Value of intra-operative Doppler sonographic measurements in predicting post-operative anastomotic leakage in rectal cancer: a prospective pilot study

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Abstract
Background: Anastomotic leakage is a serious surgical complication in rectal cancer; however, effective evaluation methods for predicting anastomotic leakage individual risk in patients are not currently available. This study aimed to develop a method to evaluate the risk of leakage during surgery.

Methods: The 163 patients with rectal cancer, who had undergone anterior resection and low-ligation procedures for Doppler sonographic hemodynamic measurement from April 2011 to January 2015 in Peking University Cancer Hospital, were prospectively recruited. A predictive model was constructed based on the associations between anastomotic leakage and alterations in the anastomotic blood supply in the patients, using both univariate and multivariate statistical analyses, as well as diagnostic methodology evaluation, including Chi-square test, logistic regression model, and receiver operating characteristic curve.

Results: The overall anastomotic leakage incidence was 9.2% (15/163). Doppler hemodynamic parameters whose reduction was significantly associated with anastomotic leakage were peak systolic velocity, pulsatility index, and resistance index. The areas under the receiver operating characteristic curve of residual rates of peak systolic velocity, pulsatility index, and resistance index in predicting anastomotic leakage were 0.703 (95% confidence interval [CI]: 0.552–0.854), 0.729 (95% CI: 0.579–0.879), and 0.689 (95% CI: 0.522–0.856), respectively. The predictive model revealed that the patients with severely reduced blood-flow signal exhibited a significantly higher incidence rate of anastomotic leakage than those with sufficient blood supply (19.6% vs. 3.7%, P = 0.003), particularly the patients with low rectal cancer (25.9% vs. 3.9%, P = 0.007) and those receiving neoadjuvant chemoradiotherapy (32.1% vs. 3.7%, P = 0.001), independent of prophylactic ileostoma. Multivariate analysis revealed that insufficient blood supply of the anastomotic bowel was an independent risk factor for anastomotic leakage (odds ratio: 10.37, 95% CI: 2.703–42.735, P = 0.001).

Conclusion: Based on this explorative study, Doppler sonographic hemodynamic measurement of the anastomotic bowel presented potential value in predicting anastomotic leakage.

Keywords: Rectal cancer; Anastomotic leakage; Doppler; Surgery

Introduction
Anastomotic leakage (AL) remains a crucial complication after low anterior resection (LAR) in rectal cancer; it is associated with high post-operative mortality and poor oncological outcomes.1,2 The reported incidence rate of AL varies between 4% and 20%, depending on multiple factors including surgical technique, neoadjuvant therapy, tumor location, sex, and intestinal bacterial infections.3–5 Although previous studies have identified several clinical risk factors for early detection markers of AL,3–6 accurately evaluating the risk of AL in an individual patient is difficult, and effective personalized methods for predicting AL during colorectal surgery are not currently available. Currently, to avoid AL and to determine the necessity of defunctioning ileostomy, most surgeons evaluate the risk of AL based on whether the patient exhibits surgical adverse events or clinical risk factors including male sex, low anastomosis, and receipt of neoadjuvant chemoradiotherapy.4,5 However, such evaluation is not accurate because only less than one-fifth of...
the patients with risk factors eventually develop AL,[7] and many patients without risk factors also develop AL.[8] By contrast, many surgeons routinely construct a defunctioning ileostomy to reduce the possibility of AL or the severity of its clinical consequences.[9,10] Although more than 80% of defunctioning ileostomy could be closed finally,[11] and it does not increase the total permanent stoma rate following anterior resection compared to non-ileostoma from long-term view,[12] the ileostomy has its own complication; moreover, it makes the patients undergo one more surgery to close it. Thus, routine ileostomy for all patients is not an optimal strategy.

Blood supply and the tension of anastomosis are two major surgical decisive factors for AL.[8,13] Assessment of blood supply of the anastomotic bowel is critical for decision making in surgery. Recently, Ris et al.[13] reported a promising result that assessing blood perfusion of colon during anastomosis procedure using the indocyanine green assay was helpful to reduce AL, despite of its non-quantification limitation. In this study, we tried to develop a simple and quantification method for predicting AL based on the evaluation of the blood perfusion of the anastomotic bowel using intra-operative Doppler sonographic hemodynamic measurements. Generally, the low-ligation procedure does not affect the perfusion of the colonic limb of the anastomosis as much as high-ligation procedure does because of the preservation of the inferior mesenteric artery (IMA).[13] However, in the low-ligation procedure, the mobilization of the proximal colonic limb and ligation of the sigmoid artery (SA) or left colic artery (LCA) branches are usually necessary after rectum excision and lymph node dissection for achieving satisfactory tension-free anastomosis.[14] Evaluating the blood supply to an anastomotic bowel after vascular ligation by observing visible pulsation at the proximal anastomotic segment is non-quantitative and unreliable. We hypothesized that vascular ligation during the mobilization of proximal colonic limb may compromise the blood supply to the anastomotic bowel in some patients, and the degree of ischemia may be predictive of AL. Thus, we assayed the blood perfusion of the anastomotic bowel before and after vascular ligation and constructed a model for predicting AL based on the alterations in hemodynamic parameters.

Methods

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Peking University Cancer Hospital. Informed written consent was obtained from all individual participants before their enrollment in this study.

Eligibility for enrollment

Patients were enrolled at Peking University Cancer Hospital between April 2011 and January 2015. The inclusion criteria were as follows: (1) Histopathologically confirmed adenocarcinoma with the inferior margin within 12 cm from the anal verge; (2) resectable lesions evaluated by magnetic resonance imaging or endorectal ultrasound; (3) the patients were scheduled to undergo open sphincter-preservation surgery, and did not exhibit clinical evidence of synchronous distant metastases; (4) the patients did not complicate with arteriosclerosis, diabetes mellitus, arrhythmia, pre-operative bowel obstruction or malnutrition (defined as hemoglobin level <110 g/L, serum albumin <30 g/L, or weight loss >10% of their pre-illness body weight). Patients with incomplete anastomotic rings or positive air leakage test results during operation, one patient died of pulmonary embolism within 1 week after surgery, and two patients failed to obtain hemodynamic measurements [Figure 1]. All the included patients underwent sphincter-preservation surgery and Doppler hemodynamic measurement using ultrasonography during surgery, as shown in Figure 2.

Neoadjuvant therapy and surgery

The treatment strategy of each patient was decided after a multidisciplinary discussion. Generally, neoadjuvant chemoradiotherapy was administered to the patients with locally advanced stages of cancer (cT3–4, or T, N positive cancer; 50.6 Gy/22f + capcitabine 825 mg/m² b.i.d.). Surgery was performed 8 to 12 weeks after the completion of neoadjuvant chemoradiotherapy.

All the included patients underwent LAR strictly according to total mesorectal excision (TME) principles.[17] Pelvic autonomic nerves were preserved as much as possible, and lateral pelvic lymphadenectomy was performed if necessary. All the included patients underwent low ligation in the LAR procedure with central ligation of superior rectal artery (SRA), which involved the division of SRA distally to the origin of the LCA with subsequent en bloc excision of the lymph nodes and bowels below it.[18] The SA or a branch of the LCA was then ligated after excision of the SRA and rectum to prolong the proximal colon limb for ensuring a tension-free colorectal anastomosis [Figure 3A and 3B]. The double-stapling technique was used, and each patient had an end-to-end stapled colorectal anastomosis. The level of anastomosis and the completeness of anastomotic donuts were examined intra-operatively. An air leakage test was compulsorily performed in all the patients. A prophylactic ileostomy was constructed based on the surgeon’s independent discretion. Pelvic drainage without vacuum was used for all the patients. All operations were performed by a group of senior colorectal surgeons. Bowel preparation was performed in all the patients by using orally administered polyethylene glycol fluid on the first pre-operative day.
Definition and diagnosis of post-operative AL

AL is defined as a defect of the intestinal wall integrity at the colorectal anastomotic site leading to communication between the intra- and extra-luminal compartments.[18] The diagnostic criteria in this study included the following: purulent or fecal discharge from the pelvic drain, peritonitis or sepsis presenting as abdominal pain, tachycardia, fever, and an increased white blood cell count caused by anastomotic dehiscence, which was confirmed through relaparotomy. The presence of pelvic abscesses near the anastomosis was diagnosed using radiological examinations. Rectovaginal fistulae and AL were observed using digital rectal examination (DRE), endoscopy, or contrast enema.

All the patients were subjected to DRE from the seventh to tenth post-operative day. Contrast enema or proctoscopy was only used in the patients with clinical suspicion of AL. The patients were followed up at 2-week intervals for 6 weeks to specially survey the AL, and then followed the routine follow-up protocol. The evaluations of anastomosis included DRE and proctoscopy, if necessary.

Doppler hemodynamic measurements

To evaluate the blood supply of the proximal anastomotic colon limb, Doppler hemodynamic measurements were recorded before and after vascular ligation at the same site near the anastomotic bowel. The measurements started after the anvil was fixed in the colon and repeated after the ligation of SA or LCA, as shown in Figures 2, 3A and 3B. The typical waveform of the blood flow signal is presented in Figure 3C. Duplex Doppler sonography was conducted using an ultrasound device (ALOKA Prosound SSD-3500, Aloka Co. Ltd., Japan) by the chief operator of the hospital together with an ultrasonographic radiologist. The device was equipped with a linear probe of 5 to 10 MHz. The chief operator was responsible for identifying the blood flow signal by placing the sonographic probe on the mesenteric border of the bowel wall [Supplementary Figure S1, http://links.lww.com/CM9/A83]. Each measurement was performed until a stable waveform was observed and recorded. Doppler hemodynamic parameters, namely the peak systolic velocity (PSV), end-diastolic velocity (EDV), mean velocity (MnV), pulsatility index (PI), and resistance index (RI), were confirmed by the ultrasonography specialist. The PSV, EDV, and MnV reflect the blood perfusion of a tissue per unit time, whereas the PI and RI reflect the pulsatility and resistance of the vessels, respectively.[19] The procedure of measurement was repeated thrice, and the medians of the three measured values were used as the final data. Anesthesiologists were asked to avoid drug administration during the measurements. The alteration of blood supply was presented by residual rate, which was calculated according to the following formula: Residual rate (%R) = (post-ligation value/pre-ligation value) × 100%; for example, PSV%R = Post-PSV/Pre-PSV × 100%.

Statistical analysis

Statistical analyses were performed using the IBM SPSS software for Macintosh, version 20.0 (IBM Corp., Armonk, NY, USA). Categorical data were compared using the Chi-square test or Fisher exact test. Numerical variables were expressed as median (range or Q1, Q3) and were examined using the normality test (Kolmogorov-Smirnov test). The Doppler hemodynamic parameters before and after vascular ligation were compared using the paired Wilcoxon sign-rank test. The predictive efficiencies of Doppler hemodynamic parameters were evaluated using receiver operator characteristic (ROC) curves and area under curve (AUC) and were compared using the method of DeLong et al.[20] In multivariate analysis, all available variables were fed into a logistic regression model to determine the independent risk factors for AL. All statistical tests were two-sided, and the level of significance was set at P < 0.05.
Results

Patient characteristics

Totally 163 eligible patients, consisting of 96 males and 67 females, were included in the final analysis, and the median age of the patients was 60 years (range: 25–83 years). The median distance between the tumor inferior edge and the anal verge was 6 cm (range: 3–10 cm). During the study, 82 patients (50.3%) were receiving neoadjuvant chemoradiotherapy. A prophylactic ileostomy was constructed in 73 patients (44.8%). In total, 15 patients developed AL (9.2%) of which three patients underwent reoperation. The median occurrence time of AL was the eighth postoperative day, ranged from day 4 to day 20. No delayed leakage was found. No patient died of AL or other complications. A pelvic drain was routinely used in all the patients, and it was removed depending on the rehabilitation condition. The demographic and oncological data of the included patients are summarized in Table 1.

Figure 3: Low-ligation surgery and Doppler sonographic blood signal of an anastomotic bowel. (A) Excision of rectum without ligation of the SA and LCA. (B) Mobilization of proximal colonic limb with ligation of the SA and LCA to obtain a tension-free anastomosis. The increase in colonic length was measured using the prolonged distance to the upper edge of the pubic symphysis (dashed line). (C) Doppler sonographic blood signal near the anastomotic bowel wall. LCA: Left colic artery; SA: Sigmoid artery.
Table 1: Demographic and oncological data of the included patients in this study (n = 163).

| Characteristics          | Values |
|--------------------------|--------|
| Gender                   |        |
| Male                     | 96 (58.9) |
| Female                   | 67 (41.1) |
| Age (years)              |        |
|                          | 60 (25–83) |
| BMI                      |        |
| <25.0 kg/m²              | 99 (60.7) |
| 25.0–29.9 kg/m²          | 55 (33.7) |
| ≥30.0 kg/m²              | 9 (5.5) |
| Tumor location           |        |
| High and middle (≥6 cm)  | 85 (52.1) |
| Low (<6 cm)              | 78 (47.9) |
| Neoadjuvant chemoradiotherapy |        |
| Yes                      | 82 (50.3) |
| No                       | 81 (49.7) |
| Histological differentiation |         |
| Complete response        | 10 (6.1) |
| Well                     | 7 (4.3) |
| Moderate                 | 113 (69.3) |
| Poor                     | 24 (14.7) |
| Mucinous and signet      | 9 (5.5) |
| Pathological stage       |        |
| 0                        | 10 (6.1) |
| 1                        | 36 (22.1) |
| II                       | 40 (24.5) |
| III                      | 77 (47.2) |
| CRM                      |        |
| Positive                 | 7 (4.3) |
| Negative                 | 156 (95.7) |
| Anastomatic leakage      |        |
| Yes                      | 15 (9.2) |
| No                       | 148 (90.8) |

The data are shown as n (%) or median (range). BMI: Body mass index; CRM: Circumferential resection margin.

Doppler hemodynamic alterations following vascular ligation and their predictive value for AL

To obtain a sufficient proximal colonic length for tension-free anastomosis, ligature of the SA or LCA was performed in all the patients. The increase in the colonic length following vascular ligation was 8.6 ± 2.6 cm (range: 4.0–18.5 cm) [Figure 3A and 3B], without palpable tensional anastomosis in this study. Doppler hemodynamic parameters of each patient were measured before and after vascular ligation. The normality tests results revealed that the hemodynamic parameters, PSV, EDV, MnV, PI, and RI, did not exhibit normal distributions [Supplementary Table S1, http://links.lww.com/CM9/A83]. The PSV, MnV, PI, and RI changed significantly after ligation (rank test, \( P < 0.001 \)), whereas the EDV before and after vascular ligation did not differ significantly (\( P = 0.521 \)) [Supplementary Table S2, http://links.lww.com/CM9/A83].

The comparison of the hemodynamic parameters between the AL and non-AL groups using Wilcoxon rank-sum test revealed that PSV%R, PI%R, and RI%R were significantly lower in the AL group, compared with the non-AL group (\( P < 0.05 \)) [Table 2 and Supplementary Figure S2, http://links.lww.com/CM9/A83]. The AUC of ROC curves of PSV%R, PI%R, and RI%R in predicting AL were 0.703 (95% confidence interval [CI]: 0.552–0.854), 0.729 (95% CI: 0.579–0.879), and 0.689 (95% CI: 0.522–0.856), respectively [Figure 4], and did not differ significantly from each other [Supplementary Table S3, http://links.lww.com/CM9/A83].

The cut-off values of PSV%R, PI%R, and RI%R in differentiating the presence and absence of AL were identified as 60 (PSV60), 60 (PI60), and 80 (RI80), respectively, to obtain maximum discriminative power. These values indicated that the post-ligation values of PSV and PI were 60% (while that of RI was 80%) of the corresponding pre-ligation values. The predictive ability of PSV60, PI60, and RI80 for AL, in terms of positive predictive value, negative predictive value, sensitivity, specificity, and accuracy, are summarized in Table 3.

Predictive model for AL

Based on the synthetic evaluation of predicting ability of hemodynamic parameters, particularly considering the optimal sensitivity, specificity, and accuracy, the predictive model reflecting anastomotic blood supply consisted of PSV60 and PI60 [Table 3]. Insufficient blood supply was defined as PSV%R or PI%R < 60 (56/163, 34.3%), while both PSV%R and PI%R ≥ 60 were classified as sufficient blood supply (107/163, 65.7%) [Table 4].

The results showed that patients with insufficient blood supply had a considerably higher hazard of AL than those with sufficient blood supply [Table 4]. To obtain additional information for identifying the patients at a high risk of AL, we analyzed the relationship between blood supply and AL (strong or weak) in different patient groups stratified according to the presence of prophylactic ileostoma, the receipt of neoadjuvant therapy, and tumor location. The analysis revealed that the patients with low rectal cancer and those receiving neoadjuvant therapy were more vulnerable to insufficient anastomotic blood supply because the patients with insufficient blood supply in these groups exhibited a higher incidence rate of AL than those with a sufficient blood supply (25.9% vs. 3.9%, \( P = 0.007; \) 32.1% vs. 3.7%, \( P = 0.001 \); respectively); however, ileostoma did not evidently reduce the risk of AL in the patients with insufficient blood supply [Table 4]. Therefore, the predictive model was relatively accurate for the patients with low rectal cancer and those receiving neoadjuvant chemoradiotherapy.

Univariate and multivariate analyses for AL

To identify the independent risk factors for AL, we used both univariate and multivariate analyses. Only a variable with statistical significance in both analyses could be considered an independent clinical risk factor for AL.

Apart from blood supply, other potential clinical factors affecting AL, such as sex, body mass index, tumor location,
neoadjuvant chemoradiotherapy, and ileostoma, were analyzed; however, none of these factors, except blood supply, was significantly related to AL in univariate analysis [Supplementary Table S4, http://links.lww.com/CM9/A83].

To investigate whether blood supply is an independent risk factor of AL, we verified blood supply as well as other variables using logistic regression model. The result showed that blood supply and neoadjuvant chemoradiotherapy were left in the equation, while tumor location, bowel resection length, distance of lengthening, and ileostoma were excluded, suggesting that blood supply and neoadjuvant chemoradiotherapy were independent risk factors of AL [Table 5].

Table 2: Comparison of blood supply between AL and non-AL groups.

| Variables   | AL group          | Non-AL group       | Z   | P     |
|-------------|-------------------|--------------------|-----|-------|
| PSV%R       | 53.01 (43.75, 83.75) | 82.96 (65.18, 100.00) | −2.589 | 0.010 |
| EDV%R       | 84.38 (67.04, 96.36) | 88.46 (69.81, 110.77) | −0.733 | 0.464 |
| MnV%R       | 73.42 (65.45, 102.22) | 88.53 (76.53, 111.61) | −1.688 | 0.091 |
| PI%R        | 53.89 (30.48, 69.61) | 84.15 (62.59, 114.93) | −2.922 | 0.003 |
| RI%R        | 70.40 (53.90, 100.00) | 95.94 (78.25, 105.91) | −2.414 | 0.016 |

The data are shown as median (Q1, Q3). AL: Anastomotic leakage; PSV%R: Residual rate of peak systolic velocity; EDV%R: Residual rate of end-diastolic velocity; MnV%R: Residual rate of mean velocity; PI%R: Residual rate of pulsatility index; RI%R: Residual rate of resistance index.

Discussion

Addressing the issue of predicting post-operative AL is crucial in rectal cancer treatment because safe anastomoses not only reduce the incidence of dangerous complications but also prevent the need for defunctioning ileostomies and possibly improve long-term outcomes in patients with rectal cancer.[2,3] In this study, we proposed a method for predicting AL based on the Doppler sonographic measurements of anastomotic blood supply and found that these data might be valuable in predicting AL following sphincter-preservation surgery.

A tension-free anastomosis with sufficient blood supply is generally considered crucial for sphincter-preservation surgery.[13,16] Although high-ligation surgery has not been definitely linked to anastomotic ischemia and leakage,[21-23] the low-ligation procedure is theoretically superior to the high-ligation procedure for improving proximal colonic blood supply by preserving the IMA and the LCA branches.[15,24] The oncological safety of low-ligation may be an issue to limit its use. However, a new coming result of a randomized clinical trial demonstrated that the low-ligation had the same lymph node harvest and long-term survival condition comparing to high-ligation.[25] Thus low-ligation is also an option for rectal cancer surgery.

From a surgical viewpoint, the high-ligation procedure maximized colonic mobility, which could provide a sufficient colon length, thereby facilitating a favorable tension-free anastomosis.[26] Whereas the low-ligation procedure limited the mobility of the proximal limb because of tethering by the SA or LCA.[24] Thus, ligation of 1 or 2 branches of the SA or LCA is effective for acquiring a favorable tension-free anastomosis in most situations of low ligation. Although a series of studies have investigated the effects of ligating IMA on blood perfusion of the anastomotic bowel in a high-ligation procedure,[15,27] studies investigating the alterations in blood supply during the low-ligation procedure are not currently available. Our data revealed that vascular ligation during the mobilization of the proximal limb evidently reduced the blood perfusion of the anastomosis in one-third of the patients; these findings were significantly different from the hypothesis that the low-ligation procedure had a relatively weak influence on the anastomotic blood supply.[15] The reasons behind why some patients had significantly lower blood supply after the ligation of the SA or LCA branches remain unclear; the absence or malfunction of the marginal arcade may cause the reduction in blood supply.[28] The high-risk of AL is well established in these patients; particularly in those with low rectal cancer and receiving neoadjuvant therapy. Because TME surgery severely damages the vascularization surrounding the rectum in low rectal cancer and radiation reduces the healing ability of the colorectal tissue,[29] we hypothesized that the patients with low cancer and those receiving neoadjuvant chemoradiotherapy were more vulnerable than the other
patients to colonic ischemia. Therefore, the predictive model based on hemodynamic measurements could be considered a determinant factor in deciding whether to construct a defunctioning ileostomy during surgery, particularly if the patients had undergone neoadjuvant therapy or had a tumor at a low location. A defunctioning ileostomy during surgery, particularly if the patients had undergone neoadjuvant therapy or had a tumor at a low location. A defunctioning ileostomy during surgery, particularly if the patients had undergone neoadjuvant therapy or had a tumor at a low location.

Conventionally, senior colorectal surgeons assess the blood supply of the proximal anastomotic segment by observing visible pulsation. However, this observation is highly subjective; moreover, observing vascular pulsation is difficult in patients with obesity. Karliczek et al. reported that the surgeons’ clinical judgment had quite a low accuracy (<50%) in predicting AL. Doppler sonography is an effective and convenient tool for measuring colonic blood perfusion, which provides sufficient hemodynamic data, thus enabling the quantitative evaluation of blood supply. According to our experience, Doppler sonographic measurement requires a total time of only 15 to 20 min for all data collection. Furthermore, this technique does not cause an additional hazard to the patients. Nevertheless, it requires surgeons to modify their operating steps. They have to identify the proximal anastomotic location and measure its blood supply before and after vascular ligation. We demonstrated that the predictive model based on hemodynamic analysis was an effective method for reflecting the degree of ischemia in an anastomotic bowel, which was predictive of AL. Although other methods for detecting blood signal such as laser Doppler flowmetry (LDF) are available, LDF only provides limited information about blood perfusion, and it is not a favorable assay to predict AL based on its low accuracy. Compared with LDF, Doppler sonography provides more detailed hemodynamic information and sonographic images, and its high predictive efficiency makes it a promising application prospect. Moreover, the convenience of this method expands the use of Doppler sonography during surgery. However, a limitation of the current technique was that evaluating the blood supply of the rectal stump by the routine probes was not available; thus, the alteration in blood perfusion of the rectal stump was unknown in this study. Some reports have pointed out that TME would decrease the blood supply of the rectal stump. If the blood flow change of the distal rectal

| Blood supply | Number | AL (%) | OR (95% CI) | P |
|--------------|--------|--------|-------------|---|
| Total        |        |        |             | 0.003 |
| Good         | 107    | 3.7    | 1           |    |
| Poor         | 56     | 19.6   | 5.25 (1.750–15.750) |    |
| Ileostoma    |        |        |             |    |
| No           |        |        |             |    |
| Good         | 68     | 5.9    | 1           | 0.036 |
| Poor         | 22     | 22.7   | 4.71 (1.140–19.460) |    |
| Yes          |        |        |             | 0.008 |
| Good         | 39     | 0      | 1           |    |
| Poor         | 34     | 17.6   | –           |    |
| Neoadjuvant chemoradiotherapy |     |        |             | 0.606 |
| No           |        |        |             |    |
| Good         | 53     | 3.8    | 1           | 0.001 |
| Poor         | 28     | 7.1    | 1.89 (0.280–12.730) |    |
| Yes          |        |        |             |    |
| Good         | 54     | 3.7    | 1           |    |
| Poor         | 28     | 32.1   | 8.68 (2.010–37.470) |    |
| Tumor location |     |        |             | 0.174 |
| High         |        |        |             |    |
| Good         | 56     | 3.6    | 1           |    |
| Poor         | 29     | 13.8   | 3.86 (0.750–19.850) |    |
| Low          |        |        |             | 0.007 |
| Good         | 51     | 3.9    | 1           |    |
| Poor         | 27     | 25.9   | 6.61 (1.470–29.650) |    |

AL: Anastomotic leakage; OR: Odds ratio; CI: Confidence interval.

| Variable      | OR   | 95% CI          | P   |
|---------------|------|-----------------|-----|
| Blood supply  |      |                 |     |
| NCT           | 5.92 | 1.402–24.975    | 0.016 |
| Ileostoma     | 0.25 | 0.060–0.997     | 0.05 |
| BRL           | 1.02 | 0.794–1.305     | 0.887 |
| DL            | 1.18 | 0.910–1.529     | 0.212 |
| Tumor location|      |                 |     |
|               | 1.18 | 0.810–1.707     | 0.395 |

OR: Odds ratio; CI: Confidence interval; NCT: Neoadjuvant chemoradiotherapy; BRL: Bowel resection length; DL: Distance of lengthening.

### Table 4: Association between colonic blood supply and AL.

### Table 5: Multivariate analysis of anastomotic leakage (Logistic regression model, Enter method).

**Table 3: Predictive ability of hemodynamic parameters on anastomotic leakage.**

| Variables | PPV (95% CI) | NPV (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) | Accuracy (95% CI) |
|-----------|-------------|--------------|----------------------|----------------------|-------------------|
| PSV<sub>60</sub> | 0.270 (0.140–0.460) | 0.950 (0.900–0.980) | 0.600 (0.330–0.830) | 0.840 (0.770–0.890) | 0.820 (0.750–0.870) |
| PL<sub>60</sub> | 0.240 (0.130–0.400) | 0.960 (0.900–0.980) | 0.670 (0.390–0.870) | 0.780 (0.710–0.850) | 0.770 (0.700–0.830) |
| RI<sub>60</sub> | 0.200 (0.110–0.340) | 0.960 (0.89–0.980) | 0.670 (0.390–0.870) | 0.730 (0.650–0.800) | 0.720 (0.650–0.790) |
| PSV<sub>60</sub> + PL<sub>60</sub> | 0.200 (0.110–0.330) | 0.960 (0.900–0.990) | 0.730 (0.450–0.910) | 0.700 (0.610–0.770) | 0.700 (0.620–0.770) |
| PSV<sub>60</sub> + RI<sub>60</sub> | 0.160 (0.090–0.280) | 0.960 (0.890–0.990) | 0.730 (0.450–0.910) | 0.620 (0.540–0.700) | 0.630 (0.550–0.700) |
| PL<sub>60</sub> + RI<sub>60</sub> | 0.190 (0.100–0.310) | 0.960 (0.900–0.990) | 0.730 (0.450–0.910) | 0.680 (0.590–0.750) | 0.680 (0.600–0.750) |

PPV: Positive predictive value; CI: Confidence interval; NPV: Negative predictive value; PSV: Peak systolic velocity; PI: Pulsatility index; RI: Resistance index.
stump could also be counted into the model, the predictive efficacy of the model might be further improved.

Another notable point of this study was that it was an exploratory study; the cut-off values here come from the single cohort which needed to be validated in other data sets. In addition, this study was a single-center study, with a relatively small population size. All the surgery and measurement were performed by a group of specialists, thus, compromising its persuasion on the repeatability between different manipulators.

In conclusion, this study implied that intraoperative Doppler hemodynamic measurement was promising in predicting AL; thus, it could be considered as an option while planning surgical strategy.

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Conflicts of interest

None.

References

1. Lu ZR, Rajendran N, Lynch AC, Heriot AG, Warrier SK. Anastomotic leaks after restorative resections for rectal cancer compromise cancer outcomes and survival. Dis Colon Rectum 2016;59:236–244. doi: 10.1097/DCR.0000000000000558.
2. Kula Y, Tarantino I, Warschewski R, Kuy S, Schmied BM, Schmed BM, et al. Anastomotic leakage is associated with impaired overall and disease-free survival after curative rectal cancer resection: a propensity score analysis. Ann Surg Oncol 2015;22:2039–2067. doi: 10.1246/sco.2014.4187-3.
3. Bostrom P, Haapamaki MM, Rutegard J, Matthiessen P, Rutegard M. Population-based cohort study of the impact on postoperative mortality of anastomotic leakage after anterior resection for rectal cancer. BJNS Open 2019;3:106–111. doi: 10.1002/bjs5.50106.
4. Kang CY, Halabi WJ, Chaudhry OO, Nguyen V, Pigazzi A, Carmichael JC, et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. JAMA Surg 2013;148:65–71. doi: 10.1001/jamasurg.2013.0008.
5. Pomermaagaard HC, Gessler B, Burchart J, Angenete E, Haglind E, Rosenberg J. Preoperative risk factors for anastomotic leakage after anterior resection for colorectal cancer: a systematic review and meta-analysis. Colorectal Dis 2014;16:662–671. doi: 10.1111/codi.12618.
6. Su’a BU, Mikaere HL, Rahim JL, Bissett IB, Hill AG. Systematic review of the role of biomarkers in diagnosing anastomotic leakage following colorectal surgery. Br J Surg 2017;104:503–512. doi: 10.1002/bjs.10487.
7. Chang JS, Keum KC, Kim NK, Bak SH, Min BS, Huh H, et al. Preoperative chemoradiotherapy effects on anastomotic leakage after rectal cancer resection: a propensity score matching analysis. Ann Surg 2014;259:516–521. doi: 10.1097/SLA.0b013e3182906d5c.
8. Morse BC, Simpson JP, Jones YR, Johnson BL, Knott BM, Kotrady JA. Determination of independent predictive factors for anastomotic leak: analysis of 682 intestinal anastomoses. Am J Surg 2013;206:950–955. doi: 10.1016/j.amjsurg.2013.07.017.
9. Gu WL, Wu SW. Meta-analysis of defunctioning stoma in low anterior resection with total mesorectal excision for rectal cancer: evidence based on thirteen studies. World J Surg Oncol 2015;13:9. doi: 10.1186/s12957-014-0417-1.
10. Tan WS, Tang CL, Shi L, Fu KW. Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. Br J Surg 2009;96:462–472. doi: 10.1002/bjs.654.
11. Pan HD, Peng YF, Wang L, Li M, Yao YF, Zhao J, et al. Risk factors for nonclosure of a temporary defunctioning ileostomy following anterior resection of rectal cancer. Dis Colon Rectum 2016;59:94–100. doi: 10.1097/DCR.0000000000000520.
12. Lindgren R, Hallbom O, Rutegard J, Spjødal R, Matthiessen P. What is the risk for a permanent stoma after low anterior resection of the rectum for cancer? A six-year follow-up of a multicenter trial. Dis Colon Rectum 2011;54:41–47. doi: 10.1007/s00384-010-9739-5.
13. Rutegard M, Rutegard J. Anastomotic leakage in rectal cancer surgery: the role of blood perfusion. World J Gastrointest Surg 2015;7:289–292. doi: 10.4240/wjgs.v7.i1.289.
14. Fiss L, Fiss E, Buchs NC, Kraus R, Israel G, Belfontali V, et al. Multicentre phase II trial of near-infrared imaging in elective colorectal surgery. Br J Surg 2018;105:1359–1367. doi: 10.1002/bjs.10844.
15. Koenen N, Sieker J, de Kort P, de Wilt JH, van der Harst E, Coene PP, et al. High tie versus low tie in rectal surgery: comparison of anastomotic perfusion. Int J Colorectal Dis 2011;26:1075–1078. doi: 10.1007/s00384-011-1188-6.
16. Yasuda K, Kawai K, Ishihara S, Murono K, Otani K, Nishikawa T, et al. Level of arterial ligation in sigmoid colon and rectal cancer surgery. World J Surg Oncol 2016;14:99. doi: 10.1186/s12957-016-0819-3.
17. Carlsson E, Schlichting E, Guldsvig I, Johnson E, Heald RJ. Effect of the introduction of total mesorectal excision for the treatment of rectal cancer. Br J Surg 1999;85:526–529. doi: 10.1046/j.1365-2168.1998.00601.x.
18. Raharian NW, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, et al. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer Surgery. Cancer 2010;147:339–351. doi: 10.1016/j.ijrobp.2009.10.012.
19. Reynolds LP, Vonhalme KA, Lemley CO, Redmer DA, Graziul-Bilska AT, Borowicz PP, et al. Maternal stress and placental vascular function and remodeling. Curr Pharm Mol Biol 2013;11:564–593. doi: 10.2174/157016111131050063.
20. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–845. doi: 10.2307/2531595.
21. Rutegard M, Henningson O, Matthiessen P, Rutegard J. High tie in anterior resection for rectal cancer confers no increased risk of anastomotic leakage. Br J Surg 2012;99:127–132. doi: 10.1002/bjs.7771.
22. Bostrom P, Haapamaki MM, Matthiessen P, Ljung R, Rutegard J, Rutegard M. High arterial ligation and risk of anastomotic leakage in anterior resection for rectal cancer in patients with increased cardiovascular risk. Colorectal Dis 2015;17:1018–1027. doi: 10.1111/cod.12971.
23. Matsuda K, Hotta T, Takifuji K, Yokoyama S, Oka Y, Watanabe T, et al. Randomized clinical trial of defaecatory function after anterior resection for rectal cancer with high versus low ligature of the inferior mesenteric artery. Br J Surg 2013;100:501–508. doi: 10.1002/bjs.9739.
24. Lange MM, Buunen M, van de Velde CJ, Lange JF. Level of arterial ligation in rectal cancer surgery: low tie preferred over high tie. A review. Dis Colon Rectum 2008;51:1139–1145. doi: 10.1007/s10350-008-9328-y.
25. Fuji S, Ishibe A, Ota M, Suwa H, Watanabe J, Komisaki C, et al. Short-term and long-term results of a randomized study comparing high tie and low tie inferior mesenteric artery ligation in laparoscopic rectal anterior resection: subanalysis of the HTLT (high tie vs. low tie) study. Surg Endosc 2019;33:1100–1114. doi: 10.1007/s00464-018-6363-1.
26. Bonnet S, Berger A, Hentati N, Abid B, Chevallier JM, Wind P, et al. High tie versus low tie vascular ligation of the inferior mesenteric artery in colorectal cancer surgery: impact on the gain in colon length and implications on the feasibility of anastomoses. Dis Colon Rectum 2012;55:515–521. doi: 10.1002/dcr.20813.
27. Dworkin MJ, Allen-Mersh TG. Effect of inferior mesenteric artery ligation on blood flow in the marginal artery-dependent sigmoid colon. J Am Coll Surg 1996;183:357–360. doi: 10.1006/jasc.1996.0360.

28. Watanabe J, Ota M, Suwa Y, Suzuki S, Suwa H, Momiyama M, et al. Evaluation of the intestinal blood flow near the rectosigmoid junction using the indocyanine green fluorescence method in a colorectal cancer surgery. Int J Colorectal Dis 2015;30:329–335. doi: 10.1007/s00384-015-2129-6.

29. Moussa L, Usunier B, Demarquay C, Benderitter M, Tamarat R, Semont A, et al. Bowel radiation injury: complexity of the pathophysiology and promises of cell and tissue engineering. Cell Transplant 2016;25:1723–1746. doi: 10.3727/096368916X691664.

30. Karliczek A, Harlaar NJ, Zeebregts CJ, Wiggers T, Baas PC, van Dam GM. Surgeons lack predictive accuracy for anastomotic leakage in gastrointestinal surgery. Int J Colorectal Dis 2009;24:569–576. doi: 10.1007/s00384-009-0658-6.

31. Seike K, Koda K, Saito N, Oda K, Kosugi C, Shimizu K, et al. Laser Doppler assessment of the influence of division at the root of the inferior mesenteric artery on anastomotic blood flow in rectosigmoid cancer surgery. Int J Colorectal Dis 2007;22:689–697. doi: 10.1007/s00384-006-0221-7.

32. Rutegard M, Hassmen N, Hemmingsson O, Haapamaki MM, Matthiessen P, Rutegard J. Anterior resection for rectal cancer and visceral blood flow: an explorative study. Scand J Surg 2016;105:78–83. doi: 10.1177/1457496915593692.

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