RESEARCH ARTICLE

Outcomes Based on Risk Assessment of Anastomotic Leakage after Rectal Cancer Surgery

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Abstract

Purpose: Anastomotic leakage (AL) is associated with high morbidity and mortality, high reoperation rates, and increased hospital length of stay. Here we investigated the risk factors for AL after anterior resection for rectal cancer with a double stapling technique. Patients and Methods: Data for 460 patients who underwent primary anterior resection with a double stapling technique for rectal carcinoma at a single institution from 2003 to 2007 were prospectively collected. All patients experienced a total mesorectal excision (TME) operation. Clinical AL was defined as the presence of leakage signs and confirmed by diagnostic work-up according to ICD-9 codes 997.4, 567.22 (abdominopelvic abscess), and 569.81 (fistula of the intestine). Univariate and logistic regression analyses of 20 variables were undertaken to determine risk factors for AL. Survival was analysed using the Cox regression method. Results: AL was noted in 35 (7.6%) of 460 patients with rectal cancer. Median age of the patients was 65 (50–74) and 161 (35%) were male. The diagnosis of AL was made between the 6th and 12th postoperative day (POD; mean 8th POD). After univariate and multivariate analysis, age (p=0.004), gender (p=0.007), tumor site (p<0.001), preoperative body mass index (BMI) (p<0.001), the reduction of TSGF on 5th POD less than 10U/ml (p=0.044) and the pH value of pelvic dranage less than or equal to 6.978 on 3rd POD (p<0.001) were selected as 6 independent risk factors for AL. It was shown that significant differences in survival of the patients were AL-related (p<0.001), high ASA score related (p=0.036), high-level BMI related (p=0.007) and advanced TNM stage related (p<0.001). Conclusions: AL after anterior resection for rectal carcinoma is related to advanced age, low tumor site, male sex, high preoperative BMI, low pH value of pelvic drainage on POD 3 and a significant reduction of TSGF on POD 5. In addition to their high risk of immediate postoperative morbidity and mortality, AL, worse physical status, severe obesity and advanced TNM stage have similarly negative impact on survival.

Keywords: Rectal cancer - anastomotic leak - survival analysis - 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; Cho, 2013; Fathallah et al., 2013; Hwang et al., 2013). 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.

AL is a severe complication after rectal surgery. Peritonitis and septicaemia lead to reoperations, admission to the intensive care unit (ICU) and a profoundly increased mortality rate (Kube et al., 2010). Furthermore, AL is a risk factor for local recurrence of colorectal cancer, and has a significant impact on disease free and overall survival (Mirnezami et al., 2011). AL 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; Law et al., 2007; Lee et al., 2008; 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 and survival analysis have

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

Variable categories	non-AL Group (n=696)	AL Group (n=57)	*p* value
Age median (IQR) y	61(50-69)	68(55-74)	
<65	325	11	*p*<0.001
≥65	100	24	
Gender			
Male	133	28	*p*<0.001
Female	292	7	
Physical status (ASA score)			
ASA≤2	368	29	*p*=0.537
ASA≥3	57	6	
Tobacco abuse			
≤4 cigarettes per day	232	11	*p*=0.008
≥5 cigarettes per day	193	24	
Alcohol abuse			
≤2 glasses per day	274	27	*p*=0.13
≥3 glasses per day	151	8	
Tumor site (from the anal verge)			
<4cm	58	28	*p*<0.001
≥4cm	367	7	
TNM stage			
I~II	229	19	*p*=0.903
III	196	16	
Preoperative BMI			
<35	407	18	*p*<0.001
≥35	18	17	
Diabetes mellitus			
Without	407	28	*p*<0.001
With	18	7	

AL, anastomotic leak; IQR, interquartile range

Table 2. Clinical Characteristics and Anastomotic Leakage

Variable categories	non-AL Group(n=696)	AL Group (n=57)	*p* value
Preventive ileostomy			
No	337	34	*p*=0.01
Yes	88	1	
Surgical approach			
Laparoscopy	70	6	*p*=0.918
Laparotomy	355	29	
Neoadjuvant chemoradiotherapy			
No	418	34	*p*=0.599
Yes	7	1	
Intraoperative hypotension			
No	411	34	*p*=0.889
Yes	14	1	
NSAID administration			
No	392	33	*p*=0.66
Yes	33	2	
Glucocorticoid administration			
No	415	34	*p*=0.851
Yes	10	1	
Operation duration			
<4 hours	424	34	*p*=0.23
≥4 hours	1	1	
The reduction of TSGF on 5th POD			
≥10 U/ml	66	20	*p*<0.001
<10 U/ml	359	15	
The value of serum albumin on 5th POD			
≥30 g/l	413	32	*p*=0.66
<30 g/l	12	3	
The level of hemoglobin on 5th POD			
≥70 g/l	392	32	*p*=0.864
<70 g/l	33	3	
The pH value of pelvic dranage on 3rd POD			
≤6.978	8	21	*p*<0.001
>6.978	417	14	

been reported in the previous investigations. However, lack of data about the risk factors and outcomes associated with AL from a single-institute of one team of doctors. In addition, risk assessment and survival analysis in previous reports have been inconsistent because of the limited power of studies. The reduction of TSGF on POD 5 less than 10 U/ml and the pH value of pelvic drainage less than or equal to 6.978 on POD 3 were adopted in this series, which had been firstly proposed as two indicators of AL in our previous studies [Yang et al., 2013 14 (7) & 14 (9)]. The main objective of the current study was to analyze the incidence of AL, risk factors for AL and cancer-related survival.

Materials and Methods

Between January 2003 and December 2007, 460 randomly collected and routinely followed up patients with rectal cancer underwent anterior resection with double stapling anastomosis for primary rectal cancer at Colorectal Cancer Center, the Affiliated Jiangsu Cancer Hospital of Nanjing Medical University & Jiangsu Institute of Cancer Research, Nanjing, China. The medical notes of those 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, antibiotics using for 7 PODs, and cancer-related decease. Exclusion criteria were as follows: Hartmann's and Miles' procedure, phrase IV of TNM stage, colon cancer, hand-sewn anastomosis, or last observation and disease-free death. 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. Various independent clinical variables were analysed and detailed in Table 1 and 2. The Ethics Committee of Science approved data collection in the register.

Patients were followed up routinely by a protocol consisting of visits every 3 months for the first 2 years, followed by visits every 6 months for the next 3 years. CEA, CA242, CA724 and CA199 levels were reviewed at each visit, and a CT scan of abdomen, pelvis, and thorax was performed at the 2-year follow-up. Colonoscopy was performed 1 year after surgery when the colon and rectum had previously been cleared of synchronous lesions, and repeated at 3-year intervals unless otherwise indicated by findings. Apart from this, patients were investigated in further detail as appropriate according to clinical symptoms and findings.

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

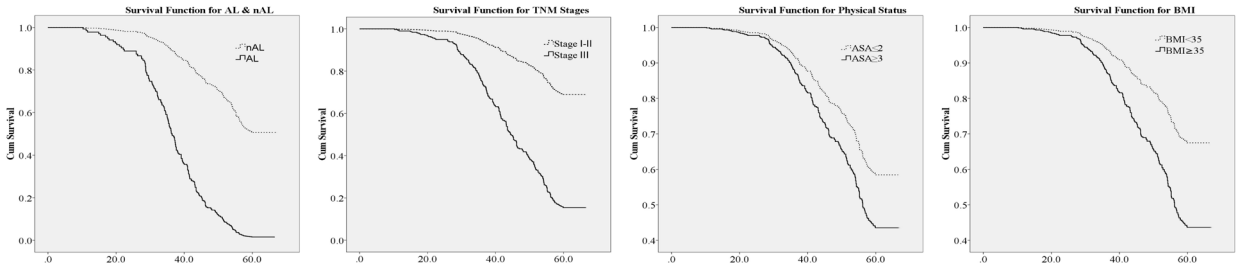

Figure 1. Survival Curves

Table 3. Multivariate Analysis of the Factors

Factors	*p* value	OR	95% C.I.for OR	
			Lower	Upper
Elder age	0.004	12.714	2.286	70.702
Male sex	0.007	13.341	2.046	86.994
Lower tumor site	0.000	63.208	8.747	456.776
The reduction of TSGF on 5th POD	0.044	5.615	1.048	30.096
High-level Preoperative BMI	0.000	181.381	19.612	1677.472
Lower pH value of pelvic drainage on 3rd POD	0.000	283.709	25.536	3152.113

OR, odds ratio; CI, confidence interval

Table 4. Survival Analysis by Cox Regression

Factors	*p* value	RR	95% CI for RR	
			Lower	Upper
AL	0.000	6.660	4.105	10.804
Physical status (ASA score)	0.036	1.550	1.028	2.336
Preoperative BMI	0.008	2.109	1.216	3.657
TNM stage	0.000	5.020	3.817	6.603

RR, relative risk; CI, confidence interval

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 AL was defined as the presence of leak 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 leak 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).

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 leak and leak groups. Multivariate analysis to detect risk factors for AL 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.

Follow-up time was defined as time between initial operation and death or last observation. Although 5-years follow-up was planned, median follow-up times were often less due to death. For example, the median follow-up time for the 460 patients with rectal cancer was 41.5 months due to death and the resultant decreased follow-up period. Disease-free survival time was calculated as the time between initial operation and recurrence or death. Survival analysis were analysed using the Cox regression method. Significance was calculated at the 95% CI and p value < 0.05. Statistical analyses were performed using IBM SPSS statistics 19.0 for Windows (SPSS Inc; IBM, Chicago, IL).

Results

The demographic data of the selected sample stratified by goup are detailed in Table 1. The overall AL rate was 7.6% (35/460 patients). A total of 460 patients [161 male patients (35.0%)] with a median age of 65 (49-72) years at the time of surgery were included. The majority of patients were ASA 1 or 2 (86.3%). Eighty six (18.7%) patients presented rectal cancer within 4 cm from the anal verge. Among all these patients, 47.2% (217) & 34.6% (159) of whom abused tobacco and alcohol, respectively. Two hundred and twelve (46.1.0%) sufferers were diagnosed with phrase III rectal cancer pathologically and postoperatively. The preoperative BMI was equal or greater than 35 (severe obesity) in 35 (7.6%) patients. Twenty five (5.4%) patients presented diabetes mellitus preoperatively. The correlations between demographic data and AL are summarized in Table 1. Univariate analysis demonstrated that AL was more common in patients with elder age (p<0.001), male gender (p<0.001), tobacco abuse (p=0.008), 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. Nine (2.0%) patients received neoadjuvant chemoradiotherapy. The reduction of TSGF in 86 (18.7%), value of serum albumin in 15 (3.2%) and level of hemoglobin in 36 (7.8%) sufferers on POD 5 were less than 10U/ml, 30g/l and 70g/l; these value were selected as the criteria of grouping according to the references. Two (0.4%) patients undergoing surgery were equal or longer than 4 hours. Fifteen (3.3%) invalids were experiencing intraoperative hypotension. A preventive ileostomy was proceeded in 89 (19.3%) sicks, and a laparoscopic surgery was performed in 76 (16.5%) patients. Thirty five (7.6%) and eleven (2.4%) patients were administrated with NSAID and glucocorticoid in early PODs, respectively. The relationship of clinical characteristics to AL are epitomized in Table 2. The reduction of TSGF (p<0.001) on 5th POD and the pH value of pelvic dranage on 3rd POD (p<0.001) were the factors

that were associated significantly with the development of clinical AL. Preventive ileostomy showed a significant effect on preventing AL (p=0.01). Operation duration tended to be associated with the development of AL, with p values equal to 0.20. Surgical approach, neoadjuvant chemoradiotherapy, intraoperative hypotension, NSAID and glucocorticoid administration, operation duration, the value of serum albumin on 5th POD and the level of hemoglobin on 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<0.004; OR, 12.714; 95% CI, 2.286-70.702), male gender (p=0.007; OR, 13.341; 95% CI., 2.046-86.994), lower tumor site (p<0.001; OR, 63.208; 95% CI, 8.747-456.776), the reduction of TSGF on 5th POD (p=0.044; OR, 5.615; 95% CI, 1.048-30.096), lower pH value of pelvic drainage on 3rd POD (p<0.001; OR, 283.709; 95% CI, 25.536-3152.113) and high-level preoperative BMI (p<0.001; OR, 181.381; 95% CI, 19.612-1677.412) were independently predictive factors of the development of clinical AL.

In addition to their high risk of immediate postoperative morbidity and mortality, Cox regression analysis confirmed that patients with AL (p<0.001; RR, 6.660; 95% CI, 4.105-10.084), poor physical status (p=0.036; RR, 1.550; 95% CI, 1.028-2.336), severe obesity (p=0.008; RR, 2.109; 95% CI, 1.216-3.657) and advanced TNM stage (p<0.001; RR, 5.020; 95% CI, 3.817-6.603) had similarly negative impacts on long-term survival (Table 4, Figure 1).

Discussion

The AL rate after colorectal surgery varies between 1% and 40%, depending on the definition of leak 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 leak rate of 10% reported in a systematic review by (Paun et al., 2010). It is also lower than the leak 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 leak 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 leak rate. Furthermore, our outcomes are similar to some others that AL is associated with a poor survival and a higher tumor recurrence rate after curative resection of colorectal cancer (Law, et al., 2007; Harris, et al., 2010).

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, AL after anterior resection was significantly related to a positionally lower tumour site, elder age, male gender, preventive BMI, the reduction of TSGF on POD 5 and the pH value of pelvic drainage on POD3. It seemed that the AL incidence of rectal cancer was unrelated to the rest of the factors 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 (Kumar et al., 2011; Peeters et al., 2005). 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 leak. In addition to be a risk factor for AL, BMI was also a risk factor for long-term survival. Studies assessing obesity and CRC outcomes have yielded concordant results. Meyerhardt and colleagues initially showed obesity was associated with a significant increase in overall mortality among women with stage II-III colon cancer. A cohort study of 4288 patients with Dukes B and C colon cancer showed increased recurrence or metachronous tumours (HR=1.38, 1.10 to 1.73), overall mortality (HR=1.28, 1.04 to 1.57) and colon cancer specific mortality (HR=1.36, 1.06 to 1.73) in very obese patients (BMI≥35 kg/m^2). According to this series, the Cancer Prevention Study II Nutrition Cohort suggested that pre diagnosis, but not post diagnosis, BMI was associated with an increased risk, cancer-related mortality (RR=1.35, 1.01 to 1.80). To sum up, it is suggested, although inconsistently, that obesity might be associated with a decrease in cancer-related survival in patients with CRC (Meyerhardt et al., 2003; Dignam et al., 2006; Campbell et al., 2012).

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 position was recorded, our results were similar to those of others showing a higher risk of leak for low tumours (Gastinger et al., 2005; Wong et al., 2005).

In the light of other studies (Marusch et al., 2002; 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 leak. 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.

It was known to all that the 5-year survival rate of phraseICRC patients was 90-95%, phraseIIwas 80-85% and phrase III was around 30%, respectively. Additionally, our findings are in conformity to that above. Moreover, it was believed that the good physical status would be a factor for improving long-term outcomes (Speed-Andrews et al., 2012), which was the explanation why the High-ASA score patients had a worse outcomes.

In conclusion, 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 leak after anterior resection with a double stapling technique. Our data suggest that a reduction of TSGF on POD 5 and the pH value of pelvic drainage, the two newly found independent risk factors in our previous studies, were the omens 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. In addition to their high risk of immediate postoperative morbidity and mortality, AL, worse physical status, severe obesity and advanced TNM stage had similarly negative impacts on survival. Efforts should be undertaken to avoid these complication to improve the long-term outcome.

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