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ORIGINAL ARTICLE

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

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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 patents 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

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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 (fever, tachycardia or increased white cell count), (iii) radiological evidence (a fluid collection in proximity to an anastomosis that was drained yielding purulent fluid or that contains gas or if 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 the 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), 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%, $P = .007$). 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, $P = 0.002$) after adjusting for pre-operative albumin level, elevated CEA and distance of tumor from anal verge (Table 3).

Male gender is associated with an increased risk for AL after laparoscopic TME

Of the 956 eligible rectal cancer patients undergoing TME, 170 (17.8%) underwent an open procedure and 786 (82.2%) underwent a laparoscopic procedure. There was a trend that male patients (9.6%) were more likely to suffer from post-operative AL than female patients (6.1%) after open TME; however, a

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
None	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/m^2	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
Family history of colorectal cancer, *n* (%)	21 (2.2)	15 (2.6)	6 (1.6)	0.34
Bowel obstruction, *n* (%)	87 (9.1)	65 (11.1)	22 (6.0)	0.007
Distance of tumor from anal verge, cm	8.1 ± 3.3	8.2 ± 3.2	7.9 ± 3.3	0.33
Tumor diameter, cm	3.9 ± 2.2	4.1 ± 2.3	3.6 ± 1.8	<0.001
Pre-operative radiotherapy, *n* (%)	123 (12.9)	81 (13.8)	42 (11.4)	0.28
Pre-operative chemotherapy, *n* (%)	327 (34.2)	182 (20.7)	145 (21.3)	0.78
Operative procedure, *n* (%)				0.73
Dixon	803 (84.0)	495 (84.3)	308 (83.5)	
Parks	153 (16.0)	92 (15.7)	61 (16.5)	
Laparoscopic surgery, *n* (%)	786 (82.2)	483 (82.3)	303 (82.1)	0.95
Anastomosis				0.46
Stapled	906 (95.0)	558 (95.4)	348 (94.3)	
Handsewn	48 (5.0)	27 (4.6)	21 (5.7)	
The need for a temporary stoma, *n* (%)	383 (40.1)	246 (41.9)	137 (37.1)	0.14
Histopathology, *n* (%)				0.55
Adenocarcinoma	856 (89.6)	528 (90.1)	328 (88.9)	
Others	99 (10.4)	58 (9.9)	41 (11.1)	
Differentiation, *n* (%)				0.41
Well	316 (36.9)	189 (35.8)	127 (38.6)	
Moderate or poor	541 (63.1)	339 (64.2)	202 (61.4)	
Clinical T stage, *n* (%)				0.53
cT1/2	192 (23.5)	116 (22.7)	76 (24.7)	
cT3/4	626 (76.5)	394 (77.3)	232 (75.3)	
Clinical N stage, *n* (%)				0.84
cN0	406 (49.9)	251 (49.6)	155 (50.3)	
cN1/2	408 (50.1)	255 (50.4)	153 (49.7)	
Pathological T stage, *n* (%)				0.21
pT0/1/2	329 (34.4)	193 (32.9)	136 (36.9)	
pT3/4	627 (65.6)	394 (67.1)	233 (63.1)	
Pathological N stage, *n* (%)				0.15
pN0	605 (63.3)	382 (65.1)	223 (60.4)	
pN1/2	351 (36.7)	205 (34.9)	146 (39.6)	
Pathological M stage, *n* (%)				0.13
pM0	855 (89.4)	518 (88.2)	337 (91.3)	
pM1	101 (10.6)	69 (11.8)	32 (8.7)	
Pathological TNM stage, *n* (%)				0.32
pTNM0/1/2	576 (60.3)	361 (61.5)	215 (58.3)	
pTNM3/4	380 (39.7)	226 (38.5)	154 (41.7)	

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 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/m^2 increase	1.04 (0.98–1.12)	0.22
Pre-operative total protein <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)	1.67 (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
Distance of tumor from anal verge, every 1-cm increase	0.91 (0.85–0.98)	0.017
Tumor diameter, every 1-cm increase	1.04 (0.94–1.14)	0.47
Clinical T stage (cT3/4 vs cT1/2)	0.97 (0.56–1.69)	0.91
Clinical N stage (cN1/2 vs cN0)	1.55 (0.96–2.52)	0.074
Pre-operative radiotherapy (yes vs no)	1.47 (0.80–2.70)	0.22
Pre-operative chemotherapy (yes vs no)	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

Table 3. Multivariate 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
Gender (male vs female)	2.41 (1.37–4.23)	0.002
Pre-operative albumin <35 g/L (yes vs no)	2.75 (0.98–7.66)	0.054
Elevated CEA (yes vs no)	1.79 (1.07–2.97)	0.026
Distance of tumor from anal verge, every 1-cm increase	0.90 (0.83–0.97)	0.009

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]. 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 rate 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 patents 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 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 (0.75–2.20)	0.36
History of abdominal surgery (yes vs no)	0.87 (0.39–1.97)	0.74
Body mass index, every 1-kg/m^2 increase	1.06 (0.99–1.15)	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

open TME, male patients also tended to suffer from an increased risk of post-operative AL than their female counterparts, although the difference was not able to reach a statistical difference, which might be due to the small number of examined patients ($n = 170$).

A low pre-operative albumin level exerted an adverse effect on tissue healing through affecting processes such as collagen and mucopolysaccharides synthesis and fibroblast proliferation [32]. Several studies have reported that the pre-operative albumin level was an independent predictor for post-operative AL [33,34]. In the current study, hypoalbuminemia was found to be a risk factor for AL in univariate analysis but failed to reach statistical difference in multivariate analysis, possibly because our sample size was not large enough to identify the difference.

CEA is an glycoprotein found in the apical surface of mature enterocytes and is overproduced by gastrointestinal cancer cells and therefore widely used as a tumor marker for adenocarcinomas, particularly colorectal cancer [35]. Beyond the function as tumor marker, several studies have reported the relationship between CEA and inflammation. CEA can stimulate macrophages or monocytes to promote the production of pro-inflammatory cytokines, such as TNF-α, IL-1b and IL-6 [36]. In our study, we found that elevated CEA was a risk factor for AL, possibly because the elevation of CEA could promote local post-operative inflammatory disorders and therefore be attributed to the occurrence of AL, as inflammation is involved in the pathophysiology of AL [37].

The location of anastomosis was another well-known risk factor for post-operative complications. The incidence of post-operative AL for rectal cancer patients with an anastomotic level less than 5 cm was reported as high as 19.1% versus 2.3% for those whose anastomosis was above 5 cm [38,39]. In the present register in which the tumor location was recorded, our results, which are similar to those of other studies, showed that the distance of the tumor from the anal verge was associated with a higher risk of post-operative AL [40].

The findings of the current study have several clinical implications. Although the predictors for post-operative AL have been previously evaluated [3], this study identified male gender as an important risk factor associated with AL due to the availability of a large number of patients examined in our hospital. This information is valuable to patients as well as colorectal surgeons, as it may help to refine the risk calculation of post-operative complications after surgical treatment in rectal cancer patients.

There are limitations to our study, particularly relating to the study design. The results of this study should be carefully evaluated due to the inherited shortcomings of a retrospective study. Post-operative outcomes might be influenced by the surgeon's techniques [41,42]. However, the limitations have been minimized in our study, since all the cases examined were operated by experienced surgeons who were trained under the same program.

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.

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