Male gender is associated with an increased risk of anastomotic leak in rectal cancer patients after total mesorectal excision

Chi Zhou†, Xian-rui Wu†, Xuan-hui Liu†, Yu-feng Chen, Jia Ke, Xiao-wen He, Xiao-sheng He, Tuo Hu, Yi-feng Zou, Xiao-bin Zheng, Hua-shan Liu, Jian-cong Hu, Xiao-jian Wu, Jian-ping Wang and Ping Lan*

Department of Colorectal Surgery, the Sixth Affiliated Hospital of Sun Yat-sen University, Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, Guangzhou, Guangdong 510655, China

*Corresponding author. The Sixth Affiliated Hospital, Sun Yat-sen University, 26 Yuancun Erheng Road, Guangzhou, Guangdong 510655, China. Tel: +86–20–38254009; Fax: +86–20–38254166; E-mail: sumslp@163.com
†Chi Zhou, Xian-rui Wu and Xuan-hui Liu contributed equally to this study.

Abstract

Background: The impact of a patient’s gender on the development of anastomotic leak (AL) in rectal cancer patients following total mesorectal excision (TME) remains controversial. The aim of this study was to evaluate the association between patients’ gender and the risk of AL.

Methods: All rectal cancer patients following TME with a primary anastomosis during the study period from 2010 to 2014 were examined. Comparisons of the post-operative AL incidence rate between male and female patients were performed.

Results: Of all patients examined (n = 956), 587 (61.4%) were males and 369 (38.6%) were females. Male patients were more likely to have a history of smoking and drinking alcohol, but less likely to have a history of abdominal surgery compared to female patients. A higher incidence rate of pre-operative bowel obstruction and larger tumor volume in male patients was observed in our study. Of all the patients, 81 (8.5%) developed post-operative AL. More male patients (n = 62, 10.6%) suffered from AL than females (n = 19, 5.1%) (P = 0.003). Multivariate logistic regression analyses confirmed the association between male gender and AL [odds ratio (OR): 2.41, 95% confidence interval (CI): 1.37–4.23, P = 0.002]. Similar results were also obtained in patients who underwent laparoscopic TME (OR: 2.11, 95% CI: 1.15–3.89, P = 0.016).

Conclusions: Male patients were found to have an increased risk for AL following TME with a primary anastomosis. A temporary protecting stoma may help to protect the anastomosis and lessen the risk for AL especially in male patients.

Key words: rectal cancer, anastomotic leak, gender, risk factor, total mesorectal excision, primary anastomosis

Introduction

Colorectal cancer is one of the most common malignancies and rectal cancer comprise 30%, with rising rates in young patients worldwide [1]. Total mesorectal excision (TME) has been adopted as the principal of choice for surgical resections in patients with rectal cancer [2]. Despite its widespread acceptance...
and use, it is technically challenging. Anastomotic leak (AL) remains one of the major complications of TME, affecting post-operative recovery as well as cancer progression. It has been reported that the incidence rate of AL after resections for rectal cancer could be up to 21% [3]. Previous studies have identified a variety of clinical risk factors associated with AL [4–6]. However, the influence of gender on AL remained controversial. Therefore, this study was designed to systematically assess the impact of gender on the AL in rectal cancer patients undergoing TME and a primary anastomosis.

**Patients and methods**

**Patients**

All rectal cancer patients who underwent TME with a primary anastomosis at the Sixth Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) during the study period from January 2010 to October 2014 were included. Demographics, clinicopathological variables and outcomes were all prospectively maintained in the Colorectal Cancer Database. Both paper charts and electronic medical records were carefully reviewed when necessary.

**Inclusion and exclusion criteria**

In order to be included in the study, patients needed to meet all the following inclusion criteria: (i) rectal cancer patients and (ii) patients undergoing TME with a primary anastomosis. The exclusion criteria included: (i) patients with colon cancer, (ii) patients who underwent palliative surgery, (iii) patients without a primary anastomosis and (iv) patients with familiar adenomatous polyposis (FAP) or inflammatory bowel disease (IBD).

**Patient groups**

In this study, patients were divided into two groups based on their gender. In the subgroup analysis, patients were further divided into laparoscopic and open-surgery groups.

**Definition and variables**

Rectal cancer is defined as tumor located less than 15 cm from the anal verge [7]. AL was defined to have occurred within 90 days after the TME surgery when there were: (i) clinical indicators (pain, tenderness, peritonism or purulent/feculent discharge from a drain or the anus), (ii) biochemical or observation abnormalities (pain, tenderness, peritonism or purulent/feculent discharge from a drain or the anus), (iii) radiological evidence (a fluid collection in proximity to an anastomosis that was drained yielding purulent fluid or that contains gas or in contrast leak was shown) and (iv) operative evidence [8,9].

Demographic and clinicopathological variables were defined and analysed as follows: general information, age at the time of surgery, race, smoking (active smoker—consumption of more than seven cigarettes per week for at least 6 months prior to data entry; ex-smoker—cessation of smoking for at least 6 months prior to data entry), alcohol (cessation of drinking for at least 6 months prior to data entry; ex-smoker—cessation of smoking for at least 6 months prior to data entry), concurrent comorbidity (other diseases which are not relative with rectal cancer, such as hypertension, diabetes and so on), history of abdominal surgery, body mass index (BMI), pre-operative total protein (<60 g/L vs ≥60 g/L), pre-operative albumin (<35 g/L vs ≥35 g/L), elevated carcinoembryonic antigen (CEA) (>5 ng/ml), elevated CA19–9 (>37 U/ml), family history of CRC, pre-operative bowel obstruction, distance of tumor from anal verge, tumor diameter, clinical T stage, clinical N stage, pre-operative radiotherapy, pre-operative chemotherapy, operative procedure (Dixon or Parks), laparoscopic surgery, anastomosis (stapled vs handsewn), the need for a temporary stoma, pathological T stage, pathological N stage, pathological M stage, pathological TNM stage, histopathology (adenocarcinoma vs others), differentiation (well vs moderate or poor).

**Statistical analysis**

Descriptive statistics were computed for all variables. These included means and standard deviations (SDs) or medians and interquartile ranges (IQRs) for continuous factors, and frequencies for categorical factors. Comparisons of the distribution of clinic-pathological characteristics between the male and female patients were made by using the two-tailed t-test (or Wilcoxon rank sum test as appropriate) for continuous variables and chi-square test (or the Fisher exact test as appropriate) for categorical variables. Both univariate and multivariate analyses of risk factors associated with post-operative AL were constructed using the logistic regression analysis. P-value less than 0.05 was considered statistically significant.

**Results**

**Patient demographics**

A total of 956 eligible patients were examined, including 587 (61.4%) males and 369 (38.6%) females. Male patients were more likely to have a history of smoking (12.6% vs 0.3%, P < 0.001) and alcohol drinking (6.6% vs 0%, P < 0.001), but less likely to have a history of abdominal surgery (8.3% vs 18.2%, P < 0.001) than their female counterparts (Table 1). A higher proportion of male patients suffered from pre-operative bowel obstruction (11.1% vs 6.0%, P = 0.007). The mean tumor diameter was 4.1 ± 2.3 cm for males versus 3.6 ± 1.8 cm for females (P < 0.001). There was no significant difference in other clinicopathological characteristics between male and female patients.

**Male gender is associated with an increased risk for AL**

Of all the patients, 81 (8.5%) developed post-operative AL, with 62 (10.6%) males and 19 (5.1%) females (P = 0.003). Univariate logistic regression analysis revealed that male gender was significantly associated with a higher risk for the development of post-operative AL, with an odds ratio (OR) of 2.18 [95% confidence interval (CI): 1.28–3.70, P = 0.004] (Table 2). Of the clinic-pathological variables, other potential risk factors for post-operative AL identified by the univariate analysis included smoking (P = 0.049), pre-operative albumin level (P = 0.01), elevated CEA (P = 0.045), distance of tumor from anal verge (P = 0.017), operative procedure (P = 0.028) and the need for a temporary stoma (P = 0.044) (Table 2). The association between male gender and the risk for post-operative AL was further confirmed using the multivariate logistic regression analysis (OR: 2.41, 95% CI: 1.37–4.23, P = 0.004) (Table 3). Of the clinic-pathological variables, other potential risk factors for post-operative AL identified by the univariate analysis included smoking (P = 0.049), pre-operative albumin level (P = 0.01), elevated CEA (P = 0.045), distance of tumor from anal verge (P = 0.017), operative procedure (P = 0.028) and the need for a temporary stoma (P = 0.044) (Table 2). The association between male gender and the risk for post-operative AL was further confirmed using the multivariate logistic regression analysis (OR: 2.41, 95% CI: 1.37–4.23, P = 0.004) (Table 3). Of the clinic-pathological variables, other potential risk factors for post-operative AL identified by the univariate analysis included smoking (P = 0.049), pre-operative albumin level (P = 0.01), elevated CEA (P = 0.045), distance of tumor from anal verge (P = 0.017), operative procedure (P = 0.028) and the need for a temporary stoma (P = 0.044) (Table 2). The association between male gender and the risk for post-operative AL was further confirmed using the multivariate logistic regression analysis (OR: 2.41, 95% CI: 1.37–4.23, P = 0.004) (Table 3). Of the clinic-pathological variables, other potential risk factors for post-operative AL identified by the univariate analysis included smoking (P = 0.049), pre-operative albumin level (P = 0.01), elevated CEA (P = 0.045), distance of tumor from anal verge (P = 0.017), operative procedure (P = 0.028) and the need for a temporary stoma (P = 0.044) (Table 2). The association between male gender and the risk for post-operative AL was further confirmed using the multivariate logistic regression analysis (OR: 2.41, 95% CI: 1.37–4.23, P = 0.004) (Table 3).
significant statistical difference was not reached ($P = 0.41$). In the univariate logistic regression analysis of patients from the laparoscopic group, male patients were shown to suffer from a higher risk for post-operative AL (OR: 2.32, 95% CI: 1.28–4.19, $P = 0.006$). Univariate analysis demonstrated that smoking ($P = 0.046$), clinical N stage ($P = 0.03$) and operative procedure ($P = 0.02$) were also significantly associated with the development of post-operative AL (Table 4). The association between male gender and the risk for post-operative AL after laparoscopic TME was further identified by the multivariate logistic

### Table 1. Patient characteristics

| Characteristic                              | All cases (n = 956) | Male patients (n = 587) | Female patients (n = 369) | P-value     |
|--------------------------------------------|---------------------|-------------------------|---------------------------|-------------|
| Age at the time of surgery, years          | 59.3 ± 13.4         | 59.1 ± 13.2             | 59.5 ± 13.6               | 0.69        |
| Race, n (%)                                |                     |                         |                           | 1.0         |
| Han                                        | 953 (99.7)          | 585 (99.7)              | 368 (99.7)                |             |
| Others                                     | 3 (0.3)             | 2 (0.3)                 | 1 (0.3)                   |             |
| Smoking, n (%)                             |                     |                         |                           | <0.001      |
| Non                                        | 881 (92.2)          | 513 (87.4)              | 368 (99.7)                |             |
| Ex or active                               | 75 (7.8)            | 74 (12.6)               | 1 (0.3)                   |             |
| Alcohol, n (%)                             |                     |                         |                           | <0.001      |
| None                                       | 917 (95.9)          | 548 (93.4)              | 369 (100)                 |             |
| Ex or active                               | 39 (4.1)            | 39 (6.6)                | 0 (0.0)                   |             |
| Concurrent comorbidity, n (%)              | 268 (28.0)          | 159 (27.1)              | 109 (29.5)                | 0.41        |
| History of abdominal surgery, n (%)        | 116 (12.1)          | 49 (8.3)                | 67 (18.2)                 | <0.001      |
| Body mass index, kg/m²                      | 22.6 ± 3.3          | 22.7 ± 3.1              | 22.6 ± 3.6                | 0.72        |
| Pre-operative total protein <60 g/L, n (%)  | 69 (7.2)            | 45 (7.7)                | 24 (6.5)                  | 0.5         |
| Pre-operative albumin <35 g/L, n (%)       | 31 (3.2)            | 16 (2.7)                | 15 (4.1)                  | 0.25        |
| Elevated CEA (>$5$ ng/ml), n (%)           | 230 (24.1)          | 141 (24.5)              | 89 (24.8)                 | 0.93        |
| Elevated CA19–9 (>37 U/ml), n (%)          | 105 (11.0)          | 57 (9.9)                | 48 (13.4)                 | 0.11        |
| Body mass index, kg/m²                      | 22.6 ± 3.3          | 22.7 ± 3.1              | 22.6 ± 3.6                | 0.72        |
| Elevated CEA (>$5$ ng/ml), n (%)           | 230 (24.1)          | 141 (24.5)              | 89 (24.8)                 | 0.93        |
| Elevated CA19–9 (>37 U/ml), n (%)          | 105 (11.0)          | 57 (9.9)                | 48 (13.4)                 | 0.11        |
| Body mass index, kg/m²                      | 22.6 ± 3.3          | 22.7 ± 3.1              | 22.6 ± 3.6                | 0.72        |
| Elevated CEA (>$5$ ng/ml), n (%)           | 230 (24.1)          | 141 (24.5)              | 89 (24.8)                 | 0.93        |
| Elevated CA19–9 (>37 U/ml), n (%)          | 105 (11.0)          | 57 (9.9)                | 48 (13.4)                 | 0.11        |
| Body mass index, kg/m²                      | 22.6 ± 3.3          | 22.7 ± 3.1              | 22.6 ± 3.6                | 0.72        |
| Elevated CEA (>$5$ ng/ml), n (%)           | 230 (24.1)          | 141 (24.5)              | 89 (24.8)                 | 0.93        |
| Elevated CA19–9 (>37 U/ml), n (%)          | 105 (11.0)          | 57 (9.9)                | 48 (13.4)                 | 0.11        |
| Body mass index, kg/m²                      | 22.6 ± 3.3          | 22.7 ± 3.1              | 22.6 ± 3.6                | 0.72        |
| Elevated CEA (>$5$ ng/ml), n (%)           | 230 (24.1)          | 141 (24.5)              | 89 (24.8)                 | 0.93        |
| Elevated CA19–9 (>37 U/ml), n (%)          | 105 (11.0)          | 57 (9.9)                | 48 (13.4)                 | 0.11        |
| Body mass index, kg/m²                      | 22.6 ± 3.3          | 22.7 ± 3.1              | 22.6 ± 3.6                | 0.72        |
| Elevated CEA (>$5$ ng/ml), n (%)           | 230 (24.1)          | 141 (24.5)              | 89 (24.8)                 | 0.93        |
| Elevated CA19–9 (>37 U/ml), n (%)          | 105 (11.0)          | 57 (9.9)                | 48 (13.4)                 | 0.11        |
| Body mass index, kg/m²                      | 22.6 ± 3.3          | 22.7 ± 3.1              | 22.6 ± 3.6                | 0.72        |
| Elevated CEA (>$5$ ng/ml), n (%)           | 230 (24.1)          | 141 (24.5)              | 89 (24.8)                 | 0.93        |
| Elevated CA19–9 (>37 U/ml), n (%)          | 105 (11.0)          | 57 (9.9)                | 48 (13.4)                 | 0.11        |
| Body mass index, kg/m²                      | 22.6 ± 3.3          | 22.7 ± 3.1              | 22.6 ± 3.6                | 0.72        |
| Elevated CEA (>$5$ ng/ml), n (%)           | 230 (24.1)          | 141 (24.5)              | 89 (24.8)                 | 0.93        |
| Elevated CA19–9 (>37 U/ml), n (%)          | 105 (11.0)          | 57 (9.9)                | 48 (13.4)                 | 0.11        |
| Body mass index, kg/m²                      | 22.6 ± 3.3          | 22.7 ± 3.1              | 22.6 ± 3.6                | 0.72        |
| Elevated CEA (>$5$ ng/ml), n (%)           | 230 (24.1)          | 141 (24.5)              | 89 (24.8)                 | 0.93        |
| Elevated CA19–9 (>37 U/ml), n (%)          | 105 (11.0)          | 57 (9.9)                | 48 (13.4)                 | 0.11        |
| Body mass index, kg/m²                      | 22.6 ± 3.3          | 22.7 ± 3.1              | 22.6 ± 3.6                | 0.72        |
| Elevated CEA (>$5$ ng/ml), n (%)           | 230 (24.1)          | 141 (24.5)              | 89 (24.8)                 | 0.93        |
| Elevated CA19–9 (>37 U/ml), n (%)          | 105 (11.0)          | 57 (9.9)                | 48 (13.4)                 | 0.11        |
| Body mass index, kg/m²                      | 22.6 ± 3.3          | 22.7 ± 3.1              | 22.6 ± 3.6                | 0.72        |
| Elevated CEA (>$5$ ng/ml), n (%)           | 230 (24.1)          | 141 (24.5)              | 89 (24.8)                 | 0.93        |
| Elevated CA19–9 (>37 U/ml), n (%)          | 105 (11.0)          | 57 (9.9)                | 48 (13.4)                 | 0.11        |
| Body mass index, kg/m²                      | 22.6 ± 3.3          | 22.7 ± 3.1              | 22.6 ± 3.6                | 0.72        |
| Elevated CEA (>$5$ ng/ml), n (%)           | 230 (24.1)          | 141 (24.5)              | 89 (24.8)                 | 0.93        |
| Elevated CA19–9 (>37 U/ml), n (%)          | 105 (11.0)          | 57 (9.9)                | 48 (13.4)                 | 0.11        |
Furthermore, previous studies also suggested that rectal cancer patients with AL had a greater likelihood of developing post-operative local recurrence, thus affecting patients’ long-term survival [13,14]. Therefore, it is important for colorectal surgeons to identify rectal cancer patients who are at a high risk for post-operative AL, facilitating the implementation of prophylactic maneuvers when necessary.

A good number of risk factors associated with the risk for the development of post-operative AL in rectal cancer patients were proposed, such as pre-operative radiation, tumor location, malnutrition, non-specialized surgeons and diabetes mellitus [15–18]. The impact of patient’s gender on post-operative AL has also been demonstrated; however, it remains controversial [19–22]. The possible reasons for the inconsistent results included: enrollment of both colon cancer and rectal cancer patients and post-operative AL was assessed as a secondary outcome. Therefore, we designed this study to systematically evaluate the association between patient’s gender and the risk for post-operative AL in a large cohort of 956 patients.

Of all the patients examined, 81 (8.5%) rectal cancer patients were identified to suffer from post-operative AL in this study—a frequency that was consistent with the reported rates ranging from 3% to 21% [10,23–30]. As expected, male patients were more likely to have a history of smoking and alcohol drinking. However, males were less likely to have a history of abdominal surgery than females. This might have resulted from the fact that a significant proportion of females underwent Caesarean section before the diagnosis of rectal cancer. A higher incidence of pre-operative bowel obstruction in male patients was observed in our study, which was at least partly explained by the notion that male patients examined in our study had larger tumors.

The major finding of this study was that male gender was shown to be a significant risk factor associated with post-operative AL in rectal cancer patients after TME. This was consistent with our observations in the clinical practice at our hospital. Similar results was also demonstrated in a previous study from our group, which showed that male patients had an increased risk for the chronic pouchitis as well as ileal pouch sinus following the construction of ileal pouch-anal anastomosis [31]. As explained in the previous study, one possible reason for this difference is that a narrower pelvis in males makes the surgical procedure, particularly the creation of an anastomosis, technically more challenging than in females. Furthermore, in the subgroup analyses of patients who underwent laparoscopic surgery, the association between patients’ gender and the risk of post-operative AL were also identified using both univariate and multivariate analyses. For the patients who underwent an

### Table 2. Univariate analysis of risk factors associated with anastomotic leak in rectal cancer patients who underwent total mesorectal excision with a primary anastomosis

| Characteristics | Odds ratio (95% confidence interval) | P-value |
|-----------------|--------------------------------------|---------|
| Age at the time of surgery, every 1-year increase | 1.00 (0.98–1.01) | 0.62 |
| Gender (male vs female) | 2.18 (1.28–3.70) | 0.004 |
| Race (others vs Han) | 2.34 (0.70–7.80) | 0.17 |
| Smoking (ever vs never) | 1.99 (1.01–3.95) | 0.049 |
| Alcohol (ever vs never) | 0.57 (0.14–2.42) | 0.45 |
| Significant comorbidities (yes vs no) | 1.48 (0.92–2.39) | 0.11 |
| History of abdominal surgery (yes vs no) | 0.90 (0.44–1.85) | 0.77 |
| Body mass index, every 1-kg/m² increase | 1.04 (0.98–1.12) | 0.22 |
| Pre-operative albumin <60 g/L (yes vs no) | 1.72 (0.82–3.60) | 0.15 |
| Pre-operative albumin <35 g/L (yes vs no) | 3.39 (1.41–8.13) | 0.01 |
| Elevated CEA (yes vs no) | 3.10 (1.01–2.75) | 0.045 |
| Elevated CA19–9 (yes vs no) | 1.22 (0.61–2.44) | 0.58 |
| Bowel obstruction (yes vs no) | 1.11 (0.51–2.38) | 0.80 |
| Clinical N stage (cN1/2 vs cN0) | 1.42 (0.90–2.25) | 0.13 |
| Pathological T stage (pT3/4 vs pT0/1) | 0.97 (0.56–1.69) | 0.91 |
| Pathological N stage (pN1/2 vs pN0) | 1.55 (0.96–2.52) | 0.074 |
| Pathological TNM stage (pTNM3/4 vs pTNM0/1/2) | 1.47 (0.80–2.70) | 0.22 |
| Pathological TN stage (pT1/2 vs pT0) | 1.07 (0.66–1.76) | 0.78 |
| Operative procedure (Parks vs Dixon) | 1.83 (1.07–3.13) | 0.028 |
| Laparoscopic surgery (yes vs no) | 1.04 (0.57–1.90) | 0.90 |
| Anastomosis (stapled vs handsewn) | 0.78 (0.30–2.02) | 0.60 |
| The need for a temporary stoma (yes vs no) | 1.60 (1.01–2.52) | 0.044 |
| Pathological T stage (pT3/4 vs pT0/1/2) | 0.94 (0.58–1.51) | 0.78 |
| Pathological N stage (pN1/2 vs pN0) | 1.42 (0.90–2.25) | 0.13 |
| Pathological M stage (pM1 vs pM0) | 0.79 (0.35–1.76) | 0.56 |
| Pathological TNM stage (pTNM3/4 vs pTNM0/1/2) | 1.38 (0.87–2.18) | 0.17 |
| Histopathology (others vs adenocarcinoma) | 1.11 (0.53–2.29) | 0.79 |
| Differentiation (moderate/poor vs well) | 1.43 (0.84–2.43) | 0.19 |

regression analysis after adjusting for clinical N stage and operative procedure, with an OR of 2.11 (OR: 95% CI: 1.15–3.89, P = 0.016) (Table 5).

### Discussion

AL was a major post-operative complication in rectal cancer patients after surgical resection, the occurrence of which was found to be associated with a poorer quality of life (QOL) [10–12]. Furthermore, previous studies also suggested that rectal cancer patients with AL had a greater likelihood of developing post-operative local recurrence, thus affecting patients’ long-term survival [13,14].
Table 4. Univariate analysis of risk factors associated with anastomotic leak in rectal cancer patients who underwent laparoscopic total mesorectal excision with a primary anastomosis

| Characteristics                                      | Odds ratio (95% confidence interval) | P-value |
|------------------------------------------------------|--------------------------------------|---------|
| Age at the time of surgery, every 1-year increase     | 0.99 (0.97–1.01)                     | 0.34    |
| Gender (male vs female)                               | 2.32 (1.28–4.19)                     | 0.006   |
| Smoking (ever vs never)                               | 2.17 (1.01–4.64)                     | 0.046   |
| Alcohol (ever vs never)                               | 0.39 (0.05–2.91)                     | 0.36    |
| Significant comorbidities (yes vs no)                | 1.29 (0.75–2.02)                     | 0.36    |
| History of abdominal surgery (yes vs no)             | 0.87 (0.39–1.97)                     | 0.74    |
| Body mass index, every 1-kg/m² increase               | 1.06 (0.99–1.13)                     | 0.10    |
| Pre-operative total protein <60 g/L (yes vs no)       | 1.33 (0.55–3.23)                     | 0.53    |
| Pre-operative albumin <35 g/L (yes vs no)            | 1.96 (0.56–6.86)                     | 0.29    |
| Elevated CEA (yes vs no)                              | 1.72 (0.99–3.00)                     | 0.054   |
| Elevated CA19-9 (yes vs no)                           | 1.32 (0.61–2.89)                     | 0.48    |
| Bowel obstruction (yes vs no)                         | 1.47 (0.64–3.37)                     | 0.37    |
| Distance of tumor from anal verge, every 1-cm increase| 0.93 (0.85–1.01)                     | 0.065   |
| Tumor diameter, every 1-cm increase                   | 1.06 (0.96–1.17)                     | 0.22    |
| Clinical T stage (cT3/4 vs cT1/2)                     | 0.99 (0.55–1.80)                     | 0.98    |
| Clinical N stage (cN1/2 vs cN0)                       | 1.81 (1.06–3.07)                     | 0.03    |
| Pre-operative radiotherapy (yes vs no)                | 1.26 (0.64–2.49)                     | 0.51    |
| Pre-operative chemotherapy (yes vs no)                | 1.05 (0.62–1.80)                     | 0.85    |
| Operative procedure (Parks vs Dixon)                  | 1.96 (1.11–3.45)                     | 0.02    |
| Anastomosis (stapled vs handsewn)                     | 1.21 (0.36–4.01)                     | 0.76    |
| The need for a temporary stoma (yes vs no)            | 1.51 (0.91–2.49)                     | 0.11    |
| Pathological T stage (pT3/4 vs pT0/1/2)               | 0.95 (0.57–1.60)                     | 0.86    |
| Pathological N stage (pN1/2 vs pN0)                   | 1.62 (0.98–2.68)                     | 0.062   |
| Pathological M stage (pM1 vs pM0)                     | 0.82 (0.34–1.96)                     | 0.66    |
| Pathological TNM, stage (pTNM3/4 vs pTNM0/1/2)       | 1.57 (0.95–2.59)                     | 0.080   |
| Histopathology (others vs adenocarcinoma)             | 0.86 (0.36–2.06)                     | 0.73    |
| Differentiation (moderate/poor vs well)               | 1.43 (0.81–2.53)                     | 0.21    |

Table 5. Multivariate analysis of risk factors associated with anastomotic leak in rectal cancer patients who underwent laparoscopic total mesorectal excision with a primary anastomosis

| Characteristics                                      | Odds ratio (95% confidence interval) | P-value |
|------------------------------------------------------|--------------------------------------|---------|
| Gender (male vs female)                               | 2.11 (1.15–3.89)                     | 0.016   |
| Clinical N stage (cN1/2 vs cN0)                       | 2.02 (1.17–3.48)                     | 0.012   |
| Operative procedure (Parks vs Dixon)                  | 2.29 (1.25–4.20)                     | 0.007   |

Conclusion
Among all of the rectal cancer patients operated on at our hospital, male patients undergoing TME with a primary anastomosis were found to have an increased risk for the post-operative AL. This finding indicated that a temporary protecting stoma...
should be under consideration when the construction of an anastomosis is less than satisfactory, especially if the patient’s gender is male.

**Acknowledgements**

Ethics approval and consent to participate: this cohort study was carried on in accordance with the precepts of the Helsinki Declaration and approved by the Institutional Review Board (IRB) of the Sixth Affiliated Hospital of Sun Yat-sen University. We obtained consent for publication from the patients. This work was supported by National Natural Science Foundation of China (No. 81400603), Guangdong Natural Science Foundation (No. 2015A030310190) and Science and Technology Planning Project of Guangdong Province (No. 2015B020229001).

**Conflict of interest statement:** none declared.

**References**

1. Chen W, Zheng R, Baade PD et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115–32.
2. Chew MH, Yeh YT, Lim E et al. Pelvic autonomic nerve preservation in radical rectal cancer surgery: changes in the past 3 decades. Gastroenterol Rep (Oxf) 2016;4:173–85.
3. Liu Y, Wen X, Wang G et al. A scoring system to predict the risk of anastomotic leakage after anterior resection for rectal cancer. J Surg Oncol 2014;109:122–5.
4. Law WI, Chu KW, Ho JW et al. Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. Am J Surg 2000;179:92–6.
5. Jestin P, Pahlman L, Gunnarsson U. Risk factors for anastomotic leakage after rectal cancer surgery: a case-control study. Colorectal Dis 2008;10:715–21.
6. Janasch O, Klinkes T, Otto R et al. Risk factors, short and long term outcome of anastomotic leaks in rectal cancer. Oncotarget 2015;6:36884–93.
7. van der Pas MH, Haglund E, Cuesta MA et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 2013;14:210–18.
8. Kulu Y, Ulrich A, Bruckner T et al. Validation of the International Study Group of Rectal Cancer Definition and severity grading of anastomotic leakage. Surgery 2013;153:753–61.
9. Rahbani NN, Weitz J, Hohenberger W 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 2010;147:339–51.
10. Brown SR, Mathew R, Keding A et al. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. Ann Surg 2014;259:916–23.
11. Eberhardt JM, Kiran RP, Laverty IC. The impact of anastomotic leak and intra-abdominal abscess on cancer-related outcomes after resection for colorectal cancer: a case control study. Dis Colon Rectum 2009;52:380–6.
12. Nachiappan S, Askari A, Maliertzis G et al. The impact of anastomotic leak and its treatment on cancer recurrence and following elective colorectal cancer resection. World J Surg 2015;39:1052–8.
13. den Dulk M, Marijnca NA, Collette L et al. Multicentre analysis of oncological and survival outcomes following anastomotic leakage after rectal cancer surgery. Br J Surg 2009;96:1066–75.
14. Penninckx F. Anastomotic leakage: a disaster or a challenge with an impact on survival after rectal cancer surgery? Colorectal Dis 2011;13:237–8.
15. McDermott FD, Heaney A, Kelly ME et al. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg 2015;102:462–79.
16. Kang CY, Halabi WJ, Chaudhry OO et al. Risk factors for anastomotic leakage after anterior resection for rectal cancer. JAMA Surg 2013;148:85–71.
17. Cong ZJ, Fu CG, Yu ED et al. [Factors associated with anastomotic leakage after anterior resection in rectal cancer]. Zhonghua Wai Ke Za Zhi 2009;47:594–9.
18. Rullier E, Laurent C, Garrelon JL et al. Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 1998;85:355–8.
19. Kang J, Lee HB, Cha JH et al. Feasibility and impact on surgical outcomes of modified double-stapling technique for patients undergoing laparoscopic anterior resection. J Gastrointest Surg 2013;17:771–5.
20. Dauser B, Braunschmid T, Ghaifari S et al. Anastomotic leakage after low anterior resection for rectal cancer: comparison of stapled versus compression anastomosis. Langenbecks Arch Surg 2013;389:957–64.
21. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. Ann Surg 2004;240:260–8.
22. Kawada K, Hasegawa S, Hida K et al. Risk factors for anastomotic leakage after laparoscopic low anterior resection with DST anastomosis. Surg Endosc 2014;28:2988–95.
23. Buchs NC, Gervaz P, Secic M et al. Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study. Int J Colorectal Dis 2008;23:265–70.
24. Damen N, Spilsbury K, Levitt M et al. Anastomotic leaks in colorectal surgery. ANZ J Surg 2014;84:763–8.
25. Eriksen MT, Wibe A, Norstein J et al. Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. Colorectal Dis 2005;7:51–7.
26. Hyman N, Manchester TL, Oesler T et al. Anastomotic leaks after intestinal anastomosis: it’s later than you think. Ann Surg 2007;245:254–8.
27. Matthiessen P, Hallbook O, Andersson M et al. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 2004;6:462–9.
28. Nesbakken A, Nygaard K, Lunde OC et al. Anastomotic leak following mesorectal excision for rectal cancer: true incidence and diagnostic challenges. Colorectal Dis 2005;7:576–81.
29. Yeh CY, Changchien CR, Wang JY et al. 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.
30. Brown SR, Mathew R, Keding A et al. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. Ann Surg 2014;259:916–23.
34. Telem DA, Chin EH, Nguyen SQ et al. Risk factors for anastomotic leak following colorectal surgery: a case-control study. *Arch Surg* 2010;145:371–6.

35. Novis BH, Gluck E, Thomas P et al. Serial levels of CA 19–9 and CEA in colonic cancer. *J Clin Oncol* 1986;4:987–93.

36. Ganguly A, Yeltsin E, Robbins J. Identification of a carcinoembryonic antigen binding protein on monocytes. *Biochem Biophys Res Commun* 2003;2:319–23.

37. Bosmans JW, Jongen AC, Bouvy ND et al. Colorectal anastomotic healing: why the biological processes that lead to anastomotic leakage should be revealed prior to conducting intervention studies. *BMC Gastroenterol* 2015;15:180.

38. Qu H, Liu Y, Bi DS. Clinical risk factors for anastomotic leakage after laparoscopic anterior resection for rectal cancer: a systematic review and meta-analysis. *Surg Endosc* 2015;29:3608–17.

39. Choi DH, Hwang JK, Ko YT et al. Risk factors for anastomotic leakage after laparoscopic rectal resection. *J Korean Soc Coloproctol* 2010;26:265–73.

40. Smith JD, Paty PB, Guillem JG et al. Anastomotic leak is not associated with oncologic outcome in patients undergoing low anterior resection for rectal cancer. *Ann Surg* 2012;256:1034–8.

41. Yeo HL, Abelson JS, Mao J et al. Surgeon annual and cumulative volumes predict early postoperative outcomes after rectal cancer resection. *Ann Surg* 2017;265:151–7.

42. Kim CN, Bae SU, Lee SG et al. Clinical and oncologic outcomes of totally robotic total mesorectal excision for rectal cancer: initial results in a center for minimally invasive surgery. *Int J Colorectal Dis* 2016;31:843–52.