Treatment strategy and outcome of anastomotic leakage after left-sided colorectal cancer surgery
–Non-surgical V.S. Surgical treatment–

Shunsuke Imanishi, Hideaki Miyauchi, Michihiro Maruyama, Gaku Ohira, Tetsuro Maruyama, Toshiharu Hanaoka, Koichiro Okada, Hisahiro Matsubara

Department of Frontier Surgery, Graduate school of medicine, Chiba University

Abstract
Anastomotic leakage (AL) after left-sided colorectal cancer surgery is one of the most serious complications. Once anastomotic leakage occurs, we have to select the treatment, non-surgical or surgical. The aim of this study is to evaluate the outcome of the treatments for AL after left-sided colorectal surgery in our institution. Fifty-five patients who had AL after left-sided colorectal surgery were included in this study. Thirty-nine were treated for non-surgical treatment (non-surgical group). In eight patients, we had to change the strategy from non-surgical to surgical during non-surgical treatment (convert group). Eight patients were treated for surgical treatment at first due to generalized peritonitis (surgical group). There were not significant differences in patient’s background and blood examination between these groups. The patients who had three symptoms (the change of drain contents, fever higher than 38°C and abdominal pain) in convert group were significantly more frequent than those of non-surgical group (50%:7.7% P = 0.01). The rate of diverting stoma in non-surgical group was significantly more frequent than those of convert and surgical groups (25.6%:6.2% P < 0.001). In all of 55 patients, the rate of permanent stoma was 9% and mortality was 0%. In selected patients without generalized peritonitis, AL after left-sided colorectal cancer can be controlled by non-surgical treatment. Furthermore it may decrease the rate of permanent stoma. Moreover, we should select surgical treatment at first step for the patients who had three clinical symptoms even in the absence of findings of generalized peritonitis.

Keywords: Anastomotic leakage, colorectal cancer, treatment

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Introduction
Anastomotic leakage (AL) after left-sided colorectal cancer increases short term morbidity and medical costs, and prolongs hospital stay. Moreover sometimes it leads to mortality rate. But once AL occurs, we have to select the treatment strategy, non-surgical or surgical. However treatment indications differ by each institutions. Usually we select non-surgical treatment unless the patients are generalized peritonitis. The purpose of this study is to evaluate the outcome of the treatment for AL after left-sided colorectal surgery retrospectively in our institution, in order to elucidate the validity of our treatment indications.

Materials
Four hundred twenty one patients underwent left-sided colorectal resection (rectal and sigmoid colon cancer) with anastomosis in our department from January 2012 to August 2019. Fifty five patients who had AL were included in this study.

Methods
We defined AL as the cases in which the properties of the drain changed into stool, or in which extra gas was confirmed around the anastomosis upon CT imaging.

The patients who were treated without re-operation were categorized into non-surgical group. The patients who had to convert the treatment strategy from non-surgical to surgical during non-surgical treatment were categorized into convert group. And the patients who were treated for surgical treatment at first step were categorized into surgical group. The patient’s backgrounds of each group were compared. Regarding the patient’s
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backgrounds, the following aspects were compared: age; sex; BMI; smoking index; serum albumin value; HbA1c; general blood test findings upon the onset of AL (WBC: white blood cell count; Hb: hemoglobin; PLT: platelet count; CRP: C-reacting protein; GOT, GPT, LDH, Creatinin, CPK); and body temperature. Three symptoms including a change in the drain properties, a fever higher than 38°C, and abdominal pain were compared as clinical findings.

Nextly, the treatment outcomes in each group were examined. The period from surgery to the AL, the median of hospital stay after surgery, drainage route, reasons of converting the treatment strategy, surgical method of the re-operation, postoperative complications, the rate of permanent stoma, and mortality rate were examined. Moreover, the rate of diverting stoma at the first surgery was compared between non-surgical group and other.

As the methods of statistical analysis, the Mann Whitney U test was used for continuous variables along with Fisher’s exact test for nominal variables, with a P value of under 0.05 defined as significantly different.

Clinical classification
We clinically categorize the levels of AL into three groups.

• "Minor" is leakage with symptoms such as a change of the drain properties or a high value of inflammatory reaction, without symptoms such as abdominal pain and fever.
• "Intermediate" is leakage with symptoms such as abdominal pain, fever, and signs of localized peritoneal irritation, without any findings of generalized peritonitis.
• "Major" is leakage with findings of generalized peritonitis.

Treatment classification
The treatments for AL are categorized into the following three groups.

• Grade A does not involve invasive treatment beyond administering antibiotics.
• Grade B requires invasive treatment other than re-operation.
• Grade C requires re-operation.

Drainage method

• Percutaneous trans-abdominal drainage
  In the surgery for left-sided colorectal cancer, we place the JVCA drain from the left lower abdomen to the proximal dorsal side of the anastomosis, applying negative pressure in all patients. It can be used as a therapeutic drain when AL occurs.
• Trans-anal intra-rectal drainage
  In cases with poor colon preparation, a trans-anal drain is placed in the rectum during surgery. This can reduce the pressure within the rectum in the event of diarrhea following surgery.
• Trans-anal intra-abscess drainage
  Sometimes AL can be diagnosed after removing the trans-abdominal drain, so we treat the leakage by placing a trans-anal silicon tube on the abscess cavity and applying negative pressure.

Results

Fifty five (13.1%) of 421 patients had AL. Forty seven of 55 patients with AL were selected non-surgical treatment at first step, but 8 patients needed to be converted to surgical treatment due to generalized peritonitis, etc. during non-surgical treatment (convert group). Eight patients had findings of generalized peritonitis at the onset of AL, resulting in surgical treatment (surgical group, Fig. 1). Eleven patients were clinically diagnosed as minor leakage. All patients with minor leakage were able to be cured by non-surgical treatment (Grade A or B). Thirty-six patients were diagnosed as intermediate leakage, among which non-surgical treatment was selected at first step. However, 8 patients converted to surgical treatment during non-surgical treatment. Twenty eight of 36 patients with intermediate leakage were treated for non-surgical (Grade B), but 8 of 36 were treated for Surgical (Grade C). Eight patients were diagnosed as major leakage and surgical treatment was required for all of these patients (Grade C, Table 1). There were no significant differences between each group in terms of the following aspects: age; sex; BMI; smoking index; serum albumin;
HbA1c; general blood test findings upon the onset of AL (WBC, Hb, PLT, CRP, GOT, GPT, LDH, Cre, CPK); and body temperature (Table 2).

In non-surgical group, the period from surgery until the onset of AL was 4 days (0–21). The median of hospital stay after surgery was 26 days (17–61). The period of drainage were 14 days (4–235). The most frequent drainage route was the transabdominal route. Three patients (7.7%) had all three symptoms, change in the drain properties, fever higher than 38°C, and abdominal pain upon the onset of AL. The rate of diverting stoma at the first surgery was 25.6%, with 90% of these undergoing stoma closure. The rate of permanent stoma was 2.6%. Moreover, the mortality rate was 0% (Table 3).

In convert group, the period from surgery until the onset of AL was 4.5 days (2–7). The median hospital stay after the first surgery was 44.5 days (19–82). Four patients (50%) had all of three symptoms upon the onset of AL. The period from the onset of AL to re-operation was one day (0–61). The rate of diverting stoma at the first surgery was 0%. The most common reason for converting the strategy to re-operation was the patient’s condition worsened to generalized peritonitis, with other reasons including oral side colonic necrosis, delay in shrinking of the residual abscess, and intestinal obstruction. Regarding the surgical method of re-operation, 6 patients underwent abdominal irrigation drainage and creating ileostomy, while only two patients underwent Hartmann’s operation. The rate of permanent stoma was 25%. In terms of postoperative complications, two patients had SSI (surgical site infection), while each of one patient had pneumonia, enteritis, and intestinal obstruction. The mortality rate was 0% (Table 5).

Regarding the days of hospitalization after the first surgery compared among the three groups, the non-surgical group had significantly fewer than the convert group (26:44.5 P = 0.012). Significantly more patients had all three symptoms in the clinical findings upon the onset of AL in convert group than non-surgical group (50%:7.7% P = 0.01, Table 6). And the rate of permanent stoma was 9% in all of 55 patients. Moreover the rate of permanent stoma in non-surgical group were significantly fewer than those in convert and surgical groups (P = 0.02) (Fig. 2). The rate of diverting stoma at the first surgery in the non-surgical group was significantly higher than those in surgical group.

### Table 2 The patient background between each treatment group

|       | A (Non-surgical) | B (Convert) | C (Surgical) | A:B P value | A:C P value | B:C P value |
|-------|-----------------|-------------|-------------|-------------|-------------|-------------|
| Age (year) | 69 (38-80) | 62 (46-73) | 65 (46-66) | 0.13 | 0.052 | 0.92 |
| Sex (M:F) | 27:12 | 6:2 | | 4:4 | 1 | 0.42 |
| BMI (kg/m²) | 22.3 (15.2-28.0) | 22.1 (19.8-23.6) | 25.2 (17.6-28.0) | 0.73 | 0.27 | 0.19 |
| Smoking Index | 710 (0-2700) | 1000 (0-1200) | 625 (0-1175) | 0.84 | 0.8 | 0.68 |
| Alb (g/dl) | 3.8 (2.7-4.5) | 4.0 (3.0-4.7) | 4.0 (3.5-4.5) | 0.2 | 0.31 | 0.64 |
| HbA1c (%) | 5.8 (4.8-9.5) | 5.7 (4.9-7.0) | 5.7 (5.1-6.4) | 0.72 | 0.69 | 1 |
| WBC (μl) | 9550 (3800-30300) | 7850 (5200-10325) | 8800 (1100-13600) | 0.31 | 0.2 | 0.8 |
| Hb (g/dl) | 10.7 (6.7-14.5) | 12.6 (9.5-13.6) | 12.0 (9.1-14.6) | 0.1 | 0.19 | 0.86 |
| PLT (10³/μl) | 229 (93-536) | 259 (114-339) | 212 (78-341) | 0.91 | 0.54 | 0.51 |
| CRP (mg/dl) | 9.9 (2.7-27.5) | 12.1 (5.2-25.9) | 14.0 (1.8-29.0) | 0.41 | 0.22 | 0.51 |
| GOT (U/l) | 20 (10-280) | 27.5 (11-88) | 35 (14-71) | 0.92 | 0.29 | 0.69 |
| GPT (U/l) | 20 (6-178) | 17 (7-82) | 19 (11-110) | 0.49 | 0.62 | 0.37 |
| LDH (U/l) | 184 (116-477) | 177 (131-357) | 227 (134-238) | 0.87 | 0.5 | 0.78 |
| Cre (mg/dl) | 0.71 (0.43-3.65) | 0.78 (0.56-0.97) | 0.74 (0.52-2.03) | 0.96 | 0.96 | 0.73 |
| CPK (U/l) | 95.0 (10-1396) | 95.5 (35-295) | 147 (37-536) | 0.6 | 0.24 | 0.34 |
| BT (℃) | 37.5 (36.1-39.6) | 38.1 (37.2-39.4) | 38.0 (37.0-38.5) | 0.07 | 0.38 | 0.32 |

### Table 3 The details of treatment outcome in Non-surgical group

| Clinical classification | Minor | Intermediate | 11 | 28 |
|-------------------------|-------|--------------|----|----|
| Median of the hospital stay after surgery (days) | 26 (17-61) | | |
| Median time to leakage from surgery (days) | 4 (0-21) | | |
| Median duration of drainage (days) | 14 (4-235) | | |
| Route of drainage | Trans abdominal | Trans anal intra rectum | Trans anal to abscess |
| Rate of diverting stoma | 25.6 % | | |
| Rate of stoma closure | 90.0 % | | |
| Rate of permanent stoma | 2.6 % | | |
| Mortality | 0 % | | |
| Three clinical symptoms | 7.7 % | | |
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Discussion

Anastomotic leakage after left-sided colorectal cancer surgery is one of the most serious complications. While various reports exist on the risk factors of AL\textsuperscript{1,2,3}, there is no standard treatment indications.

Trans-abdominal drainage was the most common drainage route for non-surgical treatment. We place an information drain in all patients with left-sided colorectal cancer. This drain can be used as a therapeutic drain when AL occurs and the trans-anal drain would lead to a decrease in quality of life in these patients.

There was one case in which 21 days was required to diagnose AL in non-surgical group. This patient had a diverting stoma, so it was difficult to find the symptoms. We need to be careful in regard to patients with diverting stoma, since their symptoms of AL may be covered and not symptomatic.

Recently, reports of endoluminal negative pressure treatment have frequently used. It is the method that can treat the AL with minimal invasion by using sponge trans-anal in abscess and apply continuous negative pressure to close the abscess cavity\textsuperscript{4-8}. However, according to a review by G.I.Popivanov et al., there were 84.5% patients who needed to create stoma, and 72.6% patients underwent stoma closure. Therefore the rate of permanent stoma was 23.2%\textsuperscript{6}. Moreover, B. Cleavin et al. reported that minimally invasive approaches was desirable in selected patients. But commonly Hartmann’s surgery was selected when patient was generalized peritonitis. So the rate of permanent stoma was 46%\textsuperscript{9}. On the other hand, we usually select non-surgical treatment at first step unless patients have the sign of generalized peritonitis. And we avoid Hartmann’s operation as much as possible even when re-operation is required. Therefore the rate of permanent stoma was lower compared with other reports. Moreover, the rate of permanent stoma in non-surgical group was significantly fewer than those in convert and surgical group. We can reduce the rate of permanent stoma after AL by selecting non-Surgical treatment as much as possible.

Both convert and surgical groups (25.6%:6.2% P > 0.001) (Fig. 3).

Table 4 The details of treatment outcome in Convert group

| Reason of the surgery          | Rate of diverting stoma | Rate of permanent stoma |
|-------------------------------|-------------------------|-------------------------|
| Generalized peritonitis       | 5                       | 25%                     |
| Oral-colon necrosis           | 1                       | 12.5%                   |
| Rest of abscess               | 1                       | 25%                     |
| Bowel obstruction             | 1                       | 0%                      |

Table 5 The details of treatment outcome in Surgical group

| Operation method          | Rate of diverting stoma | Rate of permanent stoma |
|---------------------------|-------------------------|-------------------------|
| Ileostomy + drainage      | 6                       | 25%                     |
| Hartmann                  | 2                       | 25%                     |
| Loop colostomy            | 1                       | 0%                      |

Table 6 The rate of patients who had three clinical symptoms between Non-surgical and Convert group

| Change of drain content | Fever over 38°C | Abdominal pain | Patients who had three symptoms |
|-------------------------|-----------------|---------------|-------------------------------|
| Non-Surgical Group (N=39) | 28 (7.7%) | 14 (38%) | 19 (50%) | 3 (7.7%) |
| Convert Group (N=8)          | 7               | 6            | 7                | 4 (50%)  |

Fig. 2 The rate of permanent stoma after AL

| N Stoma Stoma Closure Permanent stoma |
|---------------------------------------|
| Non-Surgical Conversion Surgical      |
| 39 10 9 1                             |
| 8 2 0 1                               |
| 8 2 0 1                               |
| 5 1 (9%)                              |
| P=0.02                                |

Fig. 3 The rate of diverting stoma at the first surgery

| Non-surgical group (N=39) Conversion group (N=8) Surgical group (N=8) |
|-----------------------------------------------------------------------|
| 10 (25.6%) 0 (0%) 1 (12.5%)                                           |

P > 0.001

6.2%
including change of drain properties, fever higher than 38°C and abdominal pain in convert group were significantly more frequent than those in non-surgical group. Therefore, we should select surgical treatment at first step for such patients with intermediate leakage.

It is known that a diverting stoma contributes to the prevention of the severe symptomatic AL. In our study, the rate of diverting stoma was also significantly high in patients who were treated without undergoing surgery, so it is necessary to consider which patients need diverting stoma.

Conclusion

In selected patients without generalized peritonitis, AL after left-sided colorectal cancer can be controlled by non-surgical treatment. Furthermore, it may decrease the rate of permanent stoma. Moreover, we should immediately conduct surgery in patients who had three clinical symptoms even in the absence of findings of generalized peritonitis.

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