Original Article

Early and Delayed Anastomotic Leakage after Colorectal Cancer Surgery

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Key Words
Colorectal cancer;
Anastomosis;
Leakage;
Complication

Purpose. Delayed anastomotic leakage is a challenging issue for colorectal surgeons. The aim of this study was to compare the related risk factors and management strategies between early and delayed anastomotic leakages after resection for colorectal cancer.
Methods. This study included 5592 patients who received resection for colorectal cancer between January 2012 and September 2019 at the Taipei Veterans General Hospital and Chi Mei Medical Center. Early and delayed anastomotic leakages were defined as the leakage diagnosed within and more than 30 days after surgery, respectively. The demographic data, chemotherapy, radiotherapy, operative methods, relaparotomy rate, anastomotic types, tumor location, disease stage, and management after the leakage were reviewed and compared the difference between the early and the delayed anastomotic leakage groups.
Results. Among the 5592 patients who underwent resection for colorectal cancer, 230 patients had anastomotic leakage, with a leakage rate of 4.1%. There were 206 (3.7%) patients with early leakage and 24 (0.4%) patients with delayed leakage. There was no difference in age, history of diabetes mellitus or chronic kidney disease, use of laparoscopic or open operation, handsewn or stapled anastomosis, tumor location, stage of disease, or preoperative albumin level between the two groups. Delayed leakage was significantly associated with female gender (OR = 0.117, 95% CI 0.039-0.348, $p < 0.01$) and neoadjuvant radiotherapy (OR = 0.135, 95% CI 0.043-0.427, $p = 0.001$). The relaparotomy rate after anastomotic leakage was similar between the two groups (22.3% vs. 20.8%, $p = 0.867$). The protective diverting stoma rate during the tumor resection was higher in the group of patients with delayed leakage (38.8% vs. 66.7%, $p = 0.009$).
Conclusions. Delayed anastomotic leakage is associated with female gender and neoadjuvant radiotherapy. Use of a protective stoma after colorectal resection did not prevent the occurrence of delayed leakage. Thus, even in the absence of early leakage episodes, it is essential to be aware of delayed anastomotic leakage possibility during follow-up surveillance.

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Surgical resection is the only curative treatment modality for colorectal cancer. Anastomotic leakage is one of the major complications following colorectal surgery, increasing patients' morbidity and mortality rates. According to a previous research study, anastomotic leakage has an incidence rate from 3% to 28%,[1] and it is related to almost one-third of all postoperative mortality cases.

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Early anastomotic leakage is usually detected during hospitalization due to several clinical or radiological symptoms, such as abdominal pain with or without peritoneal signs, fever, ileus, leukocytosis, elevated C-reactive protein, turbid postoperative drainage, and pneumoperitoneum or intra-abdominal abscess.[2] However, delayed leakage might occur several weeks after the surgery, when patients have already been discharged from the hospital, and thus, it is significantly more difficult to detect than early leakage.

Few studies have investigated the difference between early and delayed anastomotic leakages. Early and delayed leakages were considered as different complications with different clinical presentations and risk factors. These studies have also suggested female gender and preoperative radiotherapy as potential predisposing factors for delayed anastomotic leakage.[3,4] The majority of these studies have discussed delayed anastomotic leakage after rectal surgery; however, the number of cases was limited due to missed diagnosis and the reported incidence rate of delayed anastomosis was low from 1.31% to 6.38%.[4-6]

Therefore, the aim of this study was to investigate the characteristics of patients who developed delayed leakage and compare the related risk factors and management strategies between early and delayed anastomotic leakages after resection for colorectal cancer.

Methods and Patients

Study design

All patients with colorectal cancer, who received surgical resection with subsequent anastomotic leakage between January 2012 and September 2019 at the Taipei Veterans General Hospital and Chi Mei Medical Center, were included in this study. A total of 5592 patients diagnosed with colorectal cancer underwent surgical resection during this period, including simultaneous resection of other organs. Totally 238 patients had anastomotic leakage. Eight patients were excluded due to leakage from the other organ instead of colorectal anastomosis. Of the 230 remaining patients with anastomotic leakage from colorectum, 206 were diagnosed within 30 days after the operation (early leakage group), and 24 were diagnosed more than 30 days after colorectal resection (delayed leakage group).

Data collection

Anastomotic leakage was detected by clinical or radiologic findings, such as generalized or localized peritonitis, intra-abdominal abscess revealed by abdominal computed tomography, fecal materials in the postoperative drainage tube, anastomotic dehiscence found during relaparotomy, or formation of colo-vesicle or rectovaginal fistula. In both hospitals, the anastomosis status of patients with a protecting stoma was routinely checked by digital rectal examination before removal of drainage tube during admission to detect early leakage. Patients with anastomotic leakage were divided into two groups of early and delayed leakages in accordance with the time point of the diagnosis of the leakage, i.e., before or more than 30 days post-surgery, respectively. Demographic data, chemotherapy and/or radiotherapy, operative methods, relaparotomy rate, anastomotic methods, tumor location, disease stage, and management after leakage were reviewed and compared between the two groups. Tumor location at right side was defined as tumors located from cecum to transverse colon, and tumor location at left side was defined as tumors located from splenic flexure to rectum. Protecting stoma was the stoma created at the first time of radical surgery. Permanent stoma was the stoma that could not be reversed due to failure of anastomosis at the time of the last follow-up.

Statistical analysis

Categorical variables were compared using either Pearson's chi-squared test or Fisher's exact test. Continuous variables were analyzed with the Student's t-test. Logistic regression analysis was used to determine the independent predictors of delayed leakage using the significant parameters in univariate analysis. Variables differing significantly in univariate analysis were included in multivariate analysis based on logistic regression. p-value less than 0.05 was consid-

ered significant. All statistical calculations were carried out using IBM SPSS Statistics version 25.

Result

Among the 5592 patients who underwent colorectal resection, 230 patients had anastomotic leakage, with a leakage rate of 4.1%. There were 206 (3.7%) patients with early leakage and 24 (0.4%) patients with delayed leakage. The clinicopathological characteristics between the two groups are summarized in Table 1. The mean age was 66.8 years in the early leakage group and 71.3 years in the delayed group. A significantly higher proportion of female patients (58.3%) was noted in the delayed leakage group. In contrast, the prevalence of type 2 diabetes mellitus (30.6% vs. 25.0%, $p = 0.572$) or chronic kidney dis-

Table 1. The clinicopathological characteristics between the early and the delayed anastomotic leakage groups

	Early leakage (n = 206) (%)	Delayed leakage (n = 24) (%)	*p* value
Gender			***0.001***
Male	154 (74.8)	10 (41.7)	
Female	52 (25.2)	14 (58.3)	
Age (mean ± SD)	66.8 ± 13.5	71.3 ± 14.1	0.127
Type 2DM			0.572
Yes	63 (30.6)	6 (25.0)	
No	143 (69.4)	18 (75.0)	
Chronic kidney disease			0.322
Yes	9 (4.4)	2 (8.3)	
No	197 (95.6)	22 (91.7)	
Pre-operative albumin level (g/dL) (mean ± SD)	3.64 ± 0.59	3.74 ± 0.35	0.427
Tumor location			1.000
Right side	31 (15.0)	3 (12.5)	
Left side	175 (85.0)	21 (87.5)	
Disease stage			0.567
0	4 (2.0)	1 (4.2)	
I	54 (26.3)	4 (16.7)	
II	61 (29.8)	12 (50.0)	
III	49 (24.0)	4 (16.7)	
IV	38 (18.6)	3 (12.5)	
Neoadjuvant chemotherapy			0.147
Yes	72 (35.0)	12 (50.0)	
No	134 (65.0)	12 (50.0)	
Neoadjuvant radiotherapy			***< 0.001***
Yes	21 (10.2)	11 (45.8)	
No	185 (89.8)	13 (54.2)	
Laparoscopic surgery			0.318
Yes	98 (47.6)	14 (58.3)	
No	108 (52.4)	10 (41.7)	
Elective or emergent operation			0.488
Elective	201 (97.6)	23 (95.8)	
Emergent	5 (2.4)	1 (4.2)	
Anastomosis type			0.682
Handsewn	77 (37.4)	10 (41.7)	
Stapler	129 (62.6)	14 (58.3)	
Protecting stoma			***0.009***
Yes	80 (38.8)	16 (66.7)	
No	126 (61.2)	8 (33.3)	

ease (4.4% vs. 8.3%, $p = 0.322$), and the mean serum albumin level ($p = 0.427$) were not significantly different between the two groups. There were also no significant differences in tumor location, stage of disease, emergent or elective operation, the use of laparoscopic surgery, anastomotic type (handsewn or stapled), or the application of neoadjuvant chemotherapy between the two groups. However, the proportion of patients with neoadjuvant radiotherapy was significantly higher in the delayed leakage group than in the early leakage group (45.8% vs. 10.2%, $p < 0.001$). Finally, the rates of using a protective diverting stoma (66.7% vs. 38.8%, $p = 0.009$) was significantly higher in the delayed leakage group compared to the early leakage group.

Pertaining to the management after anastomotic leakage, the relaparotomy rate was similar between the two groups (22.3% vs. 20.8%, $p = 0.867$). A trend of a higher permanent stoma rate in the delayed group was noted without statistically significant difference (37.5% vs. 20.9%, $p = 0.065$) (Table 2).

Compared to the early type, identification of delayed anastomotic leakage was very difficult. Early leakage was diagnosed within a mean interval of 7.7 days, ranging from 2 to 28 days. The mean interval from surgery to delayed anastomotic leakage was 151.5 days, ranging from 31 to 466 days (Fig. 1). In the delayed leakage group, approximately half of the anastomotic leakage were diagnosed 4 months or more after colorectal resection, and in one patient the leakage was noted more than 1 year after colorectal resection. The delayed type accounted for 10.4% of all cases with anastomotic leakage. Formation of rectovaginal fistulas was found in nine (37.5%) patients, rendering these symptoms the most common clinical presentation of delayed anastomotic leakage. Delayed leakage was identified in six (25%) patients by radiographic diagnosis of intra-abdominal abscess. Dehiscence of the anastomosis was found in another six (25%) patients by means of colonoscopy or relaparotomy. However, clinical diagnosis was confirmed in

Table 2. The type and management after leakage and permanent stoma after anastomotic leakage

	Early leakage (n = 206) (%)	Delayed leakage (n = 24) (%)	*p* value
Management			0.867
Relaparotomy	46 (22.3)	5 (20.8)	
Conservative	160 (77.7)	19 (79.2)	
Permanent stoma			0.065
Yes	43 (20.9)	9 (37.5)	
No	163 (79.1)	15 (62.5)	

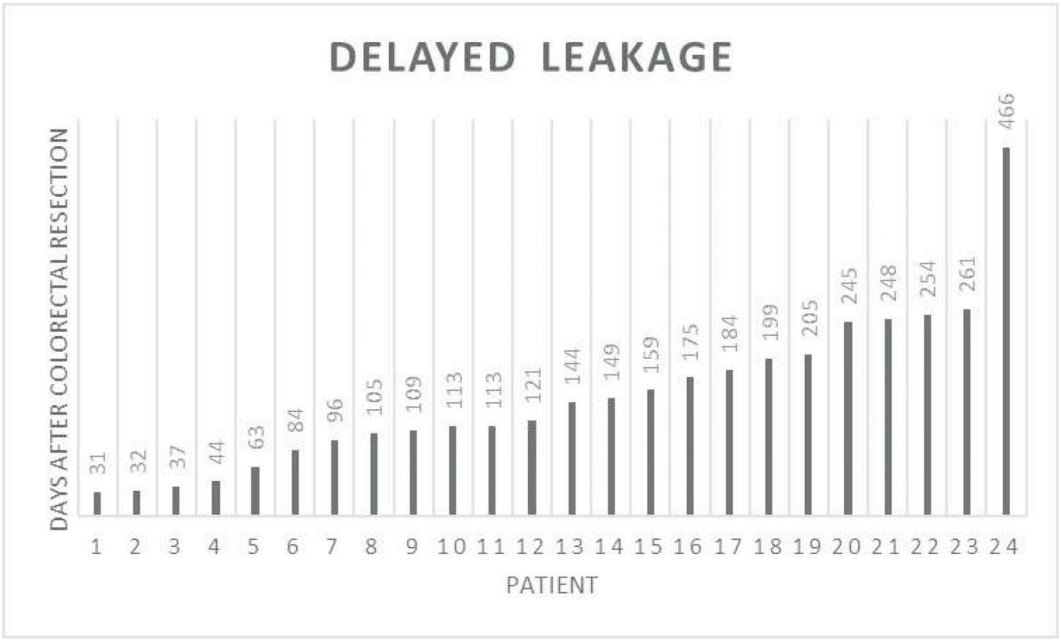

Fig. 1. The distribution of the diagnostic day of delayed anastomotic leakage after colorectal resection.

two (8.3%) of these patients by the development of localized peritonitis, and in one patient (4.17%) by the formation of a recto-vesical fistula. Delayed leakage was identified in only three patients with right-sided colon cancer, presenting with postoperative localized abdominal pain at 31, 32, and 63 days, respectively. Abdominal computed tomography revealed the presence of intra-abdominal abscess or localized free air, and two of these patients received relaparotomy, and one was managed by conservative treatment.

The univariate analysis showed that the female gender (OR = 0.241, 95% CI 0.101-0.576, $p = 0.001$), the use of a protective stoma in the radical surgery (OR = 0.317, 95% CI 0.130-0.776, $p = 0.012$), and neoadjuvant radiotherapy (OR = 0.134, 95% CI 0.053-0.337, $p < 0.001$) were associated with delayed leakage. In addition, the multivariate analysis revealed that the female gender (OR = 0.117, 95% CI 0.039-0.348, $p < 0.001$) and neoadjuvant radiotherapy (OR = 0.135, 95% CI 0.043-0.427, $p = 0.001$) were independently associated with the development of delayed anastomotic leakage (Table 3).

Discussion

The present study found that the anastomotic leakage rate after colorectal resection was 4.1% and the delayed type accounted for 10.4% of all cases. Female gender and the application of neoadjuvant radiotherapy were independent factors for the development of delayed leakage compared to the early leakage. Our results are consistent with the results of previous studies. Ui Sup Shin et al.[4] investigated postoperative anastomotic leakage in 79 patients, of whom 24 had delayed leakage. The authors identified that the female gender and preoperative radiotherapy were independent risk factors for delayed anastomotic leakage. In a retrospective study of 45 patients with anastomotic leakage after low anterior resection for rectal cancer, Floodeen et al.[7] also found that the majority of patients in the delayed group were females. A possible explanation of female predominance in the delayed leakage group was due to the natural drainage and mechanical damage to the vagina during the anastomosis procedure.[8] We have nine patients (37.5%) with recto-vaginal fistula and one with recto-vesical fistula (4.2%) in the delayed leakage group. The formation of the fistula took time. We thought it was the reason why female patients had higher chance to developed delayed anastomotic leakage presenting by the formation of rectovaginal fistula.

Neoadjuvant radiotherapy has been the standard treatment for advanced rectal cancer. Although this approach reduces the incidence of local recurrence, it is also related to higher postoperative morbidity. This is because this treatment affects the surrounding healthy tissue, including the adjacent bowel wall, and its vascularization. In a post hoc analysis of a randomized controlled trial, Qiyuan Qin et al.[9] stated that preoperative radiotherapy increases the risk of anastomotic leakage. In 2018, a nationwide research with 1573 leakage cases in the Netherland also reported preoperative radiation as an independent risk factor for delayed anastomotic leakage.[10] In our result, five patients, who had received neoadjuvant radiotherapy,

Table 3. Univariate and multivariate analysis for independent factors associated between early and delayed anastomotic leakage

	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Gender	0.241	0.101-0.576	***0.001***	0.117	0.039-0.348	***< 0.001***
Protecting stoma	0.317	0.130-0.776	***0.012***	0.344	0.110-1.070	0.065
Neoadjuvant radiotherapy	0.134	0.053-0.337	***< 0.001***	0.135	0.043-0.427	***0.001***
Type of surgery (elective or emergent)	0.572	0.064-5.112	0.617			
Laparoscopic surgery	0.648	0.275-1.526	0.321			
Neoadjuvant chemotherapy	0.537	0.230-1.257	0.152			
Tumor location	0.806	0.227-2.868	0.740			
Disease stage	1.121	0.759-1.655	0.566			

had delayed anastomosis leakage several months after reversal of the protective stoma, although the anastomosis was initially found to be intact by endoscopic evaluations or contrast studies before the reversal of the protective stoma. These patients had poor outcomes, and a permanent stoma was needed in three of these five patients.

In our study, the permanent stoma rate was higher in the delayed group than the early group without statistically significant difference (20.9% vs. 37.5%, $p = 0.065$), a finding that was also confirmed by a retrospective study performed by Ui Sup Shin et al.[4] The stoma formation rate was 100% in all 24 patients with delayed anastomotic leakage. The 3-year stoma-retention rate in patients with delayed leakage was significantly higher than the patients with early anastomotic leakage (72.2% vs. 17.5%, $p < 0.001$). Delayed anastomosis reflects a higher chance of permanent stoma, which may have a long-term negative effect on the patients' quality of life.

There was no significant difference between neoadjuvant chemotherapy and delayed anastomotic leakage. However, chemotherapy seemed to have a trend related to delayed anastomotic leakage (35% vs. 50%, $p = 0.147$). A systematic review and meta-analysis showed that neoadjuvant chemotherapy was safe with no increase in adverse consequence of anastomotic leak in locally advanced colon cancer.[11] A prospective study with high population, 17518 patients, also revealed no association between pre-operative chemotherapy and anastomotic leakage after colorectal resection.[12] These studies suggested that neoadjuvant chemotherapy may not significantly increase the risk of anastomotic leakage after colorectal surgery. However, it is important to note that the impact of chemotherapy on anastomotic healing may vary depending on several factors, including the type and duration of chemotherapy and the patient's overall health. Therefore, the decision to administer chemotherapy before colorectal surgery should be individualized and based on a careful assessment of the risks and benefits for each patient. The trend between chemotherapy and delayed anastomotic leakage in our study may attributed to the relatively small patient number in the delayed group.

In the present study, we used 30 days as the cutoff value for delayed anastomotic leakage. The postoperative day 30 was usually the day when patients returned to the outpatient department for follow-up or the day when patients received the first course of adjuvant treatment. A thorough examination by a surgeon can more reliably detect signs of delayed anastomotic leakage. Although several studies reported the same result associated with delayed anastomotic leakage, there is no consensus on the specific time that is necessary to differentiate the two types of anastomotic leakages. The definition of delayed anastomotic leakage varied from development of leakage at postoperative days 5,[13] 7,[10] and 30[6,14] or even after discharge from the hospital.[6] These broad definitions may induce selection bias, and render potential difficulty in comparisons among research studies. Consequently, it is necessary to reach a consensus on the definition of delayed anastomotic leakage to optimize such comparisons and minimize selection bias.

Nonetheless, this study revealed that protective ileostomy or colostomy after colorectal resection did not reduce the risk of delayed leakage, and the proportion of patients with a protective stoma was significantly higher in the delayed leakage group than the early group. Theoretically, the protective stoma can prevent the requirement for surgical interventions when anastomotic leakage occurs, but cannot prevent anastomotic leakage.[15] The relationship between the protective stoma and the timing of leakage has not been mentioned in current literature. Lim et al.[3] compared the differences between early and delayed anastomotic leakages and found that the proportion of using a protective stoma was significantly higher in the delayed group (8.1% vs. 44.6%, $p < 0.001$). Although the creation of a protective stoma was decided by the surgeon during the operation, inducing selection bias in this retrospective study, this finding underlines that the presence of a protective stoma may mask the symptoms and signs of anastomotic leakage in the early postoperative phase. In our hospital, the anastomosis status of patients with a protecting stoma was routinely checked by digital rectal examination before removal of drainage tube during admission. We think that the missed diagnosis rate of early anastomosis

leakage in these patients would be reduced. However, delayed leakage could still be found later. Therefore, careful anastomotic surveillance during the follow-up is necessary to detect delayed leakage.

One limitation of the present study is its retrospective design. Also, subjective parameters, such as the surgeon's decision to create a diverting stoma or to perform relaparotomy in patients with anastomotic leakage, might have induced selection bias. Furthermore, minor leakage, which is characterized by nonspecific symptoms, such as fever or abdominal pain, might be misinterpreted as a common postoperative side-effect.

Conclusions

Delayed anastomotic leakage is associated with female gender and the use of neoadjuvant radiotherapy. Protective ileostomy or colostomy after colorectal resection did not prevent the occurrence of delayed anastomotic leakage and it may occur several months or even 1 year after colorectal resection. Thus, even in the absence of early leakage episodes, it is essential to be aware of the possibility of delayed anastomotic leakage during the follow-up surveillance.

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原　著

大腸直腸癌切除術後早期和延遲性吻合處滲漏

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目的　對於大腸直腸外科醫生來說，延遲性吻合處滲漏是一個具有挑戰性的問題。本研究的目的是比較大腸直腸癌切除術後早期和延遲吻合處滲漏的危險因素和處理。

方法　自 2012 年 1 月至 2019 年 9 月在台北榮民總醫院與奇美醫學中心接受大腸直腸癌切除手術的所有病人都被收錄。早期與延遲性吻合處滲漏以術後第三十天為分界來定義。回顧比較兩組患者的基本資料、是否接受化療放療、手術方式、再手術率、吻合方式、腫瘤部位、疾病分期、滲漏後處理情況。

結果　5592 例大腸直腸癌切除術後患者中，吻合處滲漏有 230 例，滲漏率 4.1%。早期滲漏 206 例 (3.7%)，延遲滲漏 24 例 (0.4%)。兩組在年齡、糖尿病或慢性腎臟病史、是否使用腹腔鏡手術、用手或吻合器吻合、腫瘤位置、疾病分期或術前白蛋白數值方面沒有差異。延遲滲漏與女性 (OR = 0.117, 95% CI 0.039-0.348, $p < 0.01$) 和手術前輔助性放射治療的使用 (OR = 0.135, 95% CI 0.043-0.427, $p = 0.001$) 顯著相關。兩組吻合處滲漏的再手術率相似 (22.3% vs. 20.8%, $p = 0.867$)。延遲組的在腫瘤切除時接受保護性腸造口比率更高 (38.8% vs. 66.7%, $p = 0.009$)。

結論　延遲性吻合處滲漏與女性和術前輔助性放射治療的使用有關。大腸直腸切除術後的保護性腸造口並不能防止延遲性滲漏的發生。因此，即使沒有早期滲漏事件，我們在後續追蹤時仍然需要注意延遲性吻合處滲漏的可能性。

關鍵詞　大腸直腸癌、吻合、滲漏、併發症。