Am J Transl Res 2023;15(6):4390-4398
www.ajtr.org /ISSN:1943-8141/AJTR0149321

Original Article

Clinical analysis of anastomotic fistula after anal preservation in 358 cases of rectal cancer and construction of risk prediction model: a single-center retrospective study

Li Zhou[1], Qiong Liang[2], Haisheng Lan[3], Tiancheng Wang[1], Qian Wei[1], Chaochao Lin[1], Chaosheng Su[1], Qiuhao Li[1], Haige Huang[1]

[1]Department of General Surgery, The Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China; [2]Department of Respiratory Diseases and Critical Care Medicine, The Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China; [3]Department of Gastrointestinal Surgery, The Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China

Received January 26, 2023; Accepted May 8, 2023; Epub June 15, 2023; Published June 30, 2023

Abstract: Objective: To develop and validate a simple prediction model for postoperative anastomotic leakage (AL) in patients with rectal cancer who underwent Dixon surgery by combining preoperative and intraoperative risk factors. Methods: We conducted a retrospective study on 358 patients who underwent Dixon surgery for rectal cancer in the Affiliated Hospital of Youjiang Medical University for Nationalities (Guangxi Zhuang Autonomous Region, China). Based on logistic regression, the prediction model of AL after Dixon surgery was established and verified. Results: The incidence of postoperative AL in these patients was 9.2% (33/358). The results of logistic regression analysis showed that age ≥60 years, male, Tumor-Node-Metastasis (TNM) stage ≥IIIa, preoperative obstruction, and the distance from the tumor to the anus ≤7 cm were the risk factors for AL after Dixon surgery, and intraoperative defunctioning stoma was the protective factor for AL after rectal Dixon surgery (all P<0.05). The prediction model construction: Risk score =-4.275 + 0.851 × age + 1.047 × sex + 0.851 × distance + 0.934 × stage + 0.983 × obstruction. The area under receiver operating characteristic curve (ROC-AUC) was 0.762 (95% CI: 0.667-0.856). The best cutoff, sensitivity and specificity were 0.14, 79.60%, and 83.10%, respectively. Hosmer-Lemeshow: X^2=6.876, P=0.550. Clinical validation results: the sensitivity, specificity, and accuracy of the model were 82.05%, 80.06%, and 80.25%, respectively. Conclusions: Both preoperative and intraoperative risk factors were used in the prognostic model. The prediction model established on this basis was well differentiated and highly calibrated, providing a good reference for the clinical prediction model of postoperative AL in rectal cancer patients undergoing Dixon surgery.

Keywords: Rectal cancer, anastomotic leakage, defunctioning stoma, Dixon surgery

Introduction

Rectal cancer is one of the most common malignant tumors in China, mainly middle and low rectal cancer [1]. According to an analysis of tumor epidemic characteristics and disease burden in China, rectal cancer ranks third in incidence and fourth in mortality in the Guangxi region of China [2]. Postoperative anastomotic leakage (AL) is a common and severe complication of patients with rectal cancer and the leading cause of high mortality [3].

In recent years, the application of laparoscopic technique in rectal cancer has been widely popularized, and laparoscopic-assisted low anterior rectal resection (Dixon surgery) is one of the most common surgical methods. Dixon surgery provides the hope of anal preservation for many patients with middle and low rectal cancer but increases the risk of postoperative AL. The incidence of AL is not only a tricky and troublesome problem for surgeons but also increases patients' physical, mental and economic burden, seriously affecting the postoperative reha-

bilitation time and quality of life [4]. Therefore, how to effectively prevent and control postoperative AL is also a hot topic. Currently, most literature reports are about the clinical characteristics, incidence, mortality and treatment of postoperative anastomotic leakage for rectal cancer [5-7]. The study on Dixon's surgery was only discussed in the subgroup analysis of surgical procedures, and there are few reports on the independent analysis of risk factors for this surgery. Therefore, this study analyzed the risk factors of AL after laparoscopic Dixon rectal cancer surgery.

Although many studies have shown some factors affecting postoperative anastomotic leakage, with advances in surgical techniques, improvements in anastomotic instruments and the use of Neoadjuvant chemoradiotherapy (NAC), the risk factors of anastomotic leakage may have potentially changed [8, 9]. In summary, this study retrospectively analyzed the general clinical data of 358 patients undergoing laparoscopic Dixon surgery for rectal cancer, discussed and analyzed the risk factors associated with postoperative AL, and established a reliable and accurate prediction model, hoping to provide specific reference for clinical work.

Material and methods

Study design and patients

A total of 358 patients with rectal cancer who underwent Dixon surgery in the Affiliated Hospital of Youjiang Medical University for Nationalities in Guangxi, China, from March 2010 to December 2015 were selected in this study. The Medical Ethics Committee of the Affiliated Hospital of Youjiang Medical University for Nationalities approved this retrospective cohort study. Inclusion criteria: (1) All cases were confirmed as rectal cancer by postoperative pathology; (2) All were elective surgeries without complications such as acute bleeding and perforation before surgery; (3) All cases had complete medical history, including current and past medical history, preoperative laboratory and imaging results, intraoperative data; (4) All cases had diagnosis of anastomotic leakage that were consistent with the recommendations of the International Rectal Cancer Research Group in 2010 [10]; (5) All cases were ASA grade <IV. Exclusion criteria: (1) All cases with serious heart, lung and brain diseases or serious infections; (2) All cases with serious blood system diseases and blood dysfunction; (3) All cases with a history of abdominal surgery or extensive adhesion of the abdominal cavity that could not undergo laparoscopic surgery; (4) All recurrent cases; (5) All cases with incomplete data.

In addition, according to the following criteria, prospective patients who planned to receive Dixon surgery for rectal cancer from March 2016 to November 2020 were selected as the clinical validation cohort for the prediction model. Inclusion criteria: Patients were informed about the study and signed the informed consent; the rest were consistent with the inclusion criteria of retrospective design. Exclusion criteria: Patients who refused to participate and had poor compliance; The rest were consistent with the exclusion criteria for retrospective design.

Data collection

Data including patient age, gender, distance from the tumor to the anus, Tumor-Node-Metastasis (TNM) stage, preoperative albumin, preoperative anemia, preoperative obstruction, diabetes, neoadjuvant chemotherapy, and intraoperative defunctioning stoma were obtained through the electronic medical record system. For patients diagnosed with anastomotic leakage after surgery, two experienced gastroenterological specialists (Li Zhou and Haige Huang) further examined the medical records to ensure that the diagnosis met the above valid criteria and was correct.

Surgical procedure

Neoadjuvant chemoradiotherapy was administered to patients with a tumor less than 5 cm from the anus or imaging findings indicating heavy adhesion between the tumor and surrounding tissues or distant liver or lung metastasis. Anterior transabdominal resection of rectal cancer (Dixon surgery) was performed under general anesthesia following the principle of total mesangectomy, following the principle of total mesorrectal excision (TME). The same medical team performed all surgeries.

Diagnostic criteria for anastomotic leakage

AL was observed one month after the operation. The diagnosis of AL was based on the recommendations of the International Rectal Cancer Research Group in 2010 [10]: (1) Postoperative temperature increase for unknown reasons (≥38.5°C). (2) Obvious signs of peritoneal irritation, sudden increase of drainage fluid, and fecal residue after the surgery. Alternatively, the toner mixture was drained for patients with suspicious AL after oral toner. (3) Digital rectal examination revealed anastomotic defect. (4) Imaging results indicated perforation of the digestive tract and excluded the possibility of perforation in other parts.

Statistical analysis

SPSS 20.0 software was used for statistical analysis. The categorical variables were expressed by frequency and percentage and compared between the two groups using the chi squared (χ^2) test, and continuous variables were expressed by (mean ± standard deviation) and compared between the two groups using the independent sample t test. After the above test, variables with P<0.1 were screened for establishing a logistic regression model. The receiver operating characteristic curve (ROC)-area under curve (AUC) and Hosmer-Lemeshow were used to evaluate the model differentiation and calibration performance. The z-test was used to compare the ROC curves of the test and validation cohorts. A *P* value <0.05 indicated a statistical difference.

Results

Characteristics of the test and validation cohorts

There were no significant differences between the test and validation cohorts in age, gender, distance from the tumor to the anus, TNM stage, preoperative albumin, preoperative anemia, preoperative obstruction, preoperative diabetes, neoadjuvant chemotherapy, and defunctioning stoma between the two cohorts (all P>0.05, **Table 1**).

Comparison of the AL and non-AL groups

AL occurred in 33 patients (9.2%) of the 358 patients after the Dixon surgery for rectal cancer. Age, gender, distance from the tumor to the anus, TNM stage, preoperative obstruction, and preoperative diabetes were influencing factors for AL after Dixon surgery (all P<0.1, **Table 2**).

Prediction model of postoperative anastomotic leakage

Further analysis was conducted based on logistic regression, and seven risk factors were used for model construction. The results showed that the risk factors for postoperative AL with rectal cancer were age ≥60 years, male, TNM stage ≥IIIa, preoperative obstruction, and the distance from the tumor to the anus ≤7 cm, while the protective factors for postoperative AL of rectal Dixon was intraoperative defunctioning stoma (all P<0.05, **Table 3**).

The risk score of postoperative anastomotic leakage for colorectal cancer Dixon was calculated based on the following formula: Risk score =-4.275 + 0.851 × age + 1.047 × sex + 0.851 × distance + 0.934 × stage + 0.983 × obstruction. **Figure 1A** shows the AUC of the risk score in test cohort was 0.762 (95% CI: 0.667-0.856). The best cutoff, sensitivity and specificity were 0.14, 79.60%, and 83.10%, respectively, implying good differentiation of this model. The AUC of the risk score in validation cohort is shown in **Figure 1B**. The AUC of the validation cohort was not significantly different from that of the test cohort (Z=0.218, P=0.827). Meanwhile, Hosmer-Lemeshow showed X^2=6.876, P=0.550, indicating that the prediction model had good calibration capability and high accuracy (**Figure 2**).

Validation of the prediction model

We selected 400 patients with rectal cancer who planned to undergo Dixon in our hospital to verify the prediction model. A total of 39 cases (9.75%) suffered from AL in this study population. The sensitivity, specificity, and accuracy of this model for predicting AL after rectal cancer surgery were 82.05%, 80.06%, and 80.25%, respectively (**Table 4**).

Discussion

We developed and verified a prediction model for postoperative anastomotic leakage after

Table 1. Demographic and clinical characteristics of the test and validation cohorts

Variables	Test cohort (N=358)	Validation cohort (N=400)	X^2	P
Age			0.22	0.639
≥60 years	160 (44.69%)	172 (43%)		
<60 years	198 (55.31%)	228 (57%)		
Gender			0.294	0.587
Male	195 (54.47%)	210 (52.5%)		
Female	163 (45.53%)	190 (47.5%)		
Distance from the tumor to the anus			0.696	0.404
≤7 cm	197 (55.03%)	208 (52%)		
>7 cm	161 (44.97%)	192 (48%)		
TNM Stage			0.512	0.474
≥IIIa stage	165 (46.09%)	174 (43.5%)		
≤IIb stage	193 (53.91%)	226 (56.5%)		
Preoperative albumin			0.931	0.335
≤35 g/L	19 (5.31%)	28 (7%)		
>35 g/L	339 (94.69%)	372 (93%)		
Preoperative anemia			0.693	0.405
Yes	41 (11.45%)	49 (12.25%)		
No	317 (88.55%)	351 (87.75%)		
Preoperative obstruction			0.372	0.542
Yes	49 (13.69%)	61 (15.25%)		
No	309 (86.31%)	339 (84.75%)		
Diabetes			2.9	0.089
Yes	25 (6.98%)	42 (10.5%)		
No	333 (93.02%)	358 (89.5%)		
Neoadjuvant chemotherapy			1.489	0.222
Yes	16 (4.47%)	26 (6.5%)		
No	342 (95.53%)	374 (93.5%)		
Defunctioning stoma			0.864	0.353
Yes	63 (17.6%)	81 (20.25%)		
No	295 (82.4%)	319 (79.75%)		

TNM: Tumor-Node-Metastasis.

Dixon surgery for rectal cancer. We also predicted patients' postoperative AL risk by combining preoperative risk factors and whether or not the surgery was performed during the surgery. The risk-scoring model uses five easy-to-evaluate characteristics. In addition, the model has good discriminatory and calibration functions that can provide clinicians and healthcare workers with timely information on patients at risk of postoperative anastomotic leakage and to quickly allocate appropriate management, medical support, and follow-up resources.

The results of this study showed that the incidence was 9.20% and 9.75%, consistent with previous research [11, 12]. Preventing postoperative AL and correctly assessing risk factors are the keys to solve the problem. In the logistic regression model, age over 60 years, male, TNM stage ≥IIIa, preoperative combined obstruction, and distance of tumor to the anus ≤7 cm from anal margin were found to be valuable predictors of postoperative anastomotic leakage in these patients, and intraoperative defunctioning stoma could reduce the risk of postoperative anastomotic leakage.

An evidence-based medical study concluded that age >60 was a risk factor for anastomotic leakage [13]. With the increase of age, the bodies resistance has decreased, and anti-infection ability, wound healing ability and body

Table 2. Demographic and clinical characteristics of the test cohorts across anastomotic leakage (N=358)

Variables	Anastomotic leakage	Non-Anastomotic leakage	X^2	P
Age			5.277	0.022
≥60 years	21 (13.13%)	139 (38.83%)		
<60 years	12 (6.06%)	186 (51.96%)		
Gender			6.643	0.01
Male	25 (12.8%)	170 (47.49%)		
Female	8 (4.9%)			
Distance from the tumor to the anus			4.602	0.032
≤7 cm	24 (12.2%)	173 (48.32%)		
>7 cm	9 (5.6%)	152 (42.46%)		
TNM Stage			6.195	0.013
≥IIIa stage	22 (13.3%)	143 (39.94%)		
≤IIb stage	11 (5.7%)	182 (50.84%)		
Preoperative albumin			0.041	0.839
≤35 g/L	2 (10.5%)	17 (4.75%)		
>35 g/L	31 (9.1%)	308 (86.03%)		
Preoperative anemia			0.693	0.405
Yes	5 (12.2%)	36 (10.06%)		
No	28 (8.8%)	289 (80.73%)		
Preoperative obstruction			5.679	0.017
Yes	9 (18.37%)	40 (11.17%)		
No	24 (7.77%)	285 (79.61%)		
Diabetes			3.734	0.053
Yes	5 (20.0%)	20 (5.59%)		
No	28 (8.4%)	305 (85.20%)		
Neoadjuvant chemotherapy			0.216	0.642
Yes	2 (12.5%)	14 (3.91%)		
No	31 (9.1%)	311 (86.87%)		
Defunctioning stoma			5.32	0.021
Yes	1 (1.59%)	62 (17.32%)		
No	32 (10.85%)	263 (73.46%)		

metabolism ability were significantly reduced. Domestic scholars have also pointed out that elderly patients often have a variety of complications, which significantly increases the incidence of surgical complications under surgical stress [14]. The logistic regression results suggested that age significantly correlated with postoperative AL. It may be that rectal malignancy is a wasting disease, most elderly patients are affected by nutritional risks, and various underlying diseases.

A meta-analysis spanning 10 years in China reported that men had higher AL than women after laparoscopic rectal cancer surgery (OR= 2.41, P<0.05) [15]. Among the 33 patients with postoperative AL in this study, 25 cases were male. The results suggested that being a male was an independent risk factor for the occurrence of AL after laparoscopic Dixon surgery, which is also supported by other reports [16-18]. The male pelvis is smaller than the female pelvis, which increases the surgery requirements. In order to fully expose the operative field, there is often more damage to the surrounding tissue, which can easily lead to poor blood supply to the anastomosis, affecting healing and thus leading to anastomotic leakage [17, 19, 20].

Some scholars believe that in TNM staging, middle and late rectal cancer is a risk factor

Table 3. Logistic regression analysis of anastomotic leakage after rectal cancer surgery

Variables	B	Wald χ^2	P	OR	95% CI
Age ≥60 years	0.851	5.072	0.024	2.342	1.114~4.920
Male	1.047	4.135	0.042	2.849	1.248~6.504
Distance from the tumor to the anus ≤7 cm	0.851	4.516	0.034	2.343	1.056~5.198
TNM stage ≥IIIa	0.934	6.685	0.010	2.545	1.195~5.422
Preoperative intestinal obstruction	0.983	9.973	0.002	2.672	1.160~6.155
Diabetes	1.002	2.367	0.112	2.723	0.949~7.810
Prophylactic ileostomy	-2.017	9.445	0.002	0.133	0.018~0.989
Intercept	-4.275	45.019	<0.001		

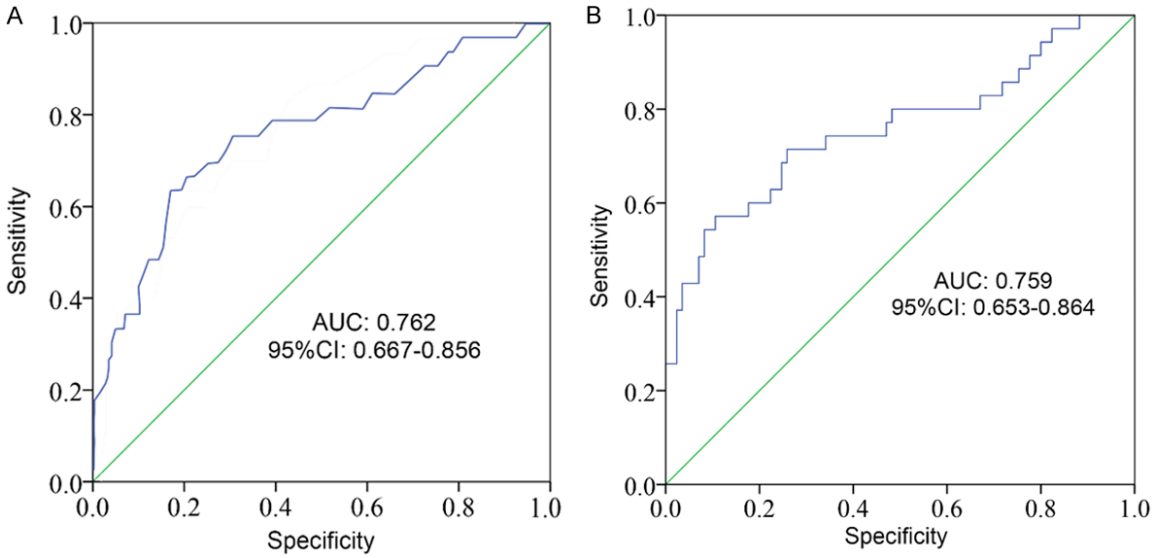

Figure 1. Receiver operating characteristic (ROC) curves of the test (A) and validation (B) cohorts.

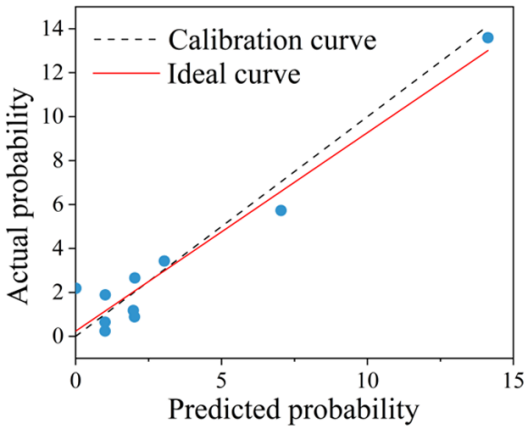

Figure 2. Calibration curves for the prediction model.

associated with AL [20]. Especially in the T stage, the more the tumor invades or adheres to the surrounding tissues, the larger the surgical scope, the smaller the operating space, the higher the requirements for surgical techniques, and the more tissues need to be removed, which would lead to increased anastomotic tension and insufficient blood supply.

The degree of preoperative obstruction is positively correlated with the risk of postoperative anastomosis. Obstruction resulted in intestinal fluid and gas expansion of different degrees, intestinal ischemia, intestinal wall edema, and brittle tissues, which can easily tear after anastomosis. In addition, the intestinal preparation before the intestinal obstruction is not ideal, which is easy to cause local infection and inflammatory reaction after the surgery, resulting in slow anastomotic healing and AL.

The distance from the tumor to the anus is closely related to postoperative AL and has been continuously reported as an essential factor. It is generally believed that the lower the

Table 4. Clinical validation of the prediction model

Predictive anastomotic leakage	Actual anastomotic leakage		Total	Sensitivity	Specificity	Accuracy rate
	Yes	No				
Yes	32	72	104			
No	7	289	296	82.05%	80.06%	80.25%
Total	39	361	400			

anastomosis position, the higher the probability of AL [21]. The shorter the distance between the tumor and the anus, the higher the risk of AL occurrence in the randomized controlled trial involving 946 cases of postoperative AL of rectal cancer [22]. Another prospective study [23] indicated that the anastomosis from the anus <5 cm was a risk factor for postoperative AL (OR=2.38, 95% CI=1.03-5.46). This study divided the distance of the tumor to the anus into ≤7 cm and >7 cm. The incidence of anastomotic leakage in the ≤7 cm group and >7 cm was 12.2% and 5.65%, respectively. The results indicated that the distance of the tumor to the anus ≤7 cm was an independent risk factor for anastomotic leakage.

As the first RCT study of prophylactic ostomy for low rectal cancer, the study of Swedish RECTODES [24] showed that prophylactic ostomy could significantly reduce the incidence of postoperative AL (10.3%/28.0%). In recent years, many results have shown that for patients with high-risk factors of AL, a defunctioning stoma is an effective measure to reduce the incidence of AL after rectal cancer surgery, shorten the healing time, and decrease the rate of reoperation as well as perioperative mortality [25]. Here, we found that prophylactic ostomy can effectively reduce the incidence of postoperative AL. We conclude that fecal diversion and reduction of postoperative rectal pressure effectively reduce postoperative AL. For the anastomotic orifice with the poor anastomotic condition, intestinal tube edema and spasm occur under the inflammatory stimulation of stool, resulting in increased intestinal pressure and subclinical AL. The incidence of postoperative AL significantly increases with the further aggregation of peripheral micro-abscess lesions in patients with other high-risk factors. A defunctioning stoma could reduce the inflammatory stimulation of postoperative stool to the anastomosis with a decline in the static pressure of the anastomosis to effectively reduce the occurrence of postoperative AL. Therefore, for patients combined with high-risk factors who undergo Dixon surgery, such as low or even ultra-low rectal cancer, older age, poor preoperative intestinal preparation, an intraoperative defunctioning stoma is undoubtedly a safe measure to prevent postoperative AL.

Diabetes patients are often accompanied by three major nutrient metabolism disorders. Insulin resistance is likely to occur during surgical stress, resulting in elevated blood sugar, slow tissue healing and weakened anti-infection ability, thus increasing the risk of poor postoperative anastomotic healing [26, 27]. Several studies have reported that diabetic tumor patients are prone to postoperative AL [28-30]. In this study, five diabetic patients developed AL (5/25). Due to the small number of diabetic patients included in this group, strong evidence of a significant correlation between preoperative diabetes mellitus and postoperative AL cannot be obtained for the time being. However, perioperative blood glucose control is required for diabetic patients, which also has a particular preventive effect on postoperative AL [31].

Other variables like surgical time and blood loss may also be important in developing anastomotic leakages [32]. We did not include these potential variables due to the following issues. The main reason is that the intraoperative management strategies of different patients are quite different. Operation duration is related to doctors' operating techniques and patients' physical conditions, so surgery duration and blood loss are not easily included in the prediction model as control variables. In addition, including these intraoperative risk factors would delay the calculation of risk assessment, which could lead to a delay in the prevention and intervention of anastomotic leakage. Since the current risk model produces good predictive performance, it is unnecessary to include additional variables further.

There are several significant limitations to this study. Constructing a prediction model based on retrospective data may add some uncertainty to the final results. First, this study includes many influencing factors, and the sample size is small, so confounding factors cannot be excluded entirely. Secondly, the timeline of medical records is long, and the influence of surgical environment, surgical equipment and other aspects on anastomotic leakage has not been determined. The large sample and multicenter prospective study will help further verify its application value for predicting postoperative anastomotic leakage.

In summary, age ≥60 years, male, preoperative obstruction, medium-low rectal cancer, medium-late tumor TMN, and preoperative diabetes can increase the risk of postoperative anastomotic leakage of rectal cancer, and intraoperative defunctioning stoma can significantly reduce the incidence of AL. The prediction model constructed based on these factors has a high predictive value for the occurrence of AL after Dixon surgery for rectal cancer, which is conducive to clinical assessment of patients' conditions, identification and early intervention of high-risk patients to reduce the risk of postoperative AL.

Acknowledgements

Study on the Mechanism of long-stranded noncoding RNA Linc00511 regulating miR-204-5p/HMGA2 expression in invasion and Metastasis of gastric Cancer.

Disclosure of conflict of interest

None.

Address correspondence to: Haige Huang, Department of General Surgery, The Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China. Tel: +86-0776-2056089; E-mail: haige.huang@ymun.edu.cn

References

[1] Tang JQ, Wang X and Wang XS. Interpretation of Chinese expert consensus on the pelvic exenteration for primary rectal cancer beyond total mesorectal excision planes and locally recurrent rectal cancer (2023 edition). Zhonghua Wei Chang Wai Ke Za Zhi 2023; 26: 222-226.

[2] Zhou ZH, Li QL, Yu JH, Rong MH, Cao J, Ge LY, Tang WZ and Yu HP. Epidemiological characteristics and disease burden of cancer in Guangxi cancer registration areas, 2017. Chinese Journal of Oncology Prevention and Treatment 2022; 14: 264-273.

[3] Boström P, Haapamäki MM, Rutegård J, Matthiessen P and Rutegård M. Population-based cohort study of the impact on postoperative mortality of anastomotic leakage after anterior resection for rectal cancer. BJS Open 2018; 3: 106-111.

[4] Song G, Guo H, Jiang C, Shi Y and Liu M. Magnetic nanoparticles detection of C-reactive protein combined with neutrophil to lymphocyte ratio to predict the occurrence of anastomotic fistula after rectal cancer surgery. Cell Mol Biol (Noisy-le-grand) 2022; 68: 116-122.

[5] Zhang Z, Hu Z, Qin Y, Qian J, Tu S and Yao J. Application of transurethral prostate resection instrumentation for treating low rectal anastomotic leakage: a pilot study. Cancer Manag Res 2022; 14: 1987-1994.

[6] Long-Zhi Z, Bin Z, Jian-Xin H and Wei L. Clinical application of terminal ileum suspension in laparoscopic radical resection for low rectal cancer. Pak J Med Sci 2022; 38: 261-266.

[7] Lu W, Huang S, Ye H, Xiang S and Zeng X. Application of laparoscopic modified Bacon operation in patients with low rectal cancer and analysis of the changes in anal function: a retrospective single-center study. Front Oncol 2023; 13: 1087642.

[8] Mankarious MM, Portolese AC, Hoskins MA, Deutsch MJ, Jeganathan NA, Scow JS and Kulaylat AS. Neoadjuvant chemotherapy does not increase risk for anastomotic leak for simultaneous resection of primary colon cancer with synchronous liver metastasis: a NSQIP-colectomy analysis. J Surg Oncol 2023; [Epub ahead of print].

[9] Ahmad NZ, Azam M, Fraser CN and Coffey JC. A systematic review and meta-analysis of the use of methylene blue to improve the lymph node harvest in rectal cancer surgery. Tech Coloproctol 2023; 27: 361-371.

[10] Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, Holm T, Wong WD, Tiret E, Moriya Y, Laurberg S, den Dulk M, van de Velde C and Büchler MW. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery 2010; 147: 339-351.

[11] Jörgren F, Johansson R, Damber L and Lindmark G. Anastomotic leakage after surgery for rectal cancer: a risk factor for local recurrence, distant metastasis and reduced cancer-specific survival? Colorectal Dis 2011; 13: 272-283.

[12] Rutegård M and Rutegård J. Anastomotic leakage in rectal cancer surgery: the role of blood

perfusion. World J Gastrointest Surg 2015; 7: 289-292.
[13] Zhou X, Wang B, Li F, Wang J and Fu W. Risk factors associated with nonclosure of defunctioning stomas after sphincter-preserving low anterior resection of rectal cancer: a meta-analysis. Dis Colon Rectum 2017; 60: 544-554.
[14] Ye L, Huang M, Huang Y, Yu K and Wang X. Risk factors of postoperative low anterior resection syndrome for colorectal cancer: a meta-analysis. Asian J Surg 2022; 45: 39-50.
[15] Zhou C, Wu XR, Liu XH, Chen YF, Ke J, He XW, He XS, Hu T, Zou YF, Zheng XB, Liu HS, Hu JC, Wu XJ, Wang JP and Lan P. Male gender is associated with an increased risk of anastomotic leak in rectal cancer patients after total mesorectal excision. Gastroenterol Rep (Oxf) 2018; 6: 137-143.
[16] Yu J, Chen Y, Li T, Sheng B, Zhen Z, Liu C, Zhang J, Yan Q and Zhu P. High and low inferior mesenteric artery ligation in laparoscopic low anterior rectal resections: a retrospective study. Front Surg 2022; 9: 1027034.
[17] Kang J, Kim H, Park H, Lee B and Lee KY. Risk factors and economic burden of postoperative anastomotic leakage related events in patients who underwent surgeries for colorectal cancer. PLoS One 2022; 17: e0267950.
[18] Arron MNN, Greijdanus NG, Ten Broek RPG, Dekker JWT, van Workum F, van Goor H, Tanis PJ and de Wilt JHW. Trends in risk factors of anastomotic leakage after colorectal cancer surgery (2011-2019): a Dutch population-based study. Colorectal Dis 2021; 23: 3251-3261.
[19] Wen R, Zheng K, Zhang Q, Zhou L, Liu Q, Yu G, Gao X, Hao L, Lou Z and Zhang W. Machine learning-based random forest predicts anastomotic leakage after anterior resection for rectal cancer. J Gastrointest Oncol 2021; 12: 921-932.
[20] Kawada K, Hasegawa S, Hida K, Hirai K, Okoshi K, Nomura A, Kawamura J, Nagayama S and Sakai Y. Risk factors for anastomotic leakage after laparoscopic low anterior resection with DST anastomosis. Surg Endosc 2014; 28: 2988-2995.
[21] Nagaoka T, Fukunaga Y, Mukai T, Yamaguchi T, Nagasaki T, Akiyoshi T, Konishi T and Nagayama S. Risk factors for anastomotic leakage after laparoscopic low anterior resection: a single-center retrospective study. Asian J Endosc Surg 2021; 14: 478-488.
[22] Emile SH, Khan SM, Garoufalia Z, Silva-Alvarenga E, Gefen R, Horesh N, Freund MR and Wexner SD. When is a diverting stoma indicated after low anterior resection? A meta-analysis of randomized trials and meta-regression of the risk factors of leakage and complications in non-diverted patients. J Gastrointest Surg 2022; 26: 2368-2379.
[23] Yeh CY, Changchien CR, Wang JY, Chen JS, Chen HH, Chiang JM and Tang R. Pelvic drainage and other risk factors for leakage after elective anterior resection in rectal cancer patients: a prospective study of 978 patients. Ann Surg 2005; 241: 9-13.
[24] Matthiessen P, Hallböök O, Rutegård J, Simert G and Sjödahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007; 246: 207-214.
[25] Yu XN, Xu LM, Bin YW, Yuan Y, Tian SB, Cai B, Tao KX, Wang L, Wang GB and Wang Z. Risk factors of anastomotic leakage after anterior resection for rectal cancer patients. Curr Med Sci 2022; 42: 1256-1266.
[26] Tan DJH, Yaow CYL, Mok HT, Ng CH, Tai CH, Tham HY, Foo FJ and Chong CS. The influence of diabetes on postoperative complications following colorectal surgery. Tech Coloproctol 2021; 25: 267-278.
[27] van Kooten RT, Voeten DM, Steyerberg EW, Hartgrink HH, van Berge Henegouwen MI, van Hillegersberg R, Tollenaar RAEM and Wouters MWJM. Patient-related prognostic factors for anastomotic leakage, major complications, and short-term mortality following esophagectomy for cancer: a systematic review and meta-analyses. Ann Surg Oncol 2022; 29: 1358-1373.
[28] Kayani B, Okabayashi K, Ashrafian H, Harling L, Rao C, Darzi A, Kitagawa Y, Athanasiou T and Zacharakis E. Does obesity affect outcomes in patients undergoing esophagectomy for cancer? A meta-analysis. World J Surg 2012; 36: 1785-1795.
[29] Li SJ, Wang ZQ, Li YJ, Fan J, Zhang WB, Che GW, Liu LX and Chen LQ. Diabetes mellitus and risk of anastomotic leakage after esophagectomy: a systematic review and meta-analysis. Dis Esophagus 2017; 30: 1-12.
[30] Dias VE, Castro PASV, Padilha HT, Pillar LV, Godinho LBR, Tinoco ACA, Amil RDC, Soares AN, Cruz GMGD, Bezerra JMT and Silva TAMD. Preoperative risk factors associated with anastomotic leakage after colectomy for colorectal cancer: a systematic review and meta-analysis. Rev Col Bras Cir 2022; 49: e20223363.
[31] Wang Z, Sun S, Li K, Huang C, Liu X, Zhang G and Li X. Feasibility analysis of combined surgery for esophageal cancer. World J Surg Oncol 2023; 21: 41.
[32] Qu H, Liu Y and Bi DS. Clinical risk factors for anastomotic leakage after laparoscopic anterior resection for rectal cancer: a systematic review and meta-analysis. Surg Endosc 2015; 29: 3608-3617.