RESEARCH ARTICLE

Risk Assessment on Anastomotic Leakage after Rectal Cancer Surgery: An Analysis of 753 Patients

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Abstract

Purpose: To investigate the risk factors for anastomotic leakage (AL) after anterior resection for rectal cancer with a double stapling technique. Patients and Methods: Between January 2004 and December 2011, 753 consecutive patients in Jiangsu Cancer Hospital and Research Institute diagnosed with rectal cancer and undergoing anterior resection with a double stapling technique were recruited. All patients experienced a total mesorectal excision (TME) operation. Additionally, decrease of postoperative tumor supplied group of factors (TSGF), which have not been reported before, was proposed as a new indicator for AL. Univariate and multivariate analysis were performed to determine risk factors for AL. Results: AL was detected in 57 (7.6%) of 753 patients with rectal cancer. The diagnosis of anastomotic leakage was confirmed between the 6th and 12th postoperative day (POD; mean 8th POD). After univariate analysis and multivariate analysis, age ($p<0.001$), gender ($p=0.002$), level of anastomosis ($p < 0.001$), preoperative body mass index (BMI) ($p = 0.001$) and reduction of TSGF in 5th POD was less than 10 μ/ml ($p < 0.001$) were selected as 5 independent risk factors for AL. It was also indicated that a temporary defunctioning transverse ileostomy ($p = 0.04$) would decrease the occurrence of AL. Conclusion: AL after anterior resection for rectal carcinoma is related to elderly status, low level site of the tumor (below the peritoneal reflection), being male, preoperative BMI and the decrease of TSGF in 5th POD is less than 10 μ/ml. Preventive ileostomy is advisable after TME for low rectal tumors to prevent AL.

Keywords: Rectal cancer - anastomotic leakage - tumor supplied group of factors - anterior resection

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Introduction

It has been found that colorectal cancer (CRC) is the third commonest cancer in males and the second in females. In 2008, more over 1.2 million new CRC cases and 608.700 deaths were reckoned to be occurred (Ahmedin et al., 2011). With the advent of stapling devices, surgical operation combining with preoperative chemo-radiation therapy (PCRT) and by means of total preventive ileostomy rate of anal sphincter preservation in present days (Tjandra et al., 2005). Nevertheless, patients with rectal cancer undergoing anterior resection can develop various postoperative complications. It is quite obvious that AL is the severest and most morbid complication.

Anastomotic leak after rectal cancer surgery has been reported to range between 5% and 25% of patients (Mileski et al., 1988; Fazio et al., 2007; Veenhof et al., 2007). Not only, the instant clinical consequences, but also AL carries long-term outcome, such as intra pelvic infection, peritonitis, sepsis, longer hospital stay, considerable extra cost, increased in-hospital morbidity and mortality, impaired pelvic organ function (Eriksen et al., 2005; Lee et al., 2008; Law et al., 2007; Riss et al., 2011).

Many studies on anterior resections regarding AL come from multi-center and different surgeons. A variety of factors predisposing to AL have been reported in the previous investigations. However, lack of data about the risk factors and incidence associated with AL from a single-institute of one team of doctors. In addition, risk factors in previous reports have been inconsistent because of the limited power of studies. The reduction of TSGF in POD 5 was adopted in this study for a risk factor that had been proposed as the indicator of both the diagnosis and prognosis for some common malignant tumors, especially for colorectal cancers in recent years (Yang et al., 2009; Bünger et al., 2011; Deng et al., 2011; Zhou et al., 2012). The main objective of the current study was to analyze the incidence of AL and risk factors included some new indicators that they have not be reported in a large population database from a single-institute in less than one decade.

Materials and Methods

Between January 2004 and December 2011, 735 consecutive patients with rectal cancer underwent anterior resection with double stapling anastomosis for primary rectal cancer at the Colorectal & Anal

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Department of Jiangsu Cancer Hospital affiliated with Nanjing Medical University, Nanjing, China. The medical notes of all patients were reviewed in detail. Eligibility criteria included rectal cancer, phrase I to III of TNM stage, histologically proven adenocarcinoma, open and laparoscopic surgery with pelvic drainage, and antibiotics using for 7 PODs. Exclusion criteria were as follows: Hartmann's procedure, phrase IV of TNM stage, colon cancer, hand-sewn anastomosis. Rectal cancer was classified according to the distance from the anal verge, as determined by rigid sigmoidoscopy. Total mesorectal excision was adopted as the standard surgical technique according to tumor location. The Ethics Committee of Science approved data collection in the register.

Various independent clinical variables were analysed. Patient age (<65 and ≥65 years) was valuated as a continuous and categorical variable. Gender, physical status (ASA ≤2 or ≥3), tumor site (<4 or ≥4 cm from the anal verge), TNM stage, operation duration (<4h or ≥4h), the level of hemoglobin in 5th POD (<70 or ≥70 g/l), the value of serum albumin in 5th POD (<30 or ≥30 g/l), preoperative BMI (<35 or ≥35), preventive ileostomy, open or laparoscopic surgery, administration of NSAID and glucocorticoid in early PODs, diabetes mellitus (DM) and neoadjuvant chemoradiotherapy were evaluated as categorical variables. Neoadjuvant therapy was defined as a regimen of oral chemotherapy (carmofur or capecitabine) combined with radiotherapy (45 Gy). The reduction of TSGF in 5th POD (<10 u/ml or ≥10 u/ml) was evaluated as a categorical variable. TSGF expression levels were determined using a biochemical assay kit, according to the manufacturer's protocol (New Continent Biochemical Technology, Fujian, China). The alcohol abuse was analysed as categorical variable (≤2 or ≥3 glasses per day). The tobacco abuse was evaluated as categorical variable (≤4 or ≥5 cigarettes per day). The relative decrease in systolic and diastolic blood pressure from baseline values (preoperative measurements) during the operation (Intraoperative blood pressure) were evaluated as categorical (>25% and >40%) variables.

The patient was placed in a modified lithotomy, right side down, Trendelenburg position. For patients undergoing laparoscopic surgery, an initial 12-mm port placement was carried out using the open technique, and pneumoperitoneum was accomplished using carbon dioxide. A standard 10-mm laparoscope was inserted through the 12-mm trocar, and then two 5-mm ports were inserted in the upper right and left abdominal quadrants and two more 12-mm ports were placed in the lower right and left abdominal quadrants under laparoscopic guidance. For patients undergoing open surgery, a median incision in lower abdomen was made to expose surgical field.

Clinical anastomotic leakage was defined as the presence of leakage signs and confirmed by diagnostic work-up; consequently, additional surgical treatment was mandatory. All patients diagnosed with AL in present study were defined as the presence of leakage signs (pelvic abscess, fecal or purulent discharge from a drainage tube or wound, peritonitis) and confirmed by radiographic work-up or by operative findings between the 6th and 12th POD (mean 8th POD). The AL in this study was determined by ICD-9 codes 997.4, 567.22 (abdominopelvic abscess), and 569.81 (fistula of the intestine).

Statistical analyses were performed using IBM SPSS statistics 19.0 for Windows (SPSS Inc; IBM, Chicago, IL). All continuous variables were dichotomized. Chi-squared or Fisher's exact test for categorical variables was used for statistical comparisons of those variables between the no leakage and leakage groups. Multivariate analysis to detect risk factors for anastomotic leakage was conducted with a logistic regression model. Difference in each variable has been analyzed using one-way analysis of variance (ANOVA) before multivariate analysis was performed. Significance was calculated at the 95% CI and p value < 0.05.

Research experience

We have enough experience in conducting medical researches, including clinical researches, and have published some results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Gong et al., 2012; Gu et al., 2012; Li et al., 2012; Yu et al., 2012; Zhan et al., 2012; Zhan et al., 2012; Deng et al., 2013; Huang et al., 2013; Chen et al., 2013; Dai et al., 2013; Liu et al., 2013; Liu et al., 2013; Liu et al., 2013; Lu et al., 2013; Wu et al., 2013; Yin et al., 2013; Yin et al., 2013).

Results

The demographic data of the selected sample stratified by goup are detailed in Table 1. The overall AL rate was 7.6% (57/753 patients). A total of 753 patients [452 male patients (60.0%)] with a median age of 65 (50–74) years at the time of surgery were included. The majority of patients were ASA 1 or 2 (86.9%). One hundred and fifty eight (21.0%) patients presented rectal cancer within 4 cm from the anal verge. Among all the patients, 45.4% (342) & 32.2% (235) of whom abused tobacco and alcohol, respectively. Three hundred and fifty four (47.0%) sufferers were diagnosed with phrase III rectal cancer pathologically and postoperatively. The preoperative BMI was equal or greater than 35 (severe obesity) in 52 (6.9%) patients. Forty one (5.4%) patients presented diabetes mellitus preoperatively. The correlations between demographic data and anastomotic leakage are summarized in Table 1. Univariate analysis demonstrated that anastomotic leakage was more common in patients with elder age (p<0.001), male gender (p<0.001), tobacco abuse (p<0.001), lower tumor site (p<0.001), high preoperative BMI (p<0.001), diabetes mellitus (p<0.001). Alcohol abuse, ASA score and TNM stage were not significant risk factors in univariate analysis.

The medical and surgical characteristics are listed in Table 2. Nineteen (2.5%) patients received neoadjuvant radiotherapy with associated chemotherapy. The reduction of TSGF in 134 (17.8%), value of serum albumin in 22 (2.9%) and level of hemoglobin in 51 (6.8%) sufferers in 5th POD were less than 10 u/ml, 30g/l and 70g/l; these value

Table 1. Demographic Data of the Selected Sample Stratified by Group

Variable	non-AL Group (n=696)	AL Group (n=57)	*p* value
Age mean (IQR) y	61(50-69)	68(55-74)	
<65	518	15	*p*<0.001
≥65	178	42	
Gender			
Male	406	46	*p*<0.001
Female	290	11	
Physical status (ASA)			
ASA≤2	607	47	*p*=0.307
ASA≥3	89	10	
Tobacco abuse			
≤4 cigarettes per day	395	16	*p*<0.001
≥5 cigarettes per day	301	41	
Alcohol abuse			
≤2 glasses per day	476	42	*p*=0.407
≥3 glasses per day	220	15	
Tumor site (from anal verge)			
<4cm	112	46	*p*<0.001
≥4cm	584	11	
TNM stage			
I~II	366	33	*p*=0.44
III	330	24	
Preoperative BMI			
<35	669	32	*p*<0.001
≥35	27	25	
Diabetes mellitus			
Abesence	664	55	*p*<0.001
Presence	32	9	

AL, anastomotic leak; IQR, interquartile range

Table 3. Multivariate Analysis of the Factors

Factors	p value	OR	95% CI of OR	
			lower limit	upper limit
Elder age	0.000	11.880	4.727	29.858
Male sex	0.002	5.181	1.839	14.592
Lower tumor site	0.000	45.818	16.480	127.388
The reduction of TSGF in 5th POD	0.000	11.152	4.449	27.957
Preventive ileostomy	0.040	0.018	0.000	0.827
Preoperative BMI	0.000	34.723	11.275	106.933

OR, odds ratio; CI, confidence interval

were selected as the criteria of grouping according to the references. Nineteen (2.5%) patients undergoing surgery were equal or longer than 4 hours. Twenty two (3.3%) invalids were experiencing intraoperative hypotension. A preventive ileostomy was proceeded in 50 (6.6%) sicks, and a laparoscopic surgery was performed in 88 (11.7%) patients. Forty four (5.8%) and seventeen (2.3%) patients were administrated with NSAID and glucocorticoid in early PODs, respectively. The relationship of clinical characteristics to anastomotic leakage are epitomized in Table 2. The reduction of TSGF (p<0.001) and value of serum albumin (p=0.006) in 5th POD were the factors that were associated significantly with the development of clinical anastomotic leakage. Preventive ileostomy and neoadjuvant therapy tended to be associated with the development of anastomotic leakage, with p values less than 0.20. Laparoscopic surgery, intraoperative hypotension, NSAID and glucocorticoid administration,

Table 2. Clinical Characteristics and Anastomotic Leakage

Variable	non-AL Group (n=696)	AL Group (n=57)	*p* value
Preventive ileostomy			
No	647	56	*P*=0.123
Yes	49	1	
Laparoscopic surgery			
No	616	49	*P*=0.566
Yes	80	8	
Neoadjuvant therapy			
No	680	54	*P*=0.170
Yes	16	3	
Intraoperative hypotension			
No	673	55	*P*=0.934
Yes	23	2	
NSAID administration			
No	654	55	*P*=0.403
Yes	42	2	
Glucocorticoid administration			
No	681	55	*P*=0.508
Yes	15	2	
Operation duration			
<4 hours	678	56	*p*=0.700
≥4 hours	18	1	
The reduction of TSGF in 5th POD			
≥10 U/ml	591	28	*p*<0.001
<10 U/ml	105	29	
The value of serum albumin in 5th POD			
≥30 g/l	679	52	*p*=0.006
<30 g/l	17	5	
The level of hemoglobin in 5th POD			
≥70 g/l	649	53	*p*=0.939
<70 g/l	47	4	

operation duration and the level of hemoglobin in 5th POD were not significant risk factors in univariate analysis.

The variables with p values less than 0.20 then were subjected to multivariate analysis using a stepwise logistic regression model. Results of multivariate analyses are detailed in Table 3. Elder age (p<0.001; odds ratio, 11.880; 95% confidence interval, 4.727–29.858), male gender (p=0.002; odds ratio, 5.181; 95% confidence interval, 1.839–14.592), lower tumor site (p<0.001; odds ratio, 45.818; 95% confidence interval, 16.480–127.388), the reduction of TSGF in 5th POD (p<0.001; odds ratio, 11.152; 95% confidence interval, 4.449–27.957), male gender (p<0.001; odds ratio, 5.181; 95% confidence interval, 1.839–14.592) and high preoperative BMI (p<0.001; odds ratio, 34.723; 95% confidence interval, 11.275–106.933) were independently predictive factors of the development of clinical anastomotic leakage, while a preventive ileostomy was found be the only independently protective factor.

Discussion

The AL rate after colorectal surgery varies between 1% and 40%, depending on the definition of leakage and on the type of resection performed, being higher in extraperitoneal anastomosis (Bellows et al., 2009). The rate of 7.6% in this study falls within the range of previously published series. This rate is, however,

lower than the average leakage rate of 10% reported in a systematic review by (Paun et al., 2010). It is also lower than the leakage rate reported in a similar study from Denmark looking at this complication using a population database (Bertelsen et al., 2009). It is not different from comparable reports that the low leakage rate in the present study could be explained by the fact that may be a reflection of technically skilled surgery. Success to mobilize the splenic flexure, success to perform high ligation of the inferior mesenteric artery to ensure the collateral blood supply, and success to test the integrity of the anastomosis can contribute to the low leakage rate.

The advantages of a single register include the sufficient number of suffers which can be collected data based on a truly unselected study population and without biasis or confounding factor. According to this research, anastomotic leakage after anterior resection was significantly related to a positionally lower tumour site, elder age, male gender, preventive BMI, the reduction of TSGF in POD 5 and the absence of fecal diversion. It seemed that the AL incidence of rectal cancer was unrelated to alcohol abuse, TNM stage, operation duration, ASA score, & the value of hemoglobin in 5th POD, laparoscopic surgery, NSAID & glucocorticoid administration, DM, neoadjuvant therapy and intraoperative duration in this study.

As in previous studies, advanced age, greater than 60 years, is the principal significant risk factor for anastomotic leaks on both univariate and multivariate analysis (Peeters et al., 2005; Kumar et al., 2011). The similarity was identified in the present series. Our observation that the risk of AL increased in parallel with the value of BMI is potentially of considerable clinical importance. The results of this study is akin to those of others reporting no association between obesity and risk of AL (Yamamoto et al., 2012), but the present register recorded no information on analysis of perioperative BMI shifting was therefore performed. The association between BMI and AL could be that obesity causes bad exposure of the surgery field followed by accidental injury, ischemia of resection margin and leakage.

The substitution of the anastomotic level for the distance of tumor from the anal verge has been commonly reported (Peeters et al., 2009) , in spite of the actual distance from the anal verge to the anastomosis (Eriksen et al., 2005). The two modus are not quite comparable, because the introduction of TME has resulted in very low anastomoses in patients with a tumour below 10 cm (ultra low tumor is below 4 cm) from the anal verge (wang er al., 2010). In the present register, the tumour level was recorded, our results were similar to those of others showing a higher risk of leakage for low tumours (Gastinger et al., 2005; Wong et al., 2005).

Even though the fecal diversion has been recommended to reduce the consequences of AL (Marusch et al., 2002; Gastinger et al., 2005; Lin et al., 2011), its influence on prevention is controversial. The present data suggest that the use of a diverting stoma is preventive factor of AL. There was a sole correlation between the fecal diversion and the significant low incidence of AL for tumours below 4 cm from the anal verge, for which the anastomosis would be very low in almost all such patients as all had a TME. In patients undergoing a protective ileostomy, by contrast, the position level of the tumour had no influence on the risk of AL. This finding may have been biased because the surgeons may have decided to make a ileostomy if the patient was deemed to be at higher risk of AL. However, the current study gives the recommendation with respect to diversion in low rectal anastomosis and indeed a recommendation based on the exact tumour level in centimetre above the anal verge is justified. Knowledge of risk factors is required to perform an educated risk assessment preoperatively, allowing a tailormade decision whether or not to construct fecal diversion.

In the light of other studies (Eriksen et al., 2005; Lipska et al., 2006; Bennis et al., 2012), we found a higher rate of AL in males. This might be due to the special anatomy of narrow male pelvis making the surgical procedure technically more difficult. Another consideration of this leads to the possibility that there is a disparate cellular pathway for collagen metabolism, tissue recovery and healing in the two genders. The strong connection of a colorectal anastomoses with the concentration of collagen in the anastomotic area had been identified through an experimental model (Agren et al., 2006). Researches of collagen formation during tissue healing indicated that aged males deposited less collagen than elder women within the first week after colorectal surgery. Obviously more collagen than men accumulated by premenopausal women implied that a young lady has a high level collagen formation capacity while the postmenopausal hasn't. These come outs manifest that the female hormones are related to collagen deposition, and the estrogen is a protected factor of AL presumably and mediately (Markiewicz et al., 2007; Aznal et al., 2012; Gormsen et al., 2012).

Tumour specific growth factor contributes to promoting the growth of tumour vessels, and has been shown greatly to correlate hyperplasia of tumour tissue to surrounding capillary vessels. Plenty of studies have demonstrated that TSGF has high sensitivity for the detection of malignant tumours (Yang et al., 2007; Bünger et al., 2011; Deng et al., 2011; Zhou et al., 2012), especially in colorectal cancers. The postoperative reduction of TSGF at 10 U/ml in day 5 was proposed as observationally diagnostic and prognostic indicator of colorectal cancer in previous research (Yang et al., 2009), and in present study, it was adopted for a risk factor that had been never reported. Less than 10 U/ml of the reduction in 5th POD was deemed to be a risk factor of AL in this study. It is interesting to note that the less decrease of TSGF after surgery, the more increase of AL, and vice versa. It is possible that less declining TSGF is a active promotion of AL, however, this remains to be confirmed by further study about molecular mechanism. Further study is also warranted in the light of this finding and the relation to the direct, intrinsic association between the postoperative reduction of TSGF and AL. The novel finding presented here most likely indicates that the reduction of TSGF in early PODS is an inchoately predictive mark of AL for a patient who undergoes a anastomosis of colon-rectum or colon-anal. A postoperative continuous monitoring

of the reductive TSGF for identifying AL could be a recommendatory step in early PODs, and also it is to be a guidelines for preventing of AL in someday when intensive studies are adequate.

Many risk factors for AL have been reported in the literature, and the majority has been analyzed in this study. Data from previous study demonstrated that baccy had been shown to impair tissue healing and increase the risk of wound complications and AL after gastrointestinal surgery (Kasperk et al., 2000; Sorensen et al., 2005). However, the current study provide evidence that smoking is not a independent factor of AL after the multivariate analysis. The similarity is that no statistically significant difference of the serum albumin POD 5 and DM was found in multivariate analysis between the groups with and without leakage. As in previous studies (Kasperk et al., 2000; Peeters et al., 2009), no association between AL and preoperative therapy was found, although the proportion of patients in this study receiving neoadjuvant therapy was small.

Present study is a retrospective analysis of a large sing-center database with limitations. Coding for comorbidities and postoperative complications may result in skewed results due to the vague nature of ICD-9 definitions for these variables. This retrospective review, however, is one of the largest and most comprehensive studies investigating the risk factors for AL after anterior resection.

In summary, being male, advanced age and severe obesity are all independent risk factors for AL. Our study also offers strong evidence that ultra low rectal cancer (lower than 4cm from anal verge) is an independent risk factor for anastomotic leakage after anterior resection with a double stapling technique. Preventive ileostomy is recommended as a mandatory norm after TME of low rectal cancer to prevent AL. Our data suggest that a reduction of TSGF in POD 5, a newly found risk factor, is an omen of early AL after anastomosis with a double stapling technique. We also believe that the safety of ultra low colorectal (coloanal) anastomosis will be improved with technical advances in the near future.

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