenteral nutrition support, and somatostatin infusion, was recommended. More importantly, a 50-mL syringe with normal saline was used to irrigate the input tube of the drainage slowly and deliberately and then suction the contents rapidly and effectively. Such kind of low-input irrigation was repeated 4 times per day, using 500 mL each time. When the quality of the outflow and inflow was almost equal and clear, the irrigation-suction was terminated, and normal drainage would resume with no further suction, and drainage was maintained through gravitational effect. Thereupon, we proceeded to observe the volumes of drainage until the flow ceased. Finally, the drainage cannula was retreated 1 to 2 cm gradually over 2 to 3 days and then completely extracted.

Relaparotomy with the intention of colostomy was performed as a salvage modality for patients with clinical AL, including (1) digital examination that demonstrated a major anastomotic ring defect more than one-third the circumference of the anastomosis; (2) signs and symptoms of infection diffused, persisted, or even worsened during conservative treatment; and (3) severe complications, such as peritonitis, rectovaginal fistula, or obstruction.

Statistical analysis

Clinical data were retrospectively collected from the institutional database. Statistical analysis was performed using SPSS software (IBM SPSS Statistics 21.0). The univariate relationship between each independent variable and clinical AL was evaluated using a logistic model for continuous variables and Pearson's chi-square test for categorical variables. Independent variables with a *P*-value ≤ 0.05 in the univariate analysis were included in the multivariate logistic regression model using a Wald statistic backward stepwise selection. A *P*-value < 0.05 was considered statistically significant.

Results

Of 578 consecutive patients who underwent LAR without diversionary stomas included in the study, 58.8% were male (340 patients) and 41.2% were female (238 patients). Their median age was 63.5 years, ranging between 25 and 87 years. The mean anastomosis height from the dentate line was 4.8 cm (range, 0.5–10 cm). Clinical AL occurred in 42 patients, and the overall leakage rate was 7.27% (42 of 578). Three of 238 women (1.26%) developed rectovaginal fistula, which accounted for 3 of 10 leakages in women. All the leakages were noted on postoperative day 5.2 ± 4.5 except one, which developed 3 months after the primary operation. Seven leakages were reoperated during the initial hospital stay due to fecal peritonitis (42.9%, 3 of the 7 patients),

rectovaginal fistula (42.9%, 3 of 7), and major anastomotic ring defect (14.2%, 1 of 7), and the reoperation rate was 16.7% (7 of 42). Relaparotomy and colostomy were performed as a salvage modality, and the postoperative recovery was uneventful. Six patients had successful closure of the diversionary stomas within 5 to 6 months except one patient who refused to undergo one operation again due to insufficient financial support and advanced age. Accordingly, the other 35 leakages were treated by conservative method, and the median pelvic irrigation-suction-drainage time was 18 days (range, 7–36 days). In this series, no patients died of AL. The mean hospital stay was 12.04 days (SD, 6.29). Among the 42 patients with AL, the mean hospital stay was of 14.57 days (SD, 5.14), which was significantly greater than the hospital stay of patients without AL [(9.43 ± 7.44) days; *P* = 0.004].

Univariate analysis

Among all the 7 examined variables relating to patient characteristics, male sex and tumor location were the only factor that was statistically associated with development of clinical AL (Table 1). The AL rates of male and female sex were 9.41 and 4.20, respectively, with statistical significance (*P* = 0.18) by Pearson's chi-square test. The AL rate of mid-low rectal cancer was significantly higher than that of high rectal cancer. A higher frequency of AL was found in patients with lower rectal cancer (≤ 10 cm from the anal verge) (9.01% vs. 4.48%; *P* = 0.041) than that with higher rectal cancer. Table 2 shows the association

Table 1 Patients' characteristics and anastomotic leakage

Variables	No. of AL/total patients	Rate (%)	<i>P</i> value
Gender			0.018
Female	10/238	4.20	
Male	32/340	9.41	
Age (year)			0.753
< 65	19/275	6.90	
≥ 65	23/303	7.59	
Body mass index (kg/m ²)			0.755
< 30	8/121	6.61	
≥ 30	34/457	7.44	
Diabetes			0.063
Present	10/82	12.20	
Absent	32/496	6.45	
Preoperative albumin (g/dL)			0.995
< 3.0	5/69	7.25	
≥ 3.0	37/509	7.27	
Tumor size (cm)			0.911
≤ 3.0	18/243	7.41	
> 3.0	24/335	7.16	
Tumor location, from anal verge (cm)			0.041
≤ 10.0	32/355	9.01	
> 10.0	10/223	4.48	

Table 2 Surgical characteristics and anastomotic leakage

Variables	No. of AL/total patients	%	P value
Blood transfusion			0.236
Present	2/67	2.99	
Absent	40/511	7.83	
Procedure			0.155
Open	24/394	6.09	
Laparoscopic	18/184	9.78	
Duration of operation (min)			0.086
≤ 210	19/192	9.90	
> 210	23/386	5.96	
Intraoperative contamination			0.069
Clean-contaminated	30/473	6.34	
Contaminated-dirty	12/105	11.43	
Other organs resection			0.986
Present	6/90	6.67	
Absent	36/488	7.38	
Resection			1.000
Curative	37/522	7.09	
Palliative	5/66	7.58	
Stages			0.208
I–II	0/26	0.00	
III–IV	42/552	7.61	

Table 3 Multivariate analysis

Variables	Odds ratio	95% CI	P value
Presence of diabetes	2.117	1.125–3.985	0.028
Duration of operation > 210 min	1.890	1.002–3.567	0.046
Contaminated or dirty operative field	2.163	1.083–4.320	0.026

between surgical characteristics and clinical AL. Presence of diabetes, duration of operation longer than 210 min, and contaminated or dirty wound were likely associated with a higher incidence of clinical leakages. Clinical leakages tended to develop in patients with the above three factors, which were evaluated in the multivariate analysis.

Multivariate analysis

After univariate analysis, significant variables were selected for multivariate analysis using a stepwise logistic regression model. Table 3 summarizes the significant results of multivariate analysis. Duration of operation longer than 210 min, contaminated or dirty wound, and presence of diabetes were independent predictive factors for clinical AL development.

Discussion

Since it was demonstrated in 1982, TME is now adopted as the standard therapy modality in low anterior resection for mid-low rectal cancer worldwide [15–17]. Despite the fact that TME is associated with lower local

recurrence, higher sphincter preservation, and better survival, it is also associated with increasing risk of AL [18–20]. Although the advent of new instruments and novel techniques enabled the anastomosis for mid-low rectal cancer to be done more easily and quickly, AL after low anterior resection still remains as a challenging problem in the clinic, resulting in significant morbidity and mortality and poor prognosis [21]. As introduced in various studies, AL rates are inconsistent among different centers and institutions, ranging from 1% to 21% [4–6] but usually higher than 10%. An acceptable definition and grading system for AL for rectal cancer was proposed by the International Study Group of Rectal Cancer (ISGRC) in 2010 [22], which helps simplify grading of ALs, judge the severity, and make a proper therapeutic decision easily. According to this system, Grade A was defined as leakages that presented no clinical symptoms and signs that were only found through imaging study requiring no therapeutic intervention; Grade B was defined as leakages that led to clinical manifestations requiring active therapeutic intervention other than relaparotomy; Grade C was defined as leakages that had caused such serious consequences that reoperation was pressed for. In our present series, only Grades B and C leakages were included to facilitate valid comparison of the clinical results.

Although defunctioning stomas is widely used in LAR for mid-low rectal cancer in order to reduce the postoperative AL, whether patients would benefit from the protective stomas remains controversial. Several retrospective or non-randomized prospective investigations have demonstrated that absence of protective stomas is a risk factor for AL after LAR, considering that diverting the feces may construct a clean circumstance for anastomosis healing and decrease local infection; a leak may be avoided in the end [23–26]. However, the critics claim that it is not essential to have a defunctioning stoma for preventing a potential AL. In contrast, AL occurrence rate after LAR is not so high. The stoma itself may lead to many complications requiring proper treatment, even another operation. Finally, reoperation is inevitable for restoration of intestinal continuity, with increased pain and added costs, and it cannot be neglected that a several of temporary protective stomas become permanent [10, 27–29]. Hence, an increasing number of surgeons prefer the view that a functional stoma may mitigate the consequences as the complication generates but not reduce the incidence of AL following LAR for mid-low rectal cancer. Partly, as a result, some new techniques are attempted to prevent AL development, replacing diversion stomas, such as extraperitonealizing anastomoses by rebuilding the pelvis and placing pelvic drainage tubes.

In the present survey, extraperitonealized anastomoses

combined with double-catheterization cannulas were performed instead of colostomy or ileostomy in LAR for rectal cancer. The combination was routinely performed in all the patients undergoing LAR with mid-low rectal cancer, since it was carried out a few years in our department, because of its advantages, such as anastomotic extraperitonealization by closing the pelvic peritoneum, localizing the bleeding and inflammatory exudation, bowel contents, and pus, and draining out such contents by pelvic cannulas, which can experientially prevent AL, effectively treating breakdown anastomoses. It was again proved valid in this study, which demonstrated that the AL rate was 7.27% in accordance with the reported data of 1% to 21%.

Irrigation-suction was carried out when signs related to AL were perceived, such as variation in the drainage status with fecal or pus discharge, peritonitis, rectovesical fistula, rectovaginal fistula, or fever. Almost 83.3% of the patients suffering from AL were treated with this irrigation-suction-drainage strategy in our study. The remaining patients had to undergo relaparotomy to create a feces-diverting stoma. In other words, only 1.2% of all patients with mid-low rectal presenting a severe condition required diversional stomas as a salvage solution. This seems to suggest that primary ostomy is not essential, and current routine application of diversional stomas should be questioned [26,30]. Moreover, the data also revealed that conjunction strategy can reduce the occurrence of AL and relaparotomy.

As reported, sex and the site of the tumor were considered risk factors for AL after LAR in this study. Male patients with mid-low rectal cancer seem to have a higher risk of AL, due to the small pelvis, which makes the operation more difficult for the surgeons, with either laparotomy or laparoscopy procedure [26,30]. In our research, although there is a lower AL occurrence rate in female than male patients, another severe complication is frequently accompanying AL, namely, rectovaginal fistula, which brings about a terrible experience and longer treatment time. LAR has been accepted for treatment of mid-low rectal cancer, and obvious improvement in sphincter preservation was brought about, but lower anastomotic level was also confirmed as a negative impact for AL in the present study and other reported literature, along with frustrating anterior resection syndrome [31–33]; therefore, much effort would be needed to balance the two aspects in order to benefit more patients. Tumor localization determines anastomosis height; a lower site actually induces lower level of anastomotic ring. Tumor localization in the middle and lower third of the rectum, with subsequent lower anastomosis below the peritoneal reflection, has been widely accepted as a hazard for anastomotic defect [27,34–35]. This may be caused by difficult mobilization of lower rectal tumors due to

anatomical inaccessibility and reduced blood supply of the rectal stump and the pressure by pelvic hematoma or hydrops [36].

Few trials addressed these issues such as duration of surgery and contaminated surrounding of anastomoses. In the present study, operative time longer than 210 min presented as a risk factor for AL in the multivariate analysis, as well as a contaminated or dirty condition. A longer operation time for LAR was associated with a confined space, lower and larger tumor bulk, and harder resection and anastomosis, which were all identified as risk factors for anastomotic dehiscence [27,34–35]. Contamination is the introduction of bacteria that cause infection and abscess development, enhancing anastomotic edema and delaying anastomotic healing, leading to development of an AL. Intraoperative contamination can be avoided by experienced professional colorectal experts; however, it is unavoidable when the preoperative intestinal preparation is poor or ileus is concomitant with the primary tumor.

Several reported research studies [37–39] illustrated that diabetes mellitus was significantly associated with AL. We obtained a similar result in the multivariate analysis in our study. Although some researchers [40] claimed that the presence of diabetes did not increase the AL rate after rectal resection, they emphasized that patients with diabetes with AL developed higher mortality compared with those without diabetes. Hence, presence of diabetes plays a significant role in the development of AL.

Based on the aforementioned results and discussion, we identified that mid-low rectal cancer and male sex were independent risk factors for developing clinical AL after LAR without diversional stomas, along with longer duration of operation, presence of diabetes, and contamination of the operative field. Moreover, we deemed that LAR without diversional stomas for mid-low rectal cancers was safe, effective, and feasible. Extraperitonealized anastomosis and pelvic drainage combined with irrigation and suction obtained a relatively low AL rate and avoided unnecessary functional stomas. Pelvic irrigation-suction-drainage was an effective procedure to resolve AL, and functional stoma was potentially used as a salvage modality for serious leakage.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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