

Risk Factors of Symptomatic Anastomotic Leakage and its Impacts on Long Term Survival after Laparoscopic Low Anterior Resection for Rectal Cancer: A Retrospective Single Center Study

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Research

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Abstract

Background: Postoperative symptomatic anastomotic leakage (AL) is a serious complication after low anterior resection (LAR) for rectal cancer. AL can potentially affect short-term patient outcomes and long-term prognosis. This study aimed to explore the risk factors and long-term survival of symptomatic AL after laparoscopic LAR for rectal cancer.

Methods: From May 2009 to May 2015, 298 consecutive patients who underwent laparoscopic LAR for rectal cancer with or without a defunctioning stoma were included in this study. Univariate and multivariate logistic regression analyses were used to explore independent risk factors for symptomatic AL. Survival analysis was performed using Kaplan–Meier curves, and log-rank tests were used for group comparisons.

Results: Among the 298 patients enrolled in this study, symptomatic AL occurred in eight patients (2.7%). The univariate analyses showed that the age \leq 65 ($P = 0.048$), neoadjuvant therapy ($P = 0.095$), distance from the anal verge ($P = 0.078$), duration of operation ($P = 0.001$), and pathological tumor (T) category ($P = 0.004$) were associated with symptomatic AL. The multivariate analysis demonstrated that only the duration of operation ($P = 0.010$) was an independent risk factor for symptomatic AL after laparoscopic LAR for rectal cancer. In the survival analysis, no statistically significant differences in the 3-year ($P = 0.785$) and 5-year ($P = 0.979$) overall survival rates were observed.

Conclusions: A prolonged duration of operation increased the risk of symptomatic AL after laparoscopic LAR for rectal cancer. An impact of symptomatic AL on long-term survival was not observed in this study, but it needs to be studied more.

Trial registration: This study was registered in the Chinese Clinical Trial Registry (ChiCTR2000033413).

Background

Postoperative anastomotic leakage (AL) after low anterior resection (LAR) for rectal cancer is a common and devastating complication, and the reported incidence of AL varies from 2.2–18.6% [1–8]. It not only significantly increases mortality rates and health care costs in short time [3, 9], but also had higher local recurrence during long-term follow-up [10]. In the past 10 years, different risk factors for AL after open LAR have been reported, but few studies exclusively focused on the risk factors of AL after laparoscopic LAR [4, 6]. Indeed, laparoscopic LAR, instead of laparotomy, has become the standard operation for rectal cancer. Kang [3] and Zheng [7] reported that laparoscopy might decrease the risk of AL because less tissue trauma occurs and a better pelvis surgical field exposure can be obtained using the laparoscopic technology. However, rectal transection and the double-stapling technique anastomosis using linear and circular staples are relatively difficult laparoscopic maneuvers compared with laparotomy. Moreover, the postoperative course is different after laparoscopic LAR compared with laparotomy [11]. Therefore, the risk factors of AL after laparoscopic LAR may differ from those after laparotomy. Furthermore, by reviewing articles published in the past 5 years, we found out that no agreement has been achieved on

whether AL has an impact on oncological outcomes or not [10, 12, 13]. Therefore, the present study has two clinical objectives: (1) to identify the risk factors of symptomatic AL after laparoscopic LAR based on patient, surgery, and tumor-related variables and (2) to investigate the impact of symptomatic AL on 3- and 5-year overall survival rates.

Methods

Patients

From May 2009 to May 2015, 312 consecutive patients with primary rectal cancer received laparoscopic LAR in our unit. Four patients who adopted laparotomy and six patients who converted from laparoscopy to laparotomy were excluded from the study. Two patients who received emergency surgery and two patients who had missing data were also excluded from the study. Thus, 298 patients with primary rectal cancer were enrolled in the study. Preoperative colonoscopy and pathological biopsy confirmed rectal cancer in all patients. All patients and their families provided written informed consent before surgery. On the basis of the total mesorectal excision principle, all patients were eligible for curative R0 resection using laparoscopic LAR. Patients on neoadjuvant therapy received 50.4–54.0 Gy of radiation and 5-FU-based chemotherapy (capecitabine) before surgery. Surgery was performed 8 weeks after the completion of chemoradiation. Postoperative chemotherapy (FOLFOX plan) was recommended to all patients with positive lymph nodes as described in the final pathology report. The patients were followed up every 3 months for the first 2 years after surgery and then every 6 months thereafter. Data from the last available follow-up visit were included in the analysis. This study was approved by the medical ethics committee of our institution and was conducted in accordance with principles of the Declaration of Helsinki of the World Medical Association. This study was registered in the Chinese Clinical Trial Registry (ChiCTR2000033413). This study report is in line with the strengthening the reporting of cohort studies in surgery criteria [14].

Surgical procedure

According to the recommended clinical pathway, all patients underwent preoperative bowel preparation 1 day before surgery. Prophylactic antibiotics were given 0.5–2 h before surgery. All procedures were conducted successively by three experienced colorectal surgeons from the same group in our unit. The laparoscopic LAR was performed as described in a previous study [5]. The integrity of the ring of tissue retained by the circular stapler after performing the anastomosis was routinely examined. Air charging test was selectively performed to assess the integrity of the anastomosis for patients at high-risk for AL. A defunctioning stoma was performed selectively at the discretion of the surgeon. Generally, a stoma was performed if any of the following adverse events occurred: (1) poor blood perfusion, (2) low level of anastomosis, (3) neoadjuvant therapy before surgery, (4) positive air charging test, (5) tissue edema, or (6) an incomplete doughnut ring. The pelvic drain was routinely placed next to the anastomosis, and the transanal tube drain was placed according to the status of the patient and the discretion of the surgeon.

The pelvic drain was removed when the output of the drain was clear and lower than 50 mL/24 h. The transanal tube drain was removed when no longer needed after surgery.

Definitions and variables

In the present study, we used the standard definition of AL to guarantee the accuracy of the diagnosis. On the basis of the International Study Group of Rectal Cancer (ISREC) recommendations of 2010, AL was defined as a defect at the anastomotic site leading to a communication between intraluminal and extraluminal compartments [15]. On the basis of the severity and clinical symptoms, AL was classified into three grades (A, B, and C). Grade A leaks are those diagnosed with slight radiological evidence that do not require treatment. Grade B leaks are those managed with conservative treatment. Grade C leaks are those requiring a second surgical intervention. Patients who meet the criterion for grade B or C were diagnosed with symptomatic AL in this study. Patients with grade A leaks were not included in the study. The location of the tumor and distance from the anal verge were determined by computed tomography or colonoscopy and confirmed during surgery. Rectal cancer histopathological staging was defined according to the Union for International Cancer Control-TNM classification (8th edition) [16].

Patient-related, surgery-related, and tumor-related variables potentially associated with symptomatic AL were recorded. Table 1 summarizes the patient-related variables, including the gender (male and female), age (≤ 65 and > 65 years), American Society of Anesthesiologists (ASA) physical status classification (I–III), smoking status, alcohol consumption, previous history of abdominal surgery, preoperative intestinal obstruction, hypertension, diabetes, body mass index (BMI) (< 25 and $\geq 25 \text{ kg/m}^2$), neoadjuvant therapy, pulmonary insufficiency, preoperative hemoglobin (< 120 and $\geq 120 \text{ g/L}$), preoperative white blood cell count (4000–12000, < 4000 , or > 12000), preoperative serum albumin (< 35 and $\geq 35 \text{ g/L}$), and preoperative carcinoembryonic antigen (< 5 and $\geq 5 \text{ ng/mL}$). Table 2 summarizes the surgery-related variables, including the distance from the anal verge (< 7 and $\geq 7 \text{ cm}$), duration of operation (< 200 and $\geq 200 \text{ min}$), intraoperative blood loss (< 100 and $\geq 100 \text{ mL}$), combined resection of other organs, perioperative blood transfusion, defunctioning stoma, and transanal tube drainage. Table 3 summarizes the tumor-related variables, including pathology type (adenocarcinoma, mucinous carcinoma, or signet-ring cell), tumor size (≤ 5 and $> 5 \text{ cm}$), tumor differentiation (well, moderate, poor, well-moderate, or moderate-poor), tumor type (ulcer, uplift, or infiltrating), tumor infiltration (1/4, 1/3, 1/2, 2/3, 3/4, or full circle), vascular invasion, nerve invasion, pathological tumor T category (T0–4), pathological node N category (N0–3), metastasis (M0–1), and cancerous node. In total, 34 potential risk factors were considered and analyzed. Three-year and five-year overall survival and follow-up time are shown in Figs. 1 and 2, respectively.

Table 1
Univariate analysis of patient-related variables with symptomatic AL

Variables	Number of case	Anastomotic leakage	χ^2	P value
Gender (%)			1.120	0.290
Male	169 (56.7)	6 (75)		
Female	129 (43.3)	2 (25)		
Age (years) (%)			3.907	0.048 [†]
≤ 65	202 (67.8)	8 (100)		
>65	96 (32.2)	0 (0)		
ASA category (%)			1.290	0.525
I	40 (13.4)	0 (0)		
II	229 (76.8)	7 (87.5)		
III	29 (9.8)	1 (12.5)		
Smoking (%)			0.148	0.701
No	205 (68.8)	6 (75)		
Yes	93 (31.2)	2 (25)		
Alcohol consumption (%)			2.408	0.121
No	247 (82.9)	5 (62.5)		
Yes	51 (17.1)	3 (37.5)		
Previous history of abdominal surgery (%)			0.175	0.676
No	244 (81.9)	7 (87.5)		
Yes	54 (18.1)	1 (12.5)		
Preoperative intestinal obstruction (%)			0.886	0.346
No	269 (90.3)	8 (100)		
Yes	29 (9.7)	0 (0)		
Hypertension (%)			0.796	0.372

AL anastomotic leakage, ASA American society of anesthesiologists, BM/body mass index, CEA carcinoembryonic antigen, χ^2 chi-square test.

[†]p<0.1

Variables	Number of case	Anastomotic leakage	χ^2	P value
No	220 (73.8)	7 (87.5)		
Yes	78 (26.2)	1 (12.5)		
Diabetes (%)			0.989	0.320
No	266 (89.3)	8 (100)		
Yes	32 (10.7)	0 (0)		
BMI (kg/m^2) (%)			1.456	0.228
<25	161 (54.0)	6 (75)		
≥ 25	137 (46.0)	2 (25)		
Neoadjuvant therapy (%)			2.784	0.095 [†]
No	250 (83.9)	5 (62.5)		
Yes	48 (16.1)	3 (37.5)		
Pulmonary insufficiency (%)			2.571	0.109
No	227 (76.2)	8 (100)		
Yes	71 (23.8)	0 (0)		
Preoperative hemoglobin(g/L) (%)			0.898	0.343
<120	70 (23.5)	3 (37.5)		
≥ 120	228 (76.5)	5 (62.5)		
Preoperative white blood cell (%)			0.591	0.442
4000–10000	278 (93.3)	8 (100)		
<4000 or >10000	20 (6.7)	0 (0)		
Preoperative serum albumin (g/L) (%)			0.440	0.507
<35	21 (7.0)	1 (12.5)		
≥ 35	278 (93)	7 (87.5)		
Preoperative CEA (ng/ml) (%)			0.732	0.392

AL anastomotic leakage, ASA American society of anesthesiologists, BMI body mass index, CEA carcinoembryonic antigen, χ^2 chi-square test.

[†]p<0.1

Variables	Number of case	Anastomotic leakage	χ^2	P value
<5	180 (60.4)	6 (75)		
≥ 5	118 (39.6)	2 (25)		
AL anastomotic leakage, ASA American society of anesthesiologists, BMI body mass index, CEA carcinoembryonic antigen, χ^2 chi-square test.				
^a p<0.1				

Table 2
Univariate analysis of surgery-related variables for symptomatic AL

Variables	Number of case	Anastomotic leakage	χ^2	P value
Distance from the anal verge (cm) (%)			3.103	0.078 [†]
<7	71 (23.8)	4 (50)		
≥ 7	227 (76.2)	4 (50)		
Duration of operation(min)(%)			11.084	0.001 [†]
<200	224 (75.2)	2 (25)		
≥ 200	74 (24.8)	6 (75)		
Intraoperative blood loss(ml)(%)			0.444	0.505
<100	232 (77.8)	7 (87.5)		
≥ 100	66 (22.1)	1 (12.5)		
Combined organ resection (%)			0.560	0.454
No	279 (93.6)	8 (100)		
Yes	19 (6.4)	0 (0)		
Intraoperative blood transfusion (%)			1.527	0.217
No	286 (96.0)	7 (87.5)		
Yes	12 (4.0)	1 (12.5)		
Defunctioning stoma (%)			1.691	0.193
No	156 (52.3)	6 (75)		
Yes	142 (47.7)	2 (25)		
Transanal tube drainage (%)			0.000	0.994
No	255 (85.6)	1 (12.5)		
Yes	43 (14.4)	7 (87.5)		
<i>AL</i> anastomotic leakage, χ^2 chi-square test				
[†] $p<0.1$				

Table 3
Univariate analysis of tumor-related variables for symptomatic AL

Variables	Number of case	Anastomotic leakage	χ^2	P value
Pathology type of tumor (%)			0.405	0.817
Adenocarcinoma	284 (95.3)	8 (100)		
Mucinous carcinoma	11 (3.7)	0 (0)		
Signet-ring cell	3 (1.0)	0 (0)		
Size of tumor(cm)(%)			0.576	0.448
≤ 5	252 (84.6)	6 (75)		
>5	46 (15.4)	2 (25)		
Tumor differentiation (%)			2.410	0.661
Well	19(6.4)	0 (0)		
Moderate	230 (77.2)	6 (75)		
Poor	9 (3.0)	0 (0)		
Well-moderate	7 (2.4)	0 (0)		
Moderate-poor	33 (11)	2 (25)		
Tumor type (%)			3.526	0.172
Ulcer	189 (63.4)	7 (87.5)		
Uplift	88 (29.5)	0 (0)		
Infiltrating	21 (7.1)	1 (12.5)		
Tumor infiltrating (%)			2.570	0.766
1/4 circle	40 (13.4)	2 (25)		
1/3 circle	80 (26.8)	1 (12.5)		
1/2 circle	70 (23.5)	2 (25)		
2/3 circle	50 (16.8)	2 (25)		
3/4 circle	27 (9.1)	0 (0)		
Full circle	31 (10.4)	1 (12.5)		
<i>AL</i> anastomotic leakage, χ^2 , chi-square test				
[†] $p<0.1$				

Variables	Number of case	Anastomotic leakage	χ^2	P value
Vascular invasion (%)			0.213	0.644
No	242 (81.2)	7 (87.5)		
Yes	56 (18.8)	1 (12.5)		
Nerve invasion (%)			0.655	0.418
No	276 (92.6)	8 (100)		
Yes	22 (7.4)	0 (0)		
Pathological tumor(T)category (%)			15.357	0.004†
T0	5 (1.7)	0 (0)		
T1	21(7.0)	0 (0)		
T2	61 (20.5)	6 (75)		
T3	164 (55.0)	1 (12.5)		
T4	47 (15.8)	1 (12.5)		
Pathological node(N)category (%)			1.945	0.584
N0	168 (56.4)	6 (75)		
N1	78 (26.2)	2 (25)		
N2	46 (15.4)	0 (0)		
N3	6 (2.0)	0 (0)		
Metastasis (%)			0.345	0.557
M0	286 (96.0)	8 (100)		
M1	12 (4.0)	0 (0)		
Cancerous node (%)			1.305	0.253
No	285 (95.6)	7 (87.5)		
Yes	13 (4.4)	1 (12.5)		
AL anastomotic leakage, χ^2 , chi-square test				
† $p < 0.1$				

Symptomatic AL interventions

The interventions for symptomatic AL were as follows: (1) conservative treatment: dietary modification, total parenteral nutritional support, use of antibiotics, transanal tube drainage, and percutaneous

drainage or (2) surgical treatment: repair, massive irrigation and drainage, and defunctioning stoma.

Statistical analyses

Statistical analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). Continuous variables were dichotomized according to the clinical situation, and standard values were stipulated by state-of-the-art guidelines or by using the median value of each variable as the cutoff point. All patients were divided into two groups according to the occurrence of symptomatic AL or no AL, and the groups were analyzed using the chi-squared test or Fisher's exact test. Variables with a probability P value < 0.1 in the univariate analysis and other factors that were thought to have important clinical significance were entered into the multivariate analysis. The multivariate analysis used a logistic regression model to determine the risk factors associated with the incidence of symptomatic AL, and a P value < 0.05 was considered statistically significant. Survival analyses were performed using Kaplan–Meier curves, and the log-rank test was used for comparisons. A P value of < 0.05 was considered statistically significant for each test.

Results

Incidence of symptomatic AL

Of the 298 consecutive patients who underwent laparoscopic LAR for rectal cancer, 169 (57.0%) were male, and 129 (43%) were female. The median age was 63 years (range, 23–85 years), and the median BMI was 25 kg/m^2 (range, $16\text{--}36 \text{ kg/m}^2$). Eight (2.7%) patients were diagnosed with symptomatic AL, and no grade A patients were included in this study. Of the eight symptomatic AL patients, three (37.5%) patients were classified as grade B and treated with irrigation and drainage through the pelvic drain, whereas five (62.5%) were classified as grade C and treated with a defunctioning stoma in our unit. The median time of AL was 3 days after surgery (range, 2–6 days), and no patients died during the perioperative period.

Patient-related variables

Table 1 shows the results of the univariate analysis of the patient-related variables for symptomatic AL. Patient characteristics, living habits, comorbidities, and nutritional status were compared and analyzed. The symptomatic AL rate in the male group (75%) was higher than that in the female group (25%), although statistically significant differences were not reached ($P = 0.290$). Moreover, all eight patients with symptomatic AL were younger than 65 years, with statistical differences ($P = 0.048$). The proportion of patients with AL who received neoadjuvant therapy was slightly below those who did not receive neoadjuvant therapy, but the difference was not statistically significant (37.5% vs. 62.5%, $P = 0.095$). Other variables, including ASA category, smoking, alcohol consumption, previous history of abdominal surgery, preoperative intestinal obstruction, hypertension, diabetes, BMI, pulmonary insufficiency, preoperative hemoglobin, white blood cell, serum albumin, and carcinoembryonic antigen, were not significantly different in symptomatic AL patients.

Surgery-related variables

Table 2 shows the results of the univariate analysis of the surgery-related variables in symptomatic AL patients. There were no statistically significant differences between the two groups with regard to intraoperative blood loss, combined organ resection, intraoperative blood transfusion, defunctioning stoma, and transanal tube drainage. However, patients with a prolonged duration of surgery (≥ 200 min) (75% vs. 25%, $P=0.001$) were at higher risk of symptomatic AL than those without prolonged surgery. Moreover, the proportion of patients who had tumors within 7 cm of the anal verge was equal to the proportion of patients with tumors more than 7 cm from the anal verge (50% vs. 50%, $P=0.078$).

Tumor-related variables

Table 3 lists the results of the univariate analysis of the tumor-related variables for symptomatic AL. The tumor pathology type, tumor size, tumor differentiation, tumor type, tumor infiltration, vascular invasion, nerve invasion, pathological node (N) category, metastasis, and cancerous node were not identified as risk factors significantly associated with symptomatic AL. Moreover, symptomatic AL occurred in stage T2–4 tumors with statistically significant differences ($P=0.004$). In general, all eight patients with AL had adenocarcinoma, with no differences in nerve invasion and metastasis in the symptomatic AL group compared with the nonAL group.

Multivariate analysis

Univariate analysis revealed that the age ≤ 65 ($P=0.048$), neoadjuvant therapy ($P=0.095$), distance from the anal verge ($P=0.078$), duration of operation ($P=0.001$), and pathological tumor (T) category ($P=0.004$) were risk factors for symptomatic AL. To adjust for confounding bias, we incorporated these and other variables that were thought to have important clinical significance in the multivariate analysis and revealed that only the duration of operation ($P=0.010$, OR 9.058 [95% CI, 1.695–48.401]) was an independent risk factor for symptomatic AL.

Long-term survival

Three and ten patients were lost to follow-up at 3 and 5 years, respectively, without statistical significance. There were no statistically significant differences in 3-year ($P=0.785$) and 5-year overall survival rates ($P=0.979$) between the two groups, as shown in Fig. 1 and Fig. 2.

Discussion

The risk factors and long-term survival of symptomatic AL were investigated in 298 consecutive patients undergoing laparoscopic LAR for rectal cancer. Univariate and multivariate analyses demonstrated that a prolonged duration of operation was an independent risk factor for symptomatic AL (Table 4). Moreover, no significant differences were found in the 3- and 5-year overall survival rates between the two groups.

Table 4
Multivariate analysis of the risk factors for symptomatic AL

Variables	Odds ratio	95 % CI	Pvalue
Age (years)	–	–	0.996
Neoadjuvant therapy	1.754	0.368–8.360	0.481
Duration of operation(min)	9.058	1.695–48.401	0.010 [†]
Distance from the anal verge (cm)	0.499	0.109–2.293	0.372
Pathological tumor(T)category	0.765	0.347–1.684	0.505
<i>AL</i> anastomotic leakage, <i>CI</i> confidence interval.			
† <i>p</i> <0.05			

The incidence of symptomatic AL was relatively low (2.7%) in this study, similar to two previous studies, which reported AL incidences of 2.2% and 3.6% [1, 6]. However, most studies reported the incidence of AL to be approximately 10–13% [3–5, 7]. This difference in AL rates is likely due to the inconsistent definition of AL, inclusion criteria of the studies, and different ratios of the patients who underwent rectal surgery. In fact, AL can be divided into symptomatic AL and asymptomatic AL, which does not require any treatment, and the standard classification criteria of AL (grades A, B, and C) advocated by ISREC are based on AL severity and the required treatment [15]. A high-quality prospective study by Qin [17] reported a total AL rate of 17% after LAR, with a clinical AL rate of 9.7%. In this study, nine (3.0%) asymptomatic patients who were evaluated as grade A were removed from the study. This patient exclusion significantly reduced the overall incidence of AL. Moreover, the three colorectal surgeons in our unit have more than 20 years of surgical experience and have completely overcome the surgical learning curve, thus improving the safety of the operation. Furthermore, patient health status was fully adjusted, and the diseases were effectively controlled before surgery. In the present study, all eight symptomatic AL patients had no preoperative intestinal obstruction or elevated white blood cells, and only one patient had hypoalbuminemia before surgery. This may also play an important role in preventing the occurrence of symptomatic AL in general.

With respect to the patient-related variables, the present study found that neoadjuvant therapy was a risk factor but not an independent risk factor for symptomatic AL. The effects of neoadjuvant therapy on AL before surgery have been controversial in recent years. Lim [18] reported that neoadjuvant chemoradiation in lower rectal cancer was not associated with higher perioperative complications. By contrast, Park[2] and Hamabe [19] demonstrated that preoperative neoadjuvant chemotherapy with or without concomitant radiotherapy was associated with an elevated risk for AL with or without a defunctioning stoma after laparoscopic LAR. We believe that neoadjuvant therapy, especially long-course radiotherapy, can cause tissue fibrosis, oligovascularization, tissue edema, and immunocompromise, which affect the healing of anastomoses and increase the incidence of postoperative symptomatic AL. Furthermore, a defunctioning stoma, an important protective factor, was often applied in patients who

were given neoadjuvant therapy before surgery, which might minimize the consequence of symptomatic AL to a certain degree. In addition, all eight symptomatic AL patients were younger (≤ 65 years) in the present study. This phenomenon was probably due to the small sample size of symptomatic AL, which was defined based on the proposal by ISREC. Therefore, we believe that if more patients were included in this study, the results might eventually change.

With respect to the surgery-related variables, the duration of operation was an independent risk factor associated with AL in previous studies [7, 20]. This study also demonstrated that prolonged operation time was associated with symptomatic AL. In a review of six patients who had prolonged operation times, we found that they were all males and 50% (3/6) of the patients received neoadjuvant therapy before surgery. The prolonged duration of operation may be caused by a relatively narrow pelvis in males, which leads to a more complicated operation compared with female patients. Although gender was not an independent risk factor, as determined by the multivariate analysis, the incidence of symptomatic AL in males was three times higher than the incidence of symptomatic AL in females (75% vs. 25%, $P=0.290$). In addition, edema, the crispiness of the tissue, and the unclear anatomical level due to neoadjuvant therapy before surgery might increase the difficulty of surgery and might prolong the duration of operation. Numerous studies reported that the distance of the tumor to the anal verge was associated with AL [7, 19]. The present study revealed that the distance of the tumor to the anal verge was associated with symptomatic AL but was not an independent risk factor for symptomatic AL. The shorter distance of the tumor to the anal verge may result in poorer blood supply in the lower rectum and increased difficulties in performing the surgery, both of which may increase the incidence of symptomatic AL.

The effects of two protective factors, namely, defunctioning stoma and transanal tube drainage, on the occurrence of AL are controversial. Two previous studies revealed that an appropriate defunctioning stoma significantly decreases the occurrence of AL in high-risk patients [7, 19]. A recent high-quality meta-analysis involving 23 observational studies further concluded that no defunctioning stoma was a significant surgical related risk factor for AL [21]. However, Shiomi [22] and Salamone [8] reported that a defunctioning stoma did not decrease the occurrence of AL but did mitigate the clinical features and reoperation rate. In the present study, the symptomatic AL rate in the nondefunctioning stoma group (75%) was significantly higher than that in the defunctioning stoma (25%), though the difference was not statistically significant ($P=0.193$). This result may be due to the low incidence (2.7%) of symptomatic AL in the present study, which is a major limitation of the study. Moreover, the influence of a defunctioning stoma on quality of life, including the uncomfortable smell, demand for special care, and fecal dermatitis, should not be ignored. Therefore, to avoid unnecessary stoma, we believe that it is necessary to correctly identify the high-risk patients of symptomatic AL before or during surgery. In addition, the criteria for placing a transanal tube drainage have not been clearly defined. Tetsuo [23] reported that the transanal tube placement can prevent AL after laparoscopic LAR due to a reduction in the unfavorable incidence of early postoperative diarrhea. A recent meta-analysis also reported that patients in the transanal tube group tended to have lower reoperation rates and shorter hospital stays compared with patients in the nontransanal tube group [24]. However, in the present study, the symptomatic AL rate was higher in the

patients who received the transanal tube drainage, although the difference was not significant (87.5% vs. 12.5%, $P= 0.994$). Thus, the transanal tube might not prevent symptomatic AL. This finding might also imply that the three surgeons could more accurately predict the patients who were prone to symptomatic AL in our unit.

With respect to long-term survival, Kim [10] reported that the 5-year overall survival rates according to each TNM classification did not differ between the leak and nonleak groups. Jang [13] further revealed that AL was not associated with a significant increase in local tumor recurrence or long-term survival after neoadjuvant therapy in rectal cancer. This study also did not find a relationship between symptomatic AL and overall survival. However, a recent meta-analysis with 35 studies reported that AL after anterior resection increased the risk of local recurrence and decreased the overall survival, cancer-specific survival, and disease-free survival [12]. This discrepancy might be due to the definition of AL, which has not been standardized. The definition of AL used in a study may have influenced the outcome. Moreover, 37.5% of patients (3/8) with symptomatic AL in the present study received neoadjuvant therapy before surgery, which may have an impact on long-term survival. Neoadjuvant therapy can decrease the tumor stage and improve local control after operation, which may influence the oncological outcomes more than the occurrence of AL [26, 27].

Two main limitations of this study should be considered. First, the incidence of symptomatic AL was much lower in this study than most previous studies, which might hinder the discovery of more risk factors of symptomatic AL, such as age, diabetes, combined organ resection, and some tumor-related variables. Second, selection bias of patients and difficulty in data collection were also inevitable because of the retrospective nature of the study. Thus, more randomized controlled trials are needed in the future.

Conclusion

In conclusion, the present study demonstrated that a prolonged duration of operation (≥ 200 min) is an independent risk factor for symptomatic AL after laparoscopic LAR for rectal cancer. Furthermore, the impact of symptomatic AL on long-term survival needs to be studied more in the future.

List Of Abbreviations

AL, anastomotic leakage; LAR, low anterior resection; ASA, american society of anesthesiologists; ISREC, international study group of rectal cancer; BMI, body mass index; CEA, carcinoembryonic antigen; χ^2 chi-square test; CI, confidence interval.

Declarations

Ethics approval and informed consent

This study was approved by the the Medical Ethics Committee of Peking University Cancer Hospital and was conducted in accordance with principles of the Declaration of Helsinki of the World Medical Association. The informed consent requirement was waved.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XK, L-MX and Q-XY participated in the acquisition, analysis, and interpretation of data, as well as in the manuscript drafting; GP and TF participated in data acquisition; Y-ZD and ZN participated in analysis and interpretation of data. S-XQ and CM contributed to the conception, design, and data interpretation. X-JD, YH and Z-CH revised the manuscript for important intellectual content. The authors read and approved the final manuscript.

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Figures

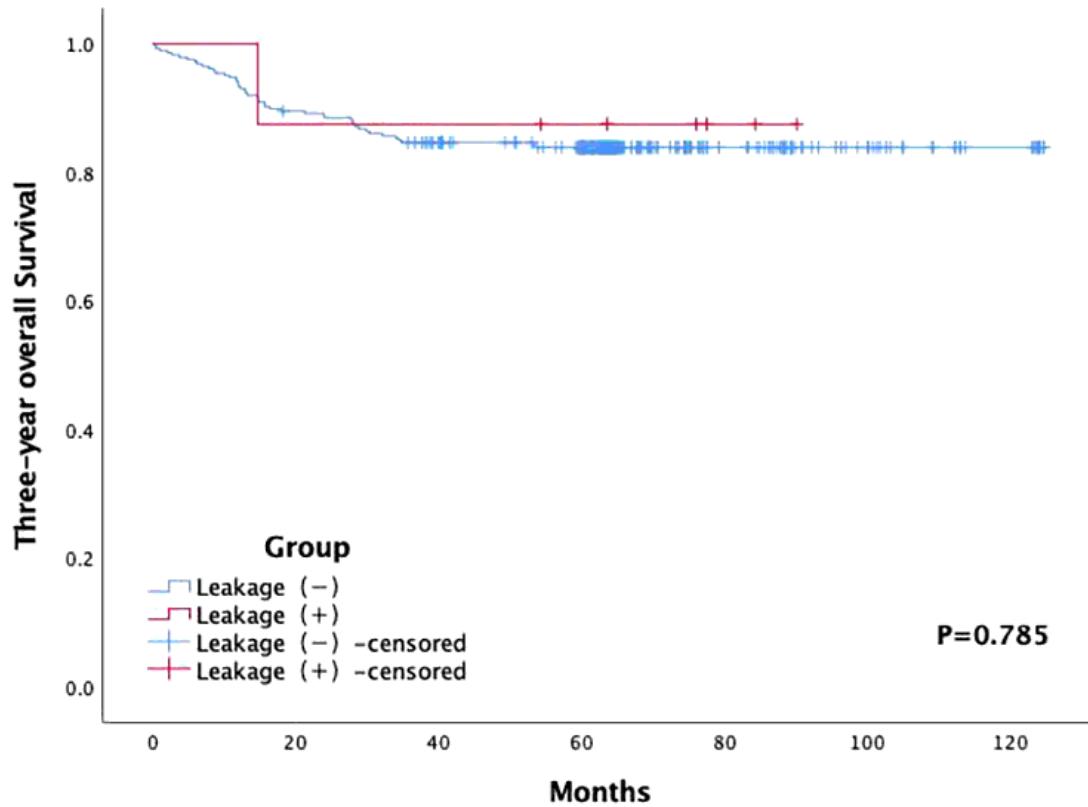


Figure 1

Three-year overall survival according to Kaplan–Meier analysis.

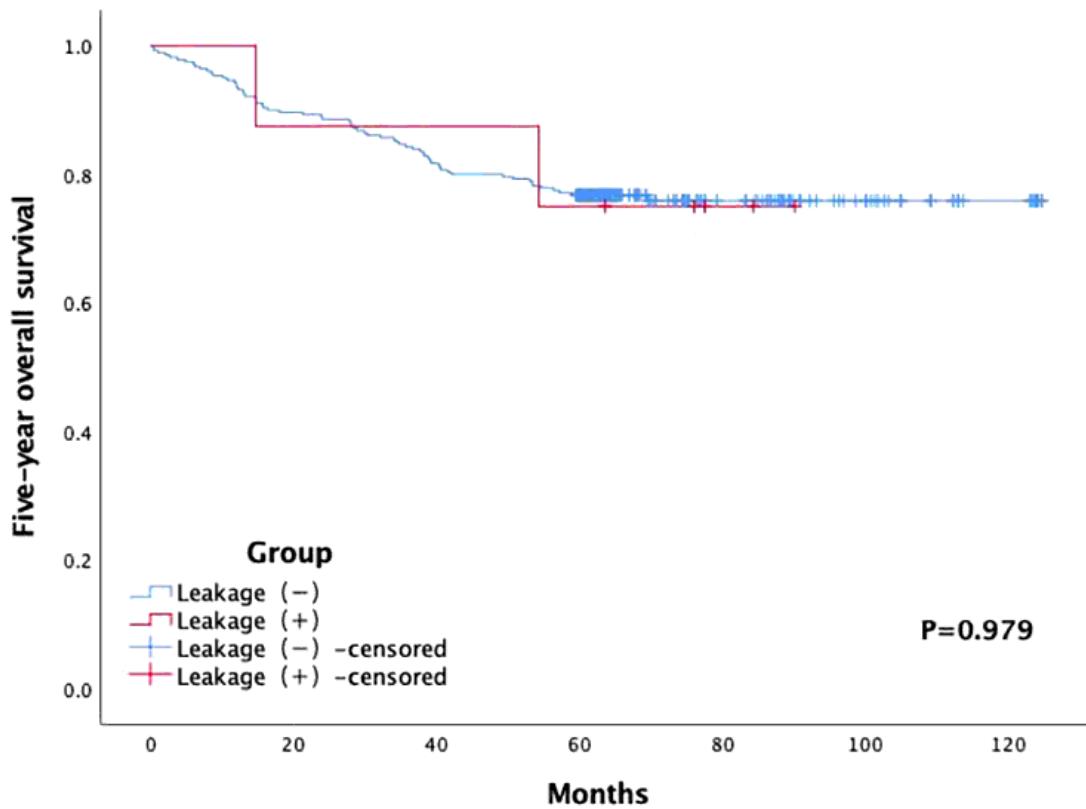


Figure 2

Five-year overall survival according to Kaplan–Meier analysis.