Anastomotic Leakage Following Colorectal Cancer Surgery: Comparison Between Conservative and Surgical Treatment

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Abstract

Backgrounds Anastomotic leakage following colorectal cancer is associated with significant morbidity and mortality. However, whether the choice of the treatment for anastomotic leakage may affect the oncological outcomes is under debate. We evaluated the oncological outcomes after colorectal cancer surgery for anastomotic leakage between conservative and surgical treatment. Methods We retrospectively analyzed data for patients with colorectal cancer who underwent curative colectomy from April 2010 to January 2020. Results A total 1039 patients underwent surgery colorectal cancer in our hospital. After exclusion, a total of 915 patients underwent a low anastomosis with diverting stoma for colorectal cancer of which 92 (10.0%) anastomotic leakage occurred. After stage Ⅳ and emergency surgery case were excluded, a total of 75 patients were included for the analysis. The surgical treatment group was 25 cases. The conservative treatment group was 50 cases. Early anastomotic leakage was more than in surgical treatment compared to conservative treatment (84% vs 54%, P =0.008). The 5-year overall survival rates and the 5-year disease free survival did not differ significantly between the two groups. The recurrence location of liver metastasis was more than in surgical treatment compared to conservative treatment (20% vs 2 %, P=0.02). On a multivariable analysis, anastomotic leak did not impact overall survival and disease free survival. Conclusion We found that the treatment for anastomotic leakage was not depended on increased local, distance recurrence, overall survival, and disease free survival. Our findings may help surgeons determine which AL treatment is most appropriate, when the decision is unclear.

Introduction

Anastomotic leakage (AL) is a major complication after colorectal cancer surgery.

Moreover, AL is an independent factor predicting poor prognosis in patients undergoing curative resection for colorectal cancer, contributing to local recurrence and decreased survival [1–10], and occurring at a rate of 4%–29% [11–14]. The consequences of AL are severe and can lead to septic shock or death [15].

The International Anastomotic Leak Study Group reported that a group of colorectal and interventional radiology experts described their practices for managing AL and abdominopelvic abscesses after colorectal surgery using a modified Delphi process [16]. Yuan-yao et al. [17] reported that managing AL depends on the clinical presentation and the severity of symptoms. High suspicion, and early recognition with an aggressive approach and intervention prior to contamination and subsequent sepsis, are important [17].

Ramphal et al. [18] reported that patients who survive abdominal sepsis in the acute phase after AL have a significant hazard of developing local recurrence. However, the decision to perform surgery is difficult in patients with AL after colorectal cancer surgery without peritonitis. To the best of our knowledge, few studies have evaluated whether the choice of AL treatment affects oncological outcomes. Therefore, the aim of this study was to compare the oncological and clinical outcomes after AL following colorectal

cancer surgery between surgical treatment (surgical group) and conservative treatment (conservative group).

Material & Methods

Study design

We retrospectively analyzed data for patients with colorectal cancer who underwent curative colectomy at Kawasaki Saiwai Hospital general surgery between April 2010 and January 2020. We recorded patients' characteristics, surgical outcomes, and oncological outcomes.

Patients without a primary anastomosis and patients for whom the day of diagnosis of AL was unknown were excluded from the analysis. We also excluded patients in whom AL occurred later than 90 days after surgery. In our hospital, data are usually registered 30 days after surgery, unless the initial hospital stay is longer. Therefore, we considered data registered for AL occurring later than 90 days after surgery as unreliable. We excluded patients who underwent Hartmann`s operation or abdominoperineal resection, patients with stage IV cancer, and patients undergoing emergency surgery.

In our institution, we generally did not perform primary anastomosis with a loop ileostomy for colon cancer. We commonly placed a diverting stoma in patients with multiple risk factors, particularly preoperative radiotherapy for rectal cancer or an anastomosis < 5 cm from the anal verge. End–to–end anastomosis was performed for colon cancer by open surgery, and we used a double-stapling technique in laparoscopic surgery.

AL was defined according to clinical evidence and was confirmed by radiological imaging. Clinical evidence was defined as the presence of peritonitis or fever (body temperature > 38.5°C), or purulent or fecal discharge from the abdominal drain. Computed tomography (CT) detected free air around the anastomosis area. We did not include pelvic abscess without free air as AL.

The management plan for AL in our institution involved surgical treatment for septic shock or peritonitis, and conservative treatment in asymptomatic patients or in those with mild symptoms, consisting of antibiotics or percutaneous drainage.

AL can be graded by patients' clinical outcomes [19], with Grade C requiring surgery for peritonitis. Grade B is treated with antibiotics or drainage, and grade A AL can be treated conservatively.

Patient follow-up in the present study ended in April, 2020. Three months after the primary surgery, we routinely performed CT and colonoscopy with diatrizoate. When AL was ruled out, we planned to perform stoma closure.

Overall survival (OS) was defined as the time from surgery to the date of death from any cause or to the last follow-up. Disease-free survival (DFS) was defined as the time from surgery to the date of recurrence or death from any cause or to the last follow-up.

This study was approved by our institutional Ethics Committee, and conformed to the provisions of the Declaration of Helsinki. This study was also approved by our Institutional Review Board for the Use of Human Subjects.

Patient follow-up

All patients were followed for survival. Recurrence and distant metastasis were diagnosed according to blood test results, which included carcinoembryonic antigen and carbohydrate antigen 19-9 levels, and CT and endoscopy. Blood testing was performed every 4 months for 3 years postoperatively, CT was performed every 6 months for 5 years postoperatively, and endoscopy was performed annually for 5 years postoperatively.

Statistical Analysis

Statistical analyses were performed using JMP Pro 10 software (SAS Institute, Cary, NC). Results are summarized as means and standard deviations, or medians and ranges for continuous variables; categorical variables are summarized as numbers and frequencies. Median and mean values were compared between groups using the Mann–Whitney test or the Chi-square test in univariate analyses. OS and DFS rates were analyzed using the Kaplan–Meier method and Cox's proportional hazards model. Comparisons between survival curves were performed using the log-rank test. Results are summarized as the hazard ratio (HR), 95% confidence interval (CI), and p-value. Significance was set at $p < 0.05$.

Results

Participants and incidence of AL

A study patient enrolment flow chart is presented in Figure 1; 1039 patients underwent surgery for colorectal cancer between April 2010 and January 2020, in our hospital. After exclusion, we identified 915 patients who underwent low anastomosis with diverting stoma for colorectal cancer, of which 92 (10.0%) developed AL. After excluding patients with stage IV cancer and patients requiring emergency surgery, 75 patients were included in the analysis. The surgical group constituted 25 patients, and the conservative group constituted 50 patients.

Patients' characteristics

There were no significant differences between the groups regarding age, sex, body mass index, and American Society of Anesthesiologists grade. Left-sided colon cancer was more common in the surgical group compared with the conservative group ($p = 0.043$, Table 1).

Surgical outcomes following the primary operation

There were no significant differences between the groups regarding operative time, bleeding volume, conversion to surgery, surgical approach, mortality, or diversion stoma rate. Postoperative stay was longer

in the surgical group compared with the conservative group (p = 0.0012, Table 2). There were no significant differences in the number of patients receiving chemotherapy or for the time from surgery to chemotherapy (32% vs 34%, respectively, p = 0.862 and 15 weeks vs 9 weeks, respectively, p = 0.142). Furthermore, there were no significant differences between the groups regarding the pathological findings (Table 3).

Leakage data

Early AL was more common in the surgical group compared with the conservative group (84% vs 54%, respectively; p = 0.008), and AL grade C was more common in the surgical group compared with the conservative group (p = 0.001; Table 4).

Oncological outcomes

The 5-year OS rates did not differ significantly between the two groups (surgical group: 84.0%, 95% CI: 45.1–90.9 vs conservative group: 96.0%, 95% CI: 76.8–98.4; p = 0.105; Fig. 2). The 5-year DFS rates also did not differ significantly between the two groups (surgical group: 80.0%, 95% CI: 57.1–90.7 vs conservative group: 88.0%, 95% CI: 67.2–92.7; p = 0.318; Fig. 3). Recurrence as liver metastasis was more common in the surgical group vs the conservative group (20% vs 2%, respectively; p = 0.02; Table 5). The median follow-up duration was 23 (3–108) months. Univariate and multivariate survival analysis revealed no significant association between treatment and OS or DFS (HR: 2.52, CI: 1.19–5.78, p = 0.938 vs HR: 1.142, CI: 0.622–2.045, p = 0.659, respectively). However, surgical treatment was associated with OS and DFS on univariate analysis (HR: 1.86, CI: 1.029–3.549, p = 0.039 and HR: 1.86, CI: 1.001–3.709, p = 0.049, respectively).

Multivariable survival analysis revealed no impact of treatment on OS (HR: 1.57, CI: 0.92–2.81, p = 0.099) or DFS (HR: 1.549, CI: 0.875–2.924, p = 0.136).

Discussion

The different treatments for AL after colorectal cancer surgery resulted in comparable 5-year OS and DFS, and distant and local recurrence rates did not differ significantly between surgical and conservative treatment. Multivariable analysis showed no association between treatment and oncological outcomes. Regarding short-term outcomes, postoperative hospital stay was shorter in the conservative group compared with the surgical group.

Previous studies indicated a rate of AL of 4%–29 %, [11–14] and several risk factors for AL after colorectal cancer surgery have been discussed [20–22], as well as methods to reduce the rate, prevent AL, and the related risk factors [23–26].

Loop ileostomy diversion has been performed for patients undergoing rectal cancer surgery (up to 5 cm from the anus), intersphincteric resection, chemoradiotherapy, and total mesorectal excision, in our institution. In the current study, 9 (18%) patients with diversion developed AL in in the conservative group,

while 3 (12%) patients with diversion developed AL in the surgical group. There were no significant differences between the groups regarding the loop ileostomy diversion rate. Kulu et al. [1] and Crippa et al. [27] reported that diversion did not protect against AL, although there might be a protective effect of diversion in patients with more severe grades of AL.

Some studies suggested that laparoscopic surgery is associated with increased anastomotic failure rates [28], while a Cochrane review found no difference in AL rates between laparoscopic and open surgery [29]. We found no difference in AL grade in our study between laparoscopic and open surgery. To our knowledge, no studies have evaluated whether the surgical approach is associated with AL grade.

AL was diagnosed postoperatively earlier in the surgical group vs the conservative group, in our study, and a previous study showed that early AL may lead to technical failure of the anastomosis [22]. However, no significant differences were found with Cox regression analysis, and for whether early vs late AL is associated with oncological outcomes.

To our knowledge, studies have not evaluated surgical and oncological outcomes once AL occurs. AL is reported to be significantly associated with increased rates of local recurrence [1–10], although large retrospective studies reported a survival advantage of chemotherapy [30, 31]. Our institution routinely prescribes chemotherapy for patients with stage II and III colorectal cancer, as a high-risk group [32, 33].

Kulu et al. [1] performed a propensity score analysis for rectal cancer, and concluded that grade B and C leaks were not associated with oncological outcomes. We consider three possibilities to explain this finding: First, excluding nine patients with grade A AL decreased statistical power and led to a loss of statistical significance. Second, the prolonged chronic inflammation associated with conservatively-treated AL led to immunosuppression and a persistence of tumor cells [34, 35]. Third, chronic inflammation prevented early adjuvant treatment, which is known to be beneficial regarding oncological outcomes [36, 37].

Some previous studies reported that microperforation could occur before or during surgery, which is associated with increased local recurrence rates [38, 39]. Vital malignant cells have been detected intraluminally and on staple and suture lines during surgery. Furthermore, in vitro and experimental animal studies have shown growth of these cells and their ability to metastasize [40–44].

Crippa et al. [27] stated that AL negatively impacted the adjuvant chemotherapy rate. In our study, 8 patients (32%) in the surgical group received adjuvant chemotherapy, and 17 patients (34%) in the conservative group received adjuvant chemotherapy. However, these differences were not statistically significant, and both rates were low. Surgical treatment for AL was associated with longer postoperative hospital stay, need for intensive care, and elevated serum inflammatory markers. The time from surgery to receiving chemotherapy did not differ significantly between the groups. Additionally, hospital stay was shorter in the conservative group vs the surgical group, and patients receiving surgical treatment required subsequent stoma closure.

Noh et al. [45] stated that a delay in initiating adjuvant treatment for patients with AL could explain their poorer DFS. den Dulk et al. [46] reported no difference in AL rates between patients undergoing neoadjuvant chemoradiotherapy and those who do not. In our study, the AL rate in patients who underwent neoadjuvant chemoradiotherapy was similar to those who did not receive preoperative radiation.

Our study suggested that the type of AL treatment was not associated with oncological outcomes. However, recurrence location was significantly different between the two groups; liver metastasis was more common in the surgical group. Additionally, more patients had left-sided colon cancer in the surgical group, and a previous study reported that left-sided colon cancer was more likely to result in liver metastasis than right-sided colon cancer [47]. Our results were consistent with these previous results.

There were several limitations in our study. First, this was a retrospective and single-institution study. Second, surgeries were performed by several surgeons, and the use of nonstandardized techniques may have affected the incidence of AL and oncological outcomes. Finally, the sample size was small, and the observation term was short.

Conclusion

our results showed that the type of AL treatment was not associated with increased local and distance recurrence, or overall survival. These findings could help surgeons choose the appropriate therapy for AL, if the decision is unclear. However, more studies are needed to validate our findings.

Declarations

Availability of data and materials

The datasets used for this study are available from corresponding author on reasonable request.

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Contributions

YI, MO, and SI contributed to the study design. YI, MO,MA and KN contributed to the data acquisition. YI,MO and MA contributed to the analysis and interpretation. YI and SI drafted the manuscript. HY, YT, and SF critically revised the manuscript. All authors approved the final version of the manuscript for publication.

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Ethical Approval: This study was approved by our institutional Ethics Committee, and conformed to the provisions of the Declaration of Helsinki. This study was also approved by our Institutional Review Board for the Use of Human Subjects.

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Tables

Table.2 surgical outcomes

	Group A (N=25),n%	Group B (N=50),n%	P<0.05[a)]
Operative time, min	251 (81-444)[b)]	260 (98-593)[b)]	0.485[c)]
Bleeding volume, mL	85 (0-937) [b)]	43 (0-3050)[b)]	0.801[c)]
postoperative stays	36 (11-183)[b)]	30 (8-74)[b)]	0.0012[c)]
Conversion to open surgery	0	0	1
Intraoperative complications			
approach			1
laparp	18 (72%)	36 (72%)	
open	7 (28%)	14 (28%)	
Diversion stoma	3 (12%)	9 (18%)	0.738
Mortality	0%	0%	1
chemothapy			0.8623
yes	8 (32%)	17 (34%)	
no	17 (68%)	33 (66%)	
Day ofchmotherapy from surgery (day)	15 (9-30)	9 (5-32)	0.142

Data are shown as n (%) unless otherwise indicated.
aP values calculated using Fisher's exact test; bdata shown as median (range); cP values calculated using the Mann-Whitney U test.
A group: Surgical treatment; B group: Conservative treatment

Table 3 Pathological findings

	Surgical Group (n=25)	Conservative Group (n=50)	*p*-value
Tumor size (mm)	35 (10–80)	35 (3–190)	0.91
Harvested lymph nodes	13 (0–42)	12.5 (2–52)	0.49
Cancer-positive nodes	0 (0–6)	0 (0–9)	0.79
Chemotherapy			0.86
yes	8 (32%)	17 (34%)	
no	17 (68%)	33 (66%)	
Differentiation			0.54
tub1	16 (64%)	31 (62%)	
tub2	7 (28%)	16 (32%)	
muc	1 (4.00%)	2 (4%)	
por1	0	1 (2%)	
pap	1 (4.00%)	0	
Ly			0.685
+	17 (68%)	30 (60%)	
–	8 (32%)	20 (40%)	
v			0.608
+	19 (76%)	33 (66%)	
–	6 (24%)	17 (34%)	
DM			1
+	0	0	
–	25	50	
Stage			0.382
1	5 (20%)	15 (30%)	
2	12 (48%)	16 (32%)	
3	8 (32%)	19 (38%)	

Table.4 Leakage Data

	Group A (n=25),n%	Group B (n=50),n%	P<0.05[a)]
AL diagonosis of day	4 (1–58)[b)]	5 (1–24)[b)]	0.868[c)]
early(<7 days)	21 (84%)	27 (54%)	0.008
late (>7 days)	4 (16%)	23 (46%)	
CRP (POD3)	15.33 (1.43–38.43)[b)]	15.8 (0.05–30.8)[b)]	0.863[c)]
Diagonosis methods			0.046
CT scan	9 (36%)	31 (62%)	
Dranage	16(64%)	19 (38%)	
Anastomosis technique			0.061
DST	18 (72%)	26 (52%)	
SST	1 (4%)	0	
hand-sew	0	3 (6%)	
FEEA	6 (24%)	21(42%)	
Grage			0.001
A	0 (0%)	19 (38%)	
B	0 (0%)	31 (62 %)	
C	25 (100%)	0 (0%)	

Data are shown as n (%) unless otherwise indicated.
aP values calculated using Fisher's exact test; bdata shown as median (range); cP values calculated using the Mann-Whitney U test.
A group: Surgical treatment; B group: Conservative treatment

Table.5 Recurrence location

	Group A (n=25),n%	Group B (n=50),n%	P<0.05[a)]
Distance	7 (28%)	6 (12%)	0.18
Lung	1 (4%)	4 (8%)	0.86
Liver	5 (20%)	1 (2%)	0.02
Dissemination	1 (4%)	1 (2%)	0.79
local	1 (4%)	2 (4%)	0.53

Data are shown as n (%) unless otherwise indicated.
aP values calculated using Fisher's exact test; bdata shown as median (range); cP values calculated using the Mann-Whitney U test; A group: Surgical treatment; B group: Conservative treatment

Table.6 Univariate and multivariate analyses of factors prognostic for Overall survival

	Univariate		Multivariate	
Parameter	OR (95% CI)	Univariate p	OR (95%CI)	Multivariate p
Age	1.02 (0.99–1.04)	0.136		
Sex				
Man/women	1.21 (0.66–2.26)	0.532		
BMI	0.99 (0.93–1.058)	0.96		
Tumor location				
colon/rectal	1.184 (0.666–2.04)	0.541		
Surgical approach				
Lap/open	1.864 (1.029–3.549)	0.0396	1.57(0.92–2.813)	0.099
TNM stage				
3/1,2	1.2(0.692–2.06)	0.5001		
Treatment				
Surgical/Conservative	2.52 (1.19–5.78)	0.938		

CI = confidence interval, HR = hazard ratio.

Table.7 Univariate and multivariate analyses of factors prognostic for disease-free survival

	Univariate		Multivariate	
Parameter	OR (95% CI)	Univariate p	OR (95%CI)	Multivariate p
Age	1.024(0.99-1.0533)	0.083		
Sex				
Man/women	1.286 (0.665-2.547)	0.457		
BMI	0.99 (0.93-1.069)	0.972		
Tumor location				
colon/rectal	1.22 (0.692-2.148)	0.48		
Surgical approach				
Lap/open	1.864 (1.001-3.709)	0.0496	1.549 (0.875-2.924)	0.1363
TNM stage				
3/1,2	1.252 (0.686-2.231)	0.455		
Treatment				
Surgical/Conservative	1.142 (0.622-2.045)	0.659		

CI = confidence interval, HR = hazard ratio.

Figures

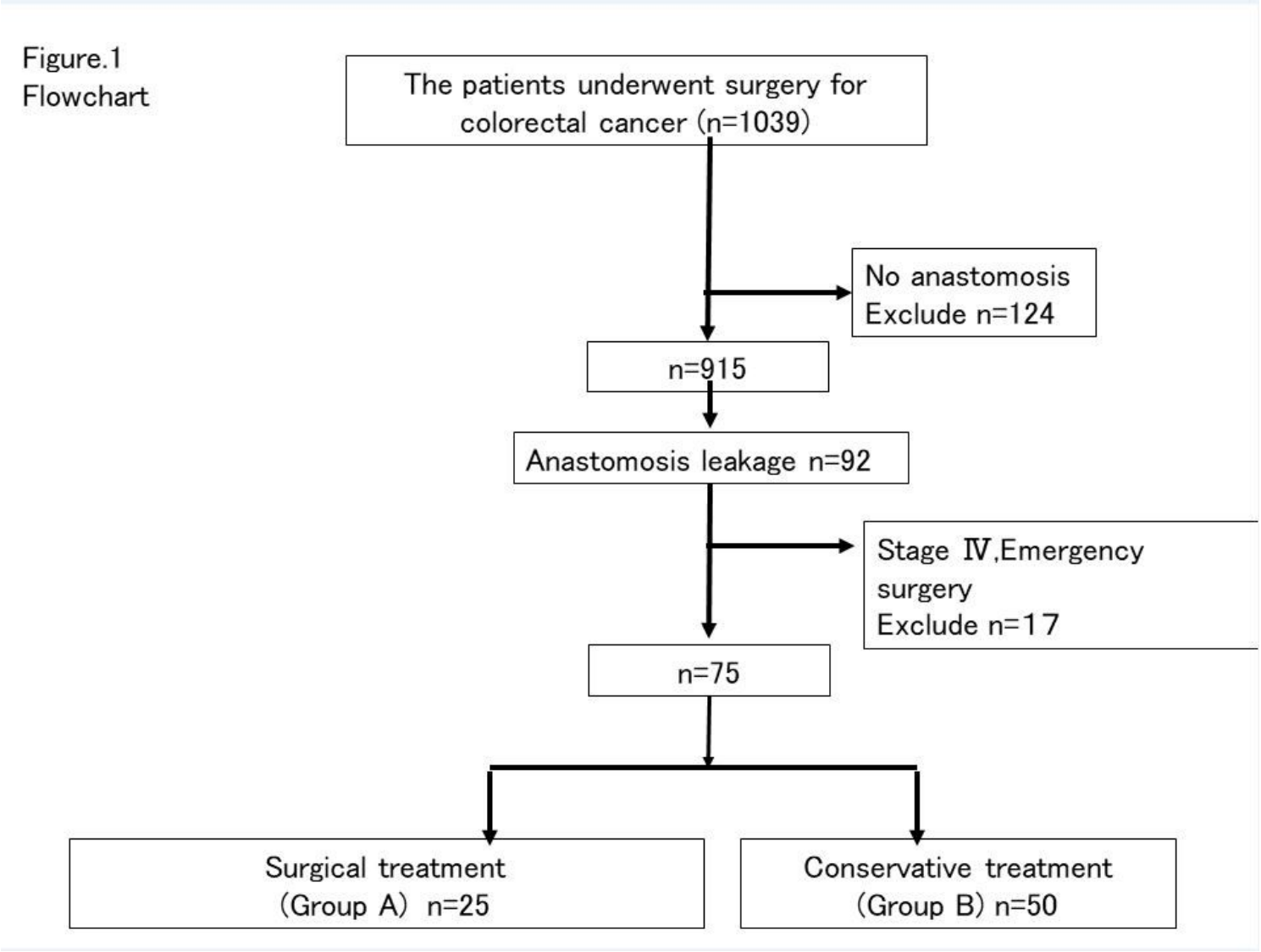

Figure 1

Study patient enrolment flowchart.

Figure.2 OS

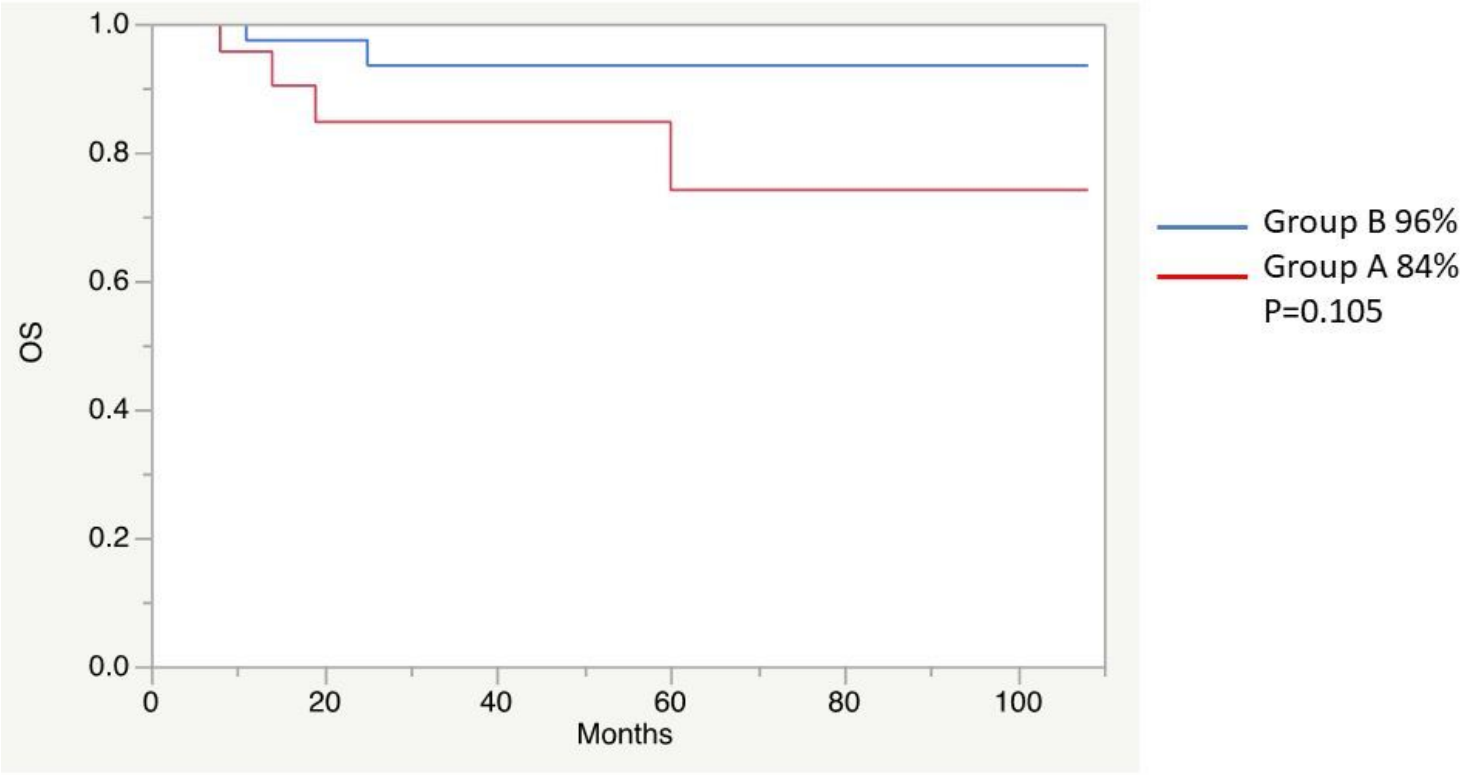

Figure 2

Overall survival curves OS overall survival

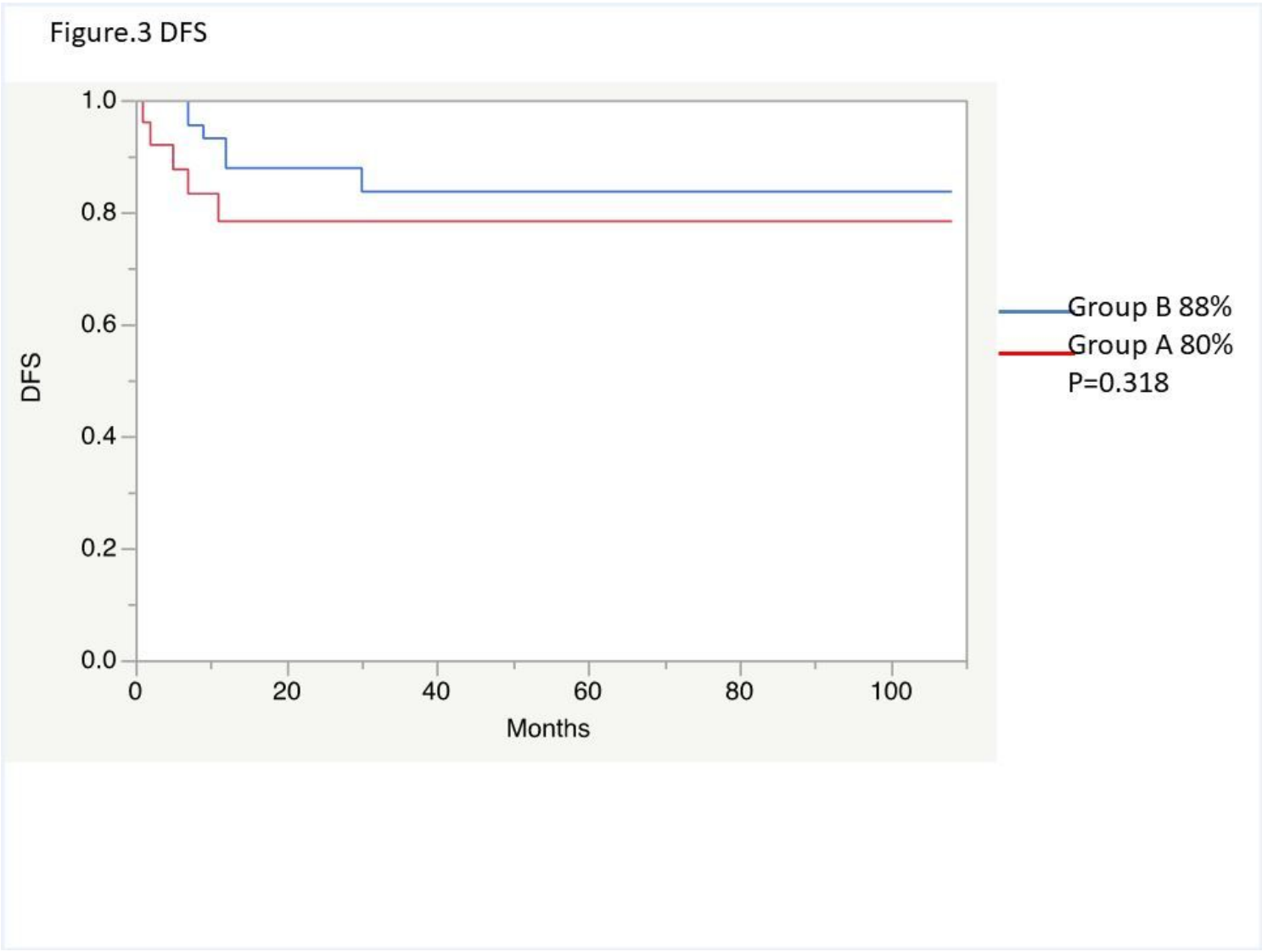

Figure 3

Disease-free survival curves DFS disease-free survival