Short-and Long-Term Outcomes of Laparoscopic Surgery in Patients with Pathological Stage II and III Colon Cancer

Takatoshi Nakamura[1], Hiroyuki Mitomi[2], Wataru Onozato[1], Takeo Sato[1], Atsushi Ikeda[1], Masanori Naito[1], Naoto Ogura[1], Hiroki Kamata[1], Akira Ooki[1] and Masahiko Watanabe[1]

[1]Department of Surgery, Kitasato University, School of Medicine, Kanagawa, Japan
[2]Department of Human Pathology, Juntendo University, School of Medicine, Japan

Corresponding author: Masahiko Watanabe M.D., Ph.D., F.A.C.S., Kitasato University School of Medicine Department of Surgery, 1-15-1 Kitasato, Minami-ku Sagamihara, Kanagawa 252-0374, Japan;
Tel: +81427788111, Fax: +81427455582; E-mail: n-toshi@kitasato-u.ac.jp

ABSTRACT

Background/Aims: In Japan, the safety and long-term outcomes of laparoscopic surgery for advanced colorectal cancer remains a matter of debate. We studied the safety and outcomes of laparoscopic surgery in patients with pathological stage II and III colon cancer. **Methodology:** The study group comprised 253 patients with colon cancer who underwent laparoscopic surgery from January 1998 through December 2006. We studied surgical outcomes, invasiveness, safety, recurrence rates, recurrence patterns, and long-term outcomes. **Results:** Median follow-up was 67 months (range, 7-149). Laparoscopic surgery was converted to open surgery in 5 patients (2%). Postoperative complications occurred in 23 patients (9%); wound infections were most common (11 patients, 4.3%), followed by ileus (5 patients, 1.9%). Recurrence developed in 66 patients (26%). Liver and lung metastases were the most common types of recurrence; there was no port-site recurrence. The 10-year recurrence-free survival rate and the overall survival rate were respectively 92.9% and 93.3% in stage II disease, 82.7% and 82.9% in stage IIIA and IIIB disease, and 70.3% and 68.6% in stage IIIC disease. **Conclusions:** In patients with pathological stage II and III colon cancer, laparoscopic surgery is safe, minimally invasive, and has good surgical outcomes, overall survival rates and recurrence-free survival rates. Our results suggest that laparoscopic surgery is a viable treatment option for pathological stage II and III colon cancer.

Key Words: Laparoscopic surgery, Colon cancer, Clinical outcome.

Abbreviations: Computed Tomography (CT).

INTRODUCTION

Laparoscopic surgery was first used to treat colorectal cancer in our hospital in 1995. To date, we have performed laparoscopic surgery in more than 800 patients with colorectal cancer. Recently, the indication range has been expanded and now includes advanced cancer as well as early cancer (1-3). The increased use of laparoscopic surgery is attributed to several advantages over open surgery, including less postoperative pain, a lower risk of postoperative ileus, a shorter length of postoperative hospital stay, and an earlier return to usual activities, *i.e.* a better postoperative quality of life (4,5). In patients with advanced cancer, however, opinions on the use of laparoscopic surgery are divided. Laparoscopic surgery does not allow surgeons to adequately visually inspect or palpate the peritoneal cavity, potentially leading to a less reliable intraoperative evaluation of disease stage and raising concerns about the risks of tumor cell dissemination and implantation in the peritoneal cavity, as well as port-site recurrence (6,7). Recent randomized, controlled studies of advanced colon cancer conducted in Western countries have reported that long-term outcomes after laparoscopic surgery are comparable to those after open surgery (8-12). In Japan, however, the surgical results, invasiveness and long-term outcomes of laparoscopic surgery in patients with advanced colon cancer remain largely uninvestigated. We therefore retrospectively studied short- and long-term outcomes after laparoscopic surgery in patients with pathological stage II and III colon cancer.

METHODOLOGY

From January 1998 through December 2006, we performed laparoscopic surgery in 595 patients with colon cancer. Of these patients, we studied 105 with pathological stage II disease and 148 with stage III disease (total, 253 patients; 136 men and 117 women). The median follow-up period was 67 months (range, 7-149) (**Table 1**). Laparoscopic surgery was indicated for patients in whom barium enema fluoroscopy, colonoscopy, abdominal ultrasonography and computed tomography of the chest and abdomen showed no distinct evidence of tumor invasion to other organs. Patients with ileus that did not respond to decompression were excluded from the study.

As for the technique for laparoscopic surgery, the first port was placed in a skin incision about 3cm in length, made 2 finger widths below the xiphoid process if the lesion was in the right side of the colon or 2 finger widths above the pubic bone if the lesion was in the left side of the colon. A Lap Disk (Johnson and Johnson Co., Ltd., USA) was placed at the incision site, and a 12-mm port was inserted. The abdomen was insufflated with carbon dioxide at a mean pressure of 8mmHg/hour. While examining the peritoneal cavity with a 5-mm flexible scope, a camera port and three or four 5-mm ports were placed in the subumbilical region. For right-sided colon cancer, the transection lines of the ileocolic artery, right colic artery and middle colic artery were decided on the basis of the site of the lesion and the disease stage. If invasion was T3 or deeper, the main blood vessels were transected at their origins. Transection and anastomosis of the in-

Hepato-Gastroenterology 2011; 58:00-00

testine were performed by extending the small abdominal incision to about 5cm. The intestine was then exteriorized, and transection and anastomosis were performed. For left-sided colon cancer, the origin of the inferior mesenteric artery was transected if the depth of invasion was T3 or deeper. If the portion of the intestine containing the lesion could be adequately elevated through the small incision, transection and anastomosis of the colon were performed extracorporeally. If the intestine could not be elevated, the mesentery was divided, and the distal colon was transected intracorporeally with the use of an automatic stapler. The portion of the colon containing the lesion was exteriorized through the small incision, and the proximal colon was transected. The tip of the automatic stapler was placed in the cut end of the intestine, and the intestine was repositioned into the peritoneal cavity. The abdomen was re-insufflated, and anastomosis was performed in the peritoneal cavity using a double-stapling technique (13).

After surgery, patients with stage III disease received adjuvant chemotherapy with an oral preparation of 5-fluorouracil for about 6 to 12 months, in principle. After discharge, patients were followed-up on an outpatient basis. In addition to physical examinations, serum carcinoembryonic antigen levels were measured (3-month to 1-year intervals), and computed tomography of the chest and abdomen (6-month intervals) and colonoscopic examinations (1-year intervals) were performed. The results of these imaging and histopathological studies were comprehensively evaluated to diagnose recurrence.

Statistical analysis was performed using the chi-square test and Mann-Whitney U test. A p value of less than 0.05 was considered to indicate statistical significance. The recurrence-free survival rate and overall survival rate were calculated with the Kaplan-Meier method. The logrank test was used to compare differences between groups.

RESULTS

Postoperative complications occurred in 9% (23/253) of the patients. Wound infection was most common (4.3%, 11/253), followed by ileus (1.9%, 5/253). The conversion rate to open surgery was 2% (5/253). The reasons for conversion to open surgery were tumor invasion to other organs in 2 patients, adhesion in 2, and difficulty in securing an adequate field of vision because of obesity in 1 patient (**Table 2**).

Postoperative recurrence occurred in 26% (66/253) of patients. As for the type of recurrence, liver metastasis was the most common (47%, 31/66), followed by lung metastasis (21%, 14/66) and lymph-node metastasis (14%, 9/66) (**Table 3**). No patient had port-site recurrence.

The 10-year recurrence-free survival rate (**Figure 1**, p=0.003) and the overall survival rate (**Figure 2**, p=0.003) were respectively 92.9% and 93.3% in pathological stage II disease, 82.7% and 82.9% in stage IIIA plus IIIB disease, and 68.6% and 70.3% in stage IIIC disease. The differences among the 3 groups were significant.

TABLE 1. Demographic characteristics of the patients.

Number of patients	253
Age (years)	64 (29-88)
Male:Female	136:117
ASA score (I:II:III)	100:133:20
BMI (kg/m^2)	23 (14-38)
Tumor site	
Right colon	115 (45%)
Left colon	138 (55%)
Tumor size (cm)	4 (1-12)
Depth of tumor invasion	
T1	4 (2%)
T2	16 (6%)
T3	230 (91%)
T4	3 (1%)
Lymph node metastasis	
N0	105 (42%)
N1	119 (47%)
N2	29 (11%)
AJCC/TNM staging	
IIA	104 (41%)
IIB	1 (1%)
IIIA	23 (9%)
IIIB	97 (38%)
IIIC	28 (11%)
Follow-up period (months)*	67 (7-149)

Values are represented as medians (range). BMI, Body Mass Index; Right colon, cecum, ascending colon and transverse colon; Left, descending colon, sigmoid and rectosigmoid colon; ASA status, Physical status according to the American Society of Anesthesiologists Classification.

TABLE 2. Operation time, blood loss and postoperative complications.

Operation time (min)*	195 (120-380)
Estimated blood loss (mL)	20 (0-3880)
Conversion to open procedure	5 cases (2.0%)
Postoperative complications	
Wound infection	11 cases (4.3%)
Intestinal obstruction	5 cases (2.0%)
Anastomotic leakage	4 cases (1.6%)
Intestinal bleeding	3 cases (1.1%)

*Values are represented as medians (range)

TABLE 3. Recurrence in patients with colon cancer.

Site of recurrence	Number of cases
Liver*	31 (47%)
Lung*	14 (21%)
Lymph nodes	9 (14%)
Peritoneum	7 (11%)
Anastomosis	4 (6%)
Ovary	1 (2%)

*Including 4 cases with synchronous metastasis of liver and lung. *The total number of recurrent cases was 66 (26%).

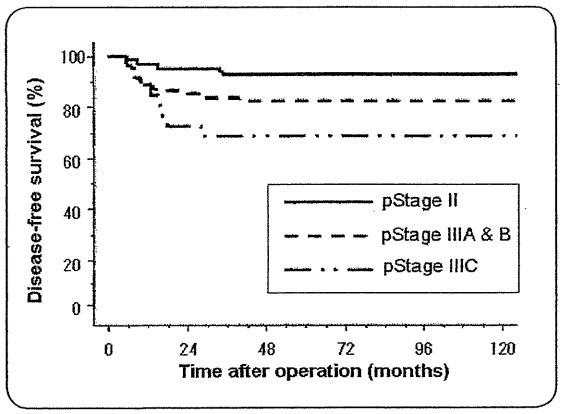

FIGURE 1. Disease-free survival according to tumor-node-metastasis stage in patients with colon cancer.

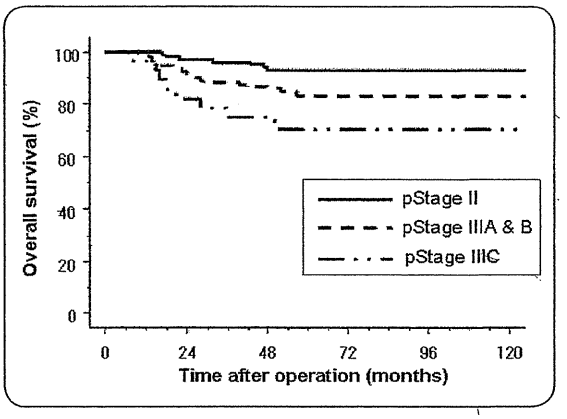

FIGURE 2. Overall survival according to tumor-node-metastasis stage in patients with colon cancer.

DISCUSSION

Our study showed that laparoscopic surgery was minimally invasive and had good surgical outcomes and a low incidence of postoperative complications in patients with pathological stage II and III colon cancer. Moreover, the 10-year recurrence-free survival rate and the overall survival rate were both good.

As for short-term outcomes, Schwenk *et al.* (14) conducted a meta-analysis of 25 randomized controlled studies. Laparoscopic surgery was found to have a longer operation time than open surgery, but was associated with less blood loss and a shorter duration of paralytic ileus after operation. Other advantages of laparoscopic surgery were better postoperative respiratory function, less postoperative pain, and fewer postoperative complications. Lourenco *et al.* (15) conducted a meta-analysis of 19 studies and reported that laparoscopic surgery was associated with a shorter hospital stay, less blood loss, less postoperative pain and an earlier return to usual activities than open surgery. However, the operation time was longer with laparoscopic surgery than with open surgery. The rate of lymph-node dissection, the resection rate of lesions and the quality of life did not differ between the 2 treatments.

As for long-term outcomes, the results of randomized controlled trials such as the Barcelona trial (8), the Clinical Outcomes of Surgical Therapy (COST) study (9), the Colon Cancer Laparoscopic or Open Resection (COLOR) trial (10), the Conventional *vs.* Laparoscopic-Assisted Surgery in Patients with Colorectal Cancer (CLASICC) trial and a prospective randomized trial conducted by Leung *et al.* (12) showed that oncological outcomes did not differ between laparoscopic surgery and open surgery. Bonjer *et al.* performed a meta-analysis of data from the Barcelona, COST, COLOR, and CLASICC trials, including a total of 1765 patients with stage I to III colon cancer (16). After excluding 229 patients, 796 underwent laparoscopic surgery and 740 underwent open surgery. The recurrence-free survival rate and the overall survival rate at 3 years did not differ significantly between the groups. Jackson *et al.* (17) conducted a meta-analysis of 10 randomized controlled trials comparing laparoscopic surgery with open surgery, including the CLASICC and COLOR trials. The study group comprised a total of 3830 patients. Patients were followed up for more than 18 months in 7 of the 10 studies. There was no difference in the recurrence rate or the overall survival rate between the laparoscopic surgery group and open surgery group.

As for long-term outcomes, randomized controlled trials such as the study by Lacy *et al.* (8) and the COAST (9) and CLASICC trials (11) demonstrated that laparoscopic surgery is superior or non-inferior to open surgery. The COLOR trial enrolled patients with T1 to T3 colon cancer and excluded those with stage IV disease. As for short-term outcomes, laparoscopic surgery was associated with less postoperative pain, earlier recovery of intestinal peristalsis and a shorter hospital stay than open surgery. The rates of postoperative complications and surgical mortality were similar in both groups, showing that laparoscopic surgery was safe. However, an intent-to-treat analysis failed to demonstrate that laparoscopic surgery is non-inferior to open surgery with respect to 3-year disease-free survival (10). The rate of conversion to open surgery was 20% among patients included in the analysis, and the number of lymph nodes removed was small. About half of patients with T4 disease were converted from laparoscopic surgery to open surgery. These results suggest that there might have been problems in the preoperative diagnosis and surgical techniques.

The current technique for laparoscopic resection of colorectal cancer is associated with several unresolved issues. Many studies, including ours, have shown that outcomes of laparoscopic surgery are generally similar to those of open surgery in patients with colorectal cancer. However, the risks of tumor cell dissemination and intraperitoneal implantation remain important concerns in patients undergoing laparoscopic surgery. Procedures that damage tumors have increased risks of the intraperitoneal dissemination of tumor cells during laparoscopic surgery. Therefore, procedures that require direct contact with tumors should be avoided whenever possible. Laparoscopic surgery has several other limitations. Firstly, laparoscopic procedures do not allow surgeons to adequately palpate or visually inspect the inside of the peritoneal cavity, negatively affecting the accuracy of intraoperative disease staging. Secondly, the effect of carbon dioxide gas on the biologic malignancy of cancer cells remains unclear. Experimentally, carbon dioxide gas has been shown to promote cancer cell adhesion and increase liver metastases (18). Thirdly, laparoscopic surgery might reduce the extent of lymph-node dissection. However, the number of removed lymph nodes after laparoscopic surgery has been reported to be similar to that after open surgery, provided that the techniques for lymph-node dissection are mastered (19,20). In our study, the number of lymph nodes removed was standard. Fourthly, port-site recur-

rence is a potential problem after laparoscopic surgery (7). However, several studies have reported that wound-site recurrence also occurs at a given rate (0.6% to 7.6%) after open surgery (21,22). To date, there have been few reports of port-site recurrence after laparoscopic surgery, initially considered an important risk factor. The incidence of port-site recurrence is estimated to be less than 1% (23).

In conclusion, short- and long-term outcomes after laparoscopic surgery for advanced colorectal cancer in our study are comparable to those in many previous randomized controlled trials. We believe that technical progress in laparoscopic surgery and increased experience among surgeons will allow the indication range of this procedure to be extended to advanced colorectal cancer. In February 2009, the enrollment of 1010 patients was completed in a randomized controlled trial (Japan Clinical Oncology Group: JCOG0404) in Japanese patients with Stage II and III colorectal cancer. The endpoints of this trial include survival rates, complications, and conversion rates to open surgery (24). This study is expected to confirm the safety and therapeutic usefulness of laparoscopic surgery in Japan.

REFERENCES

1. **Nakamura T, Mitomi H, Ohtani Y, et al.:** Comparison of long-term outcome of laparoscopic and conventional surgery for advanced colon and rectosigmoid cancer. Hepato-Gastoro 2006; 53:352-353.
2. **Nakamura T, Kokuba Y, Mitomi H, Onozato W, et al.:** Comparison between the oncologic outcome of laparoscopic surgery and open surgery for T1 and T2 rectosigmoidal and rectal carcinoma: matched case-control study. Hepato-Gastroenterol 2007; 54:1094-1097.
3. **Nakamura T, Onozato W, Mitomi H, et al.:** Retrospective, matched case-control study comparing the oncologic outcomes between laparoscopic surgery and open surgery in patients with right-side colon cancer. Surg Today 2009; 39:1040-1045.
4. **Wexner SD, Cohen SM, Johansen OB, et al.:** Laparoscopic colorectal surgery: a prospective assessment and current perspective. Br J Surg 1993; 80:1602-1605.
5. **Milsom JW, Böhm B, Hammerhofer KA, et al.:** A prospective randomized trial comparing laparoscopic versus conventional Techniques in colorectal cancer surgery: A Preliminary Report. J Am Coll Surg 1998; 187:46-54.
6. **Gerritsen van der Hoop, A:** Laparoscopic surgery for colorectal carcinoma: an overnight victory? Eur J Cancer 2002; 38:899-903.
7. **Nelson H, Petrelli N, Carlin A:** Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001; 93:583-596.
8. **Lacy AM, García-Valdecasas JC, Delgado S, et al.:** Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 2002; 359:2224-2229.
9. **Fleshman J, Sargent DJ, et al.:** Laparoscopic colorectomy for cancer is not inferior to open surgery based on 5-year date from the COST study Group trial. Lancet 2007; 359:2224-2229.
10. **Colon Cancer Laparoscopic or Open Resection Study Group:** Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomized clinical trail. Lancet Oncol 2009; 10:44-52.
11. **Jayne DV, Guillou PJ:** Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASSICC Trial Group. J Clin Oncol 2007; 25:3061-3068.
12. **Leung KL, Kwok SP, Lam SC:** Laparoscopic resection of rectosigmoid carcinoma: prospective randomized trial. Lancet 2004; 363:1187-1192.
13. **Nakamura T, Kokuba Y, Mitomi H, et al.:** New technique of laparoscopic colectomy with the lap disc and a 5-mm flexible scope. Surg Endosc 2006; 20:1501-1503.
14. **Schwenk W, Haase O, Neudecker J:** Short term benefits for laparoscopic colorectal resection. Chochrana Database Syst Rev 2005; 20:CD03145.
15. **Tania L, Alison M, Adrian G:** Laparoscopic surgery for colorectal cancer: safe and effective? - A systematic review. Surg Endosc 2008; 22:1146-1160
16. **Bonjer HJ, Hop WC, Nelson H:** Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis. Arch Surg 2007; 142:298-303.
17. **Jackson TD, Kaplan GG, Arena G:** Laparoscopic versus open resection for colorectal cancer: a meta-analysis of oncologic outcomes. J Am Coll Surg 2007; 204:439-446.
18. **Gutt CN, Kim ZG, Schemmer P:** Impact of laparoscopic and conventional surgery on Kupffer cells, tumor-associated CD44 expression, and intrahepatic tumor spread. Arch Surg 2002 ; 137: 1408-1412.
19. **Ota DM:** What's new in general surgery: surgical oncology. J Am Coll Surg 2003 ; 196: 926-932.
20. **Scheidbach H, Schneider C:** Oncological quality and preliminary long-term results in laparoscopic colorectal surgery. Surg Endosc 2003; 17: 903-910.
21. **Hughes ES, McDermmott GA:** The Clinical correlation of an autopsy study of recurrent colorectal cancer. Ann Surg 1979; 189: 496-502.
22. **Reilly WT, Nelson H, Schroader G:** Wound recurrence following conventional treatment of colorectal cancer. A rare but perhaps underestimated problem. Dis Colon Rectum 1996; 39:200-207.
23. **Watanabe M, Hasegawa H, Yamamoto S, et al.:** Laparoscopic surgery for stage I colorectal cancer-long-term outcome. Surg Endosc 2003; 17:1274-1277.
24. **Kitano S, Inomata M:** Japan Clinical Oncology Group Study: Randomized controlled trial to evaluate laparoscopic surgery for colorectal cancer: Japan Clinical Oncology Group Study JCOG 0404. Jpn. Clin Oncol 2005; 35:475-477.

日外科系連会誌 36(4):589-593, 2011

原著

下部消化管腹腔鏡手術中呼気終末二酸化炭素濃度の検討

国立病院機構大阪医療センター外科[1], 同麻酔科[2]
今田 慎也[1] 安井 昌義[1] 池永 雅一[1] 宮崎 道彦[1]
三嶋 秀行[1] 天野 栄三[2] 岡田 俊樹[2] 辻仲 利政[1]

内容要旨

目的:呼気終末二酸化炭素濃度(以下EtCO2)は,血中の二酸化炭素濃度を反映する.腹腔鏡下手術中,気腹に伴う血中二酸化炭素濃度の上昇からEtCO2も上昇する.術中のEtCO2上昇の危険因子としては,皮下気腫・気胸などがある.当院での大腸腹腔鏡手術時の高二酸化炭素血症とEtCO2上昇の術前および術中の危険因子について検討した.方法:2006年6月から2009年3月までの大腸腹腔鏡手術150例において,術中EtCO2が最高値45mmHg以上を示した症例(以下A群)と最高値45mmHg未満であった症例(以下B群)の2群間で,年齢,性別,BMI,術前合併症,術前呼吸機能検査,喫煙歴,手術時間,気腹時間,出血量,皮下気腫について検討した.結果:皮下気腫の発生率でA群とB群間に有意な差を認めた.考察:今回の検討からは,術前因子で高二酸化炭素血症を予測するのは困難であった.

索引用語:腹腔鏡手術,高二酸化炭素血症,EtCO2

はじめに

呼気終末二酸化炭素濃度(以下EtCO2)は,血中の二酸化炭素濃度(以下PaCO2)を反映する.肺胞死腔が大きい慢性肺疾患や肺血流量が減少する肺塞栓といった病態を除くと,EtCO2とPaCO2との差は通常5mmHg以下とされている[1].一般的にPaCO2が45mmHg以上を高二酸化炭素血症と定義されており,高二酸化炭素血症では,中枢神経が抑制されることもあり,臓器の別を問わず,外科周術期には慎重な呼吸管理が必要である.気腹を用いた腹腔鏡下手術中,稀に高二酸化炭素血症を合併し,著明なEtCO2の上昇を認めることがある.当院での腹腔鏡下大腸手術時の高二酸化炭素血症の合併について,EtCO2値を用いてretrospectiveに検討し,高二酸化炭素血症の術前および術中危険因子について検討した.

対象と方法

対象は,2006年6月から2009年3月まで当院で施行した腹腔鏡下大腸手術150例とした.150例の性別,年齢,疾患,手術時間,気腹時間,出血量,術後入院日数,術前後の合併症を**Table 1**に示した.

Table 1で示したように,今回の検討症例の中には術前に慢性肺疾患や肺塞栓症の患者は存在しなかった.このためPaCO2とEtCO2の差はほとんどないと考え,術中EtCO2が徐々に上昇し呼吸器設定変更にも関わらず一時点でも最高値が45mmHg以上であった症例を高二酸化炭素血症群(A群)とし,EtCO2が45mmHg未満であった症例を正常群(B群)として,2群間で患者因子である年齢,性別,BMI,術前合併症,術前呼吸機能検査,喫煙歴と,また手術因子である手術時間,気腹時間,出血量,皮下気腫についてそれぞれ比較検討した.2群間の比較は,Fisherの直接法あるいはMann-WhitneyのU検定を用いて行っ

受付:2011年3月17日,採用:2011年5月6日
連絡先 今田慎也
〒537-0025 大阪府大阪市東成区中道1—3—3
大阪府立成人病センター外科

Table 1 Subject summaries (150 cases)

Gender (Male/Female)	83/67
Age (years)	63.0 (13—89)
Diagnosis	Colorectal cancer 134 (colon 104, rectum 30) Rectal prolapse 4 Appendicitis 9 Diverticulitis 3
Operating time (m)	213 (46—526)
Insufflation time (m)	144 (22—347)
Blood loss (ml)	26.0 (2—360)
Postoperative hospital stay (days)	11.7 (3—124)
Preoperative complications	Cranial disease 6 Cardiovascular disease 18 Hepatic disease 6 Endocrine/Renal disease 15 Malformation 1 Malignant tumor 10 Steroids 2
Postoperative complications	Pulmonary embolism 1 Ileus 6 Surgical site infection 7 (Organ abscess 3, leakage 4) Hemorrhage 2 Urinary infection 2 Wound separation 2

Table 2 Peak EtCO2 exceeding 45 mmHg

Case	Gender (Male/ Female)	Age (years)	Diagnosis	BMI	Smoking history (cigarettes per day)	Insufflation time (m)	Subcutaneous emphysema
1	Female	59	Adenoma	20	30	197	No
2	Female	70	Colon cancer	17.9	0	163	Yes
3	Female	58	Colon cancer	34.3	0	131	No
4	Male	77	Rectal prolapse	21.5	0	164	No
5	Female	34	Colon cancer	18.2	0	143	No
6	Female	38	Rectal cancer	21.7	0	310	No
7	Female	80	Colon cancer	16.9	0	204	Yes
8	Female	13	Appendicitis	14.9	0	78	No
9	Male	66	Rectal cancer	24.4	20	156	No
10	Male	65	Colon cancer	31.8	0	119	No
11	Male	65	Rectal cancer	19.9	12	187	No

Note : Preoperative respiratory results were within the normal range in these subjects.

た．$P<0.05$をもって有意とした．

術前呼吸機能検査については，1秒率（1秒量/努力性肺活量）が70％以下の閉塞性換気障害があるか，あるいは％肺活量が80％以下の拘束性換気障害のいずれかの場合を呼吸機能異常とした．喫煙歴は，入院前まで喫煙していた場合を喫煙歴ありとし,過去の喫煙は今回の検討では，喫煙歴なしとした．

また，麻酔中は，心電図，経皮的動脈酸素飽和度（以下SpO2），EtCO2，膀胱温を連続的にモニターし，5分ごとに非観血的動脈圧測定を行った．呼吸は，気管内挿管直後より1回換気量8～

Table 3　Preoperative factors

	Group A (n=11)	Group B (n=139)	P
Age (years)	56.8 (13−77)	63.8 (27−89)	0.09
Gender (Male/Female)	4/7	79/60	0.22
BMI	22.0 (14.9−34.3)	23.1 (16.2−41)	0.41
Preoperative complication (cases)	4 (36.4%)	54 (38.8%)	>0.99
Preoperative respiratory examination (cases)	Normal 11	Normal 119 Abnormal 20	0.36
Smoking history (cases)	3 (27.2%)	25 (18.0%)	0.43

Table 4　Operative factors

	Group A (n=11)	Group B (n=139)	P
Operating time (m)	216 (106−351)	213 (46−526)	0.88
Insufflation time (m)	168 (78−310)	142 (25−347)	0.19
Blood loss (ml)	22.3 (5−130)	26.2 (2−360)	0.79
Subcutaneous emphysema (cases)	2	0	0.005

10ml/kg，呼吸回数10～12回/分の調節呼吸として，最高気道内圧が30cmH2Oを，EtCO2が40mmHgを超えないように呼吸回数と１回換気量を増減した．動脈内留置カテーテル（以下A-line）は，通常は確保せず，術前のAmerican Society of Anesthesiologists分類が高い場合にA-line確保することを考慮した．腹腔鏡下の手技は，気腹圧8mmH2Oで二酸化炭素を用いた気腹下に行った．

結　果

150例のうち男性83例，女性67例であり，平均年齢は63.0歳（13歳～89歳）であった．疾患の内訳は大腸癌134例（結腸癌104例，直腸癌30例），直腸脱４例，虫垂炎９例，憩室炎３例であった．平均手術時間は213分（46分～526分），平均気腹時間は144分（22分～347分），平均出血量は26.0ml（２～360ml），平均術後在院日数は11.7日（３日～124日）であった．術前の合併症は，58例（38.7%）に認められ，内訳は先天疾患から悪性腫瘍，心・循環器疾患，内分泌・代謝・腎疾患などと多岐に及んだ．術後合併症は19例（12.7%）で認めた．中でもSSIが７例，腸閉塞が６例と多かったが，肺梗塞による死亡例１例を除き保存的あるいは再手術により病態改善し，退院した．

EtCO2最高値が45mmHg以上であったA群（**Table 2**）は11例で，EtCO2の平均値は49.6mmHg（45～68mmHg）であった．一方，45mmHg以下であったB群は139例であり，平均値は37.5mmHg（33～44mmHg）であった．

1．患者因子

A群とB群における平均年齢はそれぞれ56.8歳，63.9歳（p＝0.09）であった．性別はA群が男性４例，女性７例に対してB群では，男性79例，女性60例（p＝0.22）であった．BMIは，A群22.0，B群23.1（p＝0.41）であり，年齢，性別，BMIで２群間で統計学的に有意な差は認めなかった．術前合併症は，A群で４例（36.4%），B群で54例（38.8%）（p＞0.99）であった．また，術前呼吸機能検査は，A群全例で異常を認めず，B群では119例（85.6%）で異常を認めなかった（p＝0.36）．術前まで喫煙をしていたのは，A群で３例（27.2%），B群で25例（18.0%）であり（p＝0.43），術前合併症，術前呼吸機能検査，喫煙歴でも有意な差を認めなかった（**Table 3**）．

2．手術因子

A群とB群における手術時間の平均値はそれぞれ216分，212分（P＝0.88）であった．気腹時間の平均値はそれぞれ168分，142分（P＝0.19）であり，

術中出血量は，A群で22.3ml，B群で26.2ml（P＝0.79）であり，手術時間，気腹時間と出血量では有意な差を認めなかった．術中の皮下気腫をA群で2例に認めた一方，B群では認めず（P＝0.005），A群，B群で統計学的に有意な差を認めた（**Table 4**）．

術後，A群全ての症例で換気不全などによる再挿管は不要であった．また，11例とも気胸，二酸化炭素塞栓，気道閉塞などの合併症は認めなかった．皮下気腫2例については，術後皮下気腫の増悪を認めなかった．

考　察

二酸化炭素を使用した気腹中は，腹腔内圧の上昇と横隔膜の挙上により全肺気量，機能的残気量，肺・胸郭コンプライアンスが低下し[2]，加えて二酸化炭素が腹膜から吸収されることにより血中の二酸化炭素濃度が上昇する．二酸化炭素を利用した気腹により，PaCO2は通常10mmHg程度上昇する[3)4)]が，分時換気量の増加で通常是正が可能である．今回，EtCO2の著明な上昇を呈した11例は，調節呼吸と気腹終了により，全例EtCO2は45mmHg以下に低下し，腹腔鏡下手術を完遂することができた．是正されない二酸化炭素血症をきたした場合には，皮下気腫，気胸，二酸化炭素塞栓，気道閉塞などの合併を考えなければならず，腹腔鏡下の手技の中止や，手術そのものの中断，中止も考慮する必要もある．今回の検討では，高二酸化炭素血症をきたした11例のうち2例で皮下気腫を認めたが，その他の合併症は認めなかった．術中皮下気腫を認めた2症例については，皮下からの二酸化炭素の吸収により高二酸化炭素血症をきたしたと考えられる．また，Conettaら[5]やEveloffら[6]が，広範な皮下気腫による胸壁の圧迫により胸郭の運動が制限され，呼吸不全となった症例を報告しているように，皮下気腫による胸郭の運動制限により高二酸化炭素血症を助長させた可能性もある．

真弓ら[7]は，皮下気腫を生じる原因には，外科手技上の問題と患者側因子があると報告している．外科手技としては，トロカール刺入部からの二酸化炭素の流入および過度の腹腔内圧の上昇が考えられる．患者側因子としては，皮下組織の脆弱性，横隔膜組織の脆弱性などが挙げられ，女性，高齢者，痩せ型の人に皮下気腫の発生が多いとされる[8)9)]．今回われわれが行ったA，B2群間の比較検討では，トロカールが不安定であったかどうかは不明である．腹腔内圧は，8mmHg前後で調節されているため皮下気腫の原因としては，否定的と考える．一方，患者側因子としては，2症例とも高齢の女性であり，BMIも17と18であり，いずれも痩せ型であった．以上のことから，本症例における皮下気腫を生じた2例については，患者側因子によるものである可能性が高いと考えられる．

今回の患者因子とEtCO2の関連性の検討では，年齢，性別，BMI，術前合併症，術前呼吸機能検査，喫煙歴はいずれも高二酸化炭素血症の明らかな要因とはならず，術前から高二酸化炭素血症を予測するのは困難であった．

文　献

1) 田中具治，古谷秀勝，播岡徳也，他：動脈血二酸化炭素分圧と呼気終末二酸化炭素分圧との間に著明な解離をきたした腹腔鏡下大腸切除術の1例．日臨麻会誌 26：82-85，2006
2) Manner T, Aantaa R, Alanen M, et al: Lung compliance during laparoscopic surgery in paediatric patients. Pediatr Anaesth 8:25-29, 1998
3) 謝　宗安，山田倫子，浅川喜裕，他：腹腔鏡下胆嚢摘出術の麻酔511例の検討．臨床麻酔 19：31-34，1995
4) 島　英樹，安田信彦，加賀谷慎，他：腹腔鏡下胆嚢摘出術が動脈二酸化炭素分圧に及ぼす影響.臨床麻酔 15：767-768，1991
5) Conetta R, Barman AA, Iakovou C, et al: Acute ventilatory failure from massive subcutaneous emphysema. Chest 104:978-980, 1993
6) Eveloff SE, Doant WE, Aisenbergal R, et al: Pneumatic chest wall compression. A cause of respiratory gailure from massive subcutaneous emphysema. Chest 99:1021-1023, 1991
7) 真弓雅子，佐藤重仁：高二酸化炭素症のために開腹となった腹腔鏡下胆嚢摘出術の1症例．日臨麻会誌 7：689-692，2007
8) Gerges FJ, Kanazi GE, Jabbour-Khoury SI: Anesthesia for laparoscopy: a review. J Clin Anesth 18:67-78, 2006
9) 鈴木昭宏：胸・腹腔鏡下手術の麻酔に必要なスキル．日臨麻会誌 26：239-245，2006

End-Tidal Carbon Dioxide Examination Following Laparoscopic Colorectal Surgery

Shinya Imada[1)], Masayoshi Yasui[1)], Masakazu Ikenaga[1)], Michihiko Miyazaki[1)], Hideyuki Mishima[1)], Eizo Amano[2)], Toshiki Okada[2)] and Toshimasa Tsujinaka[1)]

[1)]Department of Surgery and [2)]Department of Anesthesia, Osaka National Hospital

End-tidal carbon dioxide (EtCO2), reflecting the blood carbon dioxide level, rises during laparoscopic surgery as blood carbon dioxide density increases with insufflation. We studied risk factors for hypercarbia and EtCO2 increase during laparoscopic colorectal surgery. The 150 subjects, operated on between June 2006 and March 2009, were divided into those whose EtCO2 peaked during surgery at over 45 mmHg (group A, n=11) and those whose EtCO2 did not (group B, n=139). We compared the 2 groups for age, gender, body mass index (BMI), presurgical complications, presurgical respiratory function, smoking, insufflation time, bleeding volume, and subcutaneous emphysema. No significant differences were found except in subcutaneous emphysema. We concluded that hypercarbia is difficult to estimate preoperatively.

Key words: laparoscopy, end-tidal carbon dioxide, hypercarbia

Int J Colorectal Dis
DOI 10.1007/s00384-010-1036-0

ORIGINAL ARTICLE

Diverting stoma in rectal cancer surgery. A retrospective study of 329 patients from Japanese cancer centers

Akio Shiomi · Masaaki Ito · Norio Saito · Masayuki Ohue · Takashi Hirai · Yoshiro Kubo · Yoshihiro Moriya

Accepted: 22 July 2010

Abstract
Background A diverting stoma (DS) has been constructed for many patients with low anterior resection (LAR), but it is still controversial whether DS can prevent anastomotic leakages. The aim of this study was to investigate the risk factors of anastomotic leakage including DS construction, and to evaluate the clinical course affected by DS according to the necessity of urgent abdominal reoperation for anastomotic leakage.

Patients and methods This was a retrospective analysis of 329 middle or lower rectal cancer patients who underwent LAR with mechanical reconstruction using circular staplers. Clinical data were collected from five cancer centers in Japan.

Results The overall anastomotic leakage rate was 10.0% (33 of 329). We experienced one mortality in this series (0.3%; 1/329). Clinical factors associated with DS construction included tumor location, operation time, intraoperative bleeding, lateral lymph node dissection, simultaneous resection of other organs, and the level of anastomosis, respectively.

On univariate analysis, high ligation of the inferior mesenteric artery had a significantly high leakage rate, but not on multivariate analysis. DS construction had no connection with the overall leakage rate. Concerning the clinical course affected by DS, the frequency of urgent reoperation was significantly increased in patients without DS compared with those with DS, 11.1% and 54.2%, respectively (p=0.04).

Conclusions LAR was the safe and preferred option for rectal cancer patients with very low mortality and an acceptable leakage rate. DS did not have a relationship with overall anastomotic leakage, but did seem to mitigate its consequences and reduce the requirement for urgent abdominal reoperation.

Keywords Rectal cancer · Anastomotic leakage · Diverting stoma · Defunctioning stoma · Low anterior resection

A. Shiomi (✉)
Department of Colorectal Surgery,
Shizuoka Cancer Center Hospital,
1007 Shimonagakubo, Nagaizumi-cho,
Sunto-gun, Shizuoka 411-8777, Japan
e-mail: a.shiomi@scchr.jp

M. Ito · N. Saito
Department of Colorectal Surgery,
National Cancer Center Hospital East,
Kashiwa, Chiba, Japan

Y. Moriya
Department of Colorectal Surgery,
National Cancer Center Hospital,
Tokyo, Japan

M. Ohue
Department of Surgical Oncology,
Osaka Medical Center for Cancer and Cardiovascular Diseases,
Osaka, Japan

T. Hirai
Department of Gastroenterological Surgery,
Aichi Cancer Center Hospital,
Nagoya, Japan

Y. Kubo
Department of Surgical Oncology,
Shikoku Cancer Center Hospital,
Matsuyama, Japan

Published online: 05 August 2010

Introduction

Anastomotic leakage is a major problem in rectal cancer surgery, because a sphincter-preserving operation has become standard for many rectal cancer patients. A

temporary diverting stoma (DS) has been constructed for many patients in low anterior resection (LAR). But the indication of DS construction for patients without intraoperative adverse events has not been clarified for a long time. Theoretically, DS was constructed to divert the fecal stream from anastomotic sites, and to protect fragile anastomotic sites. But it remains unproven whether diverting the fecal stream in itself directly prevents leakage. Several retrospective studies showed that the absence of DS was a risk factor for leakage in LAR, whereas others did not. Therefore, it is controversial whether DS can prevent anastomotic leakage. Although recent randomized studies [1, 2] and meta-analyses [3, 4] have shown that DS reduced the incidence of symptomatic leakage in LAR for rectal cancer, there is still limited evidence as to the impact of DS on leakage. Moreover, there have been few analyses about this issue in multicenter studies with a large number of patients from Japan.

The aim of this study was to investigate the risk factors of anastomotic leakage including DS construction, and to evaluate the clinical course affected by DS according to the necessity of urgent abdominal reoperation for such leakage using data collected from five cancer centers in Japan.

Patients and method

Patients

We reviewed the clinical data from five cancer centers in Japan which participated in the "Studies on the standardization for diagnosis, treatment, and follow-up of colorectal cancer patients", sponsored by Grant-in-Aid 18-2 for Cancer Research from the Ministry of Health, Welfare and Labor of Japan. All data on patient demographics, comorbidities, and the histological results were investigated retrospectively from the clinical records of each hospital.

From 2002 to 2004, a total of 329 consecutive patients with primary rectal cancer underwent LAR, and were investigated in this series. LAR was performed on patients with middle or lower rectal cancer, and reconstructions were done using circular staplers. Coloanal anastomosis using the hand-sewn technique was excluded from this study. Patients with subtotal colectomy, total proctocolectomy, abdominoperineal resection, Hartmann's procedure, or with pull-through procedures were also excluded.

Surgical procedure

The inferior mesenteric artery (IMA) was divided either at its origin or below the origin of the left colic artery (LCA). High ligation of IMA was defined as dividing IMA at its origin, while low ligation was defined as dividing IMA below the origin of LCA. For oncological lymph node dissection, we classify regional lymph nodes into three groups: perirectal, intermediate, and main lymph nodes. Perirectal nodes are lymph nodes in the mesorectum along the superior rectal artery. Intermediate nodes are lymph nodes along IMA between the origin of the left colic artery and the origin of the terminal sigmoid artery. Main nodes mean the lymph nodes along the IMA proximal to the origin of the LCA [5]. Lymph node dissection for UICC stage I is complete dissection of perirectal and intermediate lymph nodes, that is, low ligation without lymph node dissection around the root of IMA. Lymph node dissection for stage II, III, and IV is complete dissection of all regional lymph nodes, that is, high or low ligation with lymph node dissection around the root of IMA [6].

After total mesorectal excision or tumor-specific mesorectal excision [7], we performed rectal irrigation, while clamping the anal side of the tumor. The rectum was then divided transversely or vertically [8]. After that, we usually added lateral lymph node dissection for patients diagnosed with stage II, III, and IV [9]. Although the extent of lymphadenectomy for stage IV is still debatable, in the case that every distant metastasis (stage IV) was resectable, we perform full lymph node dissection.

Reconstruction was done using a circular stapler. Most anastomoses were straight, and colonic J pouch or transverse coloplasty pouch was sometimes used at the discretion of the operating surgeon. Intraoperative leakage test by transanal instillation of fluid or air was performed depending on the surgeon. Pelvic drain was used routinely.

Indication of DS construction

No clear applicable criteria for DS construction were stipulated in the present study. The DS construction decision was made by the individual surgeon in each case.

Definition of anastomotic leakage

Anastomotic leakage was defined clinically by the presence of the following: discharge of gas, pus, or feces from the drain or wound; discharge of pus per rectum; or rectovaginal fistula. All clinically suspicious anastomotic leakages were confirmed by one or more of the following image diagnoses: contrast study; CT scan; rectoscopy. If these cases were proven not to show anastomotic insufficiency by these imaging studies, they were defined as pelvic abscess

and not as anastomotic leakage. We did not perform routine diagnostic imaging after LAR to detect anastomotic dehiscence in clinically stable patients.

Variables analyzed

Variables included in this analysis were age, gender, body mass index (BMI), bowel obstruction, tumor location, tumor invasion, adjuvant therapy, level of IMA ligation, lateral lymph node dissection, type of anastomosis (single stapling technique, SST; or double stapling technique, DST), pouch surgery, intraoperative blood loss, operating time, DS construction, synchronous resections of other organs (hepatectomies for simultaneous liver metastasis or extended surgery to adherent organs, or additional cancer resections for double cancers), tumor size, and distal resection margin of specimen.

Bowel obstruction was defined as stenosis preventing the passage of a colon fiberscope. Tumor location was classified into middle or lower rectum according to the main part of the tumor. Tumors in the lower rectum were defined as those in which the main part was located below the peritoneal reflection. Tumor location in relation to the anal verge was preoperatively measured using rigid scope or digital examination. Tumor invasion was classified according to the UICC-TNM classification (6th edition [10]) preoperatively. Tumor size and distal resection margin were measured on the specimen before fixation with formalin. The level of anastomosis from the anal verge was measured with a digital examination. But due to the retrospective nature of this study, when the data were not available, the distance was calculated from the tumor location and distal resection margin.

Statistical analysis

In the univariate analysis, the chi-squared test and Mann–Whitney test were used. After univariate analysis, variables with a p value$\leq$0.1 were selected for multivariate analysis. A multivariate analysis was performed using a binary logistic regression model. All p values $<$0.05 were considered statistically significant.

Table 1 Patient characteristics

Gender	
Male	215
Female	114
Age(years)	59.0±10.5 (23–87)
Tumor location (cm)	6.1±1.7 (4.0–12.0)
Bowel obstruction	
No	305
Yes	18
Missing	6
Tumor invasion	
T1,T2	108
T3,T4	215
Missing	6
Neoadjuvant chemo Tx	
No	324
Yes	5
Anastomosis	
SST	15
DST	314
High ligation	
No	142
Yes	183
Missing	4
LLND	
No	197
Yes	132
Level of anastomosis (cm)	4.1±1.4 (1.0–9.5)
Intraoperative bleeding (ml)	598±590 (10–3723)
Operating time (min)	240±104.1 (90–620)
BMI (k/m^2)	22.6±3.1 (14.1–31.2)
Tumor size (cm)	4.4±2.3 (0–12.0)
Simultaneous resection	
No	292
Yes	37
DS construction	
No	209
Yes	120

Values are number or mean±standard deviation (ranges)

DS diverting stoma, *BMI* body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Results

Patient characteristics

From 2002 to 2004, a total of 329 consecutive patients underwent LAR. Patient characteristics were shown in Table 1. One hundred and eighteen middle rectal cancer patients and 211 low rectal cancer patients were investigated in this series. Average distance from the lower edge of the tumor to the anal verge was 6.1 cm (4.0–12.0 cm). Average distance from anastomosis to the anal verge was 4.1 cm (1.0–9.5 cm).

Neoadjuvant chemotherapy was performed for five patients, but others were treated by surgery alone. Neo-

adjuvant radiotherapy or chemoradiotherapy was not performed in this series, because preoperative therapy for resectable rectal cancer was not standard in Japan.

Synchronous resections included 20 extended resections for direct invasion of adjacent organs, 13 hepatectomies for liver metastasis, and five resections of double primary cancers.

Morbidity and mortality

The overall rate of anastomotic leakage was 10.0% (33 of 329). We experienced only one mortality in this series (0.3%; 1/329). This patient died from a septic complication caused by anastomotic leakage in the case of LAR with DS 6 days after initial surgery.

Diverting stoma

A DS was constructed in 120 patients (36.5%; 120 of 329) in initial LAR, respectively. Among the colorectal surgeons participating in this study, ileostomy was major and chosen for 92 (76.7%) patients, while transverse colostomy was done for 28 (23.3%) patients.

The DS construction rate had a significant association with tumor location. DS was constructed in only 12.7% of middle rectal cancer patients, but in 48.3% of low rectal cancer patients who experienced temporary stoma at initial LAR, respectively.

Other factors found to be significantly associated with DS construction included tumor location, operation time, intraoperative bleeding, lateral lymph node dissection,

Table 2 Univariate analysis of factors related with DS construction

	Diverting stoma		Rate	*p*-value
	DS(−)	DS(+)		
Gender				
Male	130	85	39.5	0.11
Female	79	35	30.7	
Age (years)	58.8±10.7 (23–87)	59.4±10.2 (29–75)		0.42
Tumor location (cm)	6.4±1.6 (4.0–12.0)	5.9±1.7 (4.0–12.0)		0.001
Bowel obstruction				
No	195	110	36.1	0.76
Yes	11	7	38.9	
Tumor invasion				
T1,T2	71	37	34.6	0.50
T3,T4	133	82	38.1	
Neoadjuvant chemo Tx				
No	204	120	37.0	0.10
Yes	5	0	0.0	
Anastomosis				
SST	8	7	46.7	0.40
DST	201	113	36.0	
High ligation				
No	125	58	31.7	0.12
Yes	82	60	42.3	
LLND				
No	146	51	25.9	<0.0001
Yes	63	69	52.3	
Level of anastomosis (cm)	4.2±1.4 (1.0–9.0)	3.8±1.4 (1.0–9.5)		0.002
Intraoperative bleeding (ml)	505±524 (10–2985)	760±662 (17–3723)		<0.0001
Operating time (min)	231±90.6 (90–559)	318±102.7 (130–620)		<0.0001
BMI (k/m^2)	22.9±3.0 (14.1–31.2)	22.3±3.2 (15.8–30.8)		0.07
Tumor size (cm)	4.4±2. (0–12.0)	4.4±2.3 (1.0–10.0)		0.97
Simultaneous resection				
No	192	100	34.2	0.02
Yes	17	20	54.1	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

simultaneous resection of other organs, and level of anastomosis (Table 2).

Risk factors of anastomotic leakage

Clinical variables were analyzed to investigate the risk factors for anastomotic leakage (Table 3). On univariate analysis, LAR with high ligation of IMA had a significantly high leakage rate ($p<0.05$). There were increased but statistically insignificant impacts on leakage in males, bowel obstruction, massive intraoperative bleeding, and simultaneous resection of other organs.

Nine (7.5%) of 120 patients with DS had leakage, compared with 24 (11.5%) of 209 patients without DS ($p=0.25$). DS construction also had no relevance to the overall anastomotic leakage.

Risk factors of leakage limited to the LAR without DS were also investigated. As shown in Table 4, no obvious statistical significance was found with any clinical factor.

A multivariate analysis of risk factors for anastomotic leakage showed every factor including high ligation of IMA construction as not statistically significant (Table 5).

Table 3 Univariate analysis of leakage risk factors

	Leakage		Rate	*p*-value
	No leakage	Leakage		
Gender				
Male	190	25	11.6	0.19
Female	106	8	0.7	
Age(years)	58.8±10.6 (23–87)	61.1±10.0 (40–76)		0.20
Tumor location (cm)	6.2±1.7 (4.0–12.0)	6.5±1.7 (4.0–10.0)		0.31
Bowel obstruction				
No	276	29	9.5	0.16
Yes	14	4	22.2	
Tumor invasion				
T1,T2	101	7	6.5	0.12
T3,T4	189	26	12.1	
Neoadjuvant chemo Tx				
No	291	33	10.2	0.59
Yes	5	0	0.0	
Anastomosis				
SST	13	2	13.3	0.66
DST	283	31	9.9	
High ligation				
No	135	7	4.9	0.02
Yes	157	26	14.2	
LLND				
No	177	20	10.1	0.93
Yes	119	13	9.8	
Level of anastomosis (cm)	4.1±1.4 (1.0–9.5)	4.4±1.3 (1.9–7.0)		0.13
Intraoperative bleeding (ml)	573±559 (10–3365)	817±791 (40–3723)		0.06
Operating time (min)	261±102 (90–616)	273±118 (113–620)		0.70
BMI (k/m^2)	22.7±3.1 (14.1–31.2)	22.5±3.2 (16.1–27.0)		0.87
Tumor size (cm)	4.4±2.3 (0–12.0)	5.0±2.3 (2.0–11.0)		0.18
Simultaneous resection				
No	266	26	8.9	0.06
Yes	30	7	18.9	
DS construction				
No	185	24	11.5	0.25
Yes	111	9	7.5	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Table 4 Univariate analysis of leakage risk factors (without DS patients)

	Leakage		Rate	*p*-value
	No leakage	Leakage		
Gender				
Male	114	16	12.3	0.63
Female	71	8	10.1	
Age(years)	58.7±10.8 (23–87)	59.7±10.1 (40–76)		0.65
Tumor location (cm)	6.4±1.6(4.0–12.0)	6.3±1.6 (4.0–10.0)		0.61
Bowel obstruction				
No	173	22	11.3	0.64
Yes	9	2	18.2	
Tumor invasion				
T1,T2	65	6	8.5	0.28
T3,T4	115	18	13.5	
Neoadjuvant chemo Tx				
No	180	24	11.8	0.54
Yes	5	0	0.0	
Anastomosis				
SST	7	1	12.5	0.63
DST	178	23	11.4	
High ligation				
No	108	17	13.6	0.47
Yes	75	7	8.5	
LLND				
No	130	16	11.0	0.72
Yes	55	8	12.7	
Level of anastomosis (cm)	4.2±1.4 (1.0–9.0)	4.2±1.1(2.2–7.0)		0.89
Intraoperative bleeding (cm)	480±502 (10–2985)	703±650 (40–2720)		0.07
Operating time (cm)	228±88 (90–552)	248±108(113–559)		0.60
BMI (k/m^2)	22.9±3.0 (14.1–31.2)	22.7±3.1 (16.1–27.0)		0.82
Tumor size (cm)	4.3±2.3 (0–12.0)	5.0±2.4 (2.0–11.0)		0.26
Simultaneous resection				
No	171	21	10.9	0.31
Yes	14	3	17.6	

Values are number or mean± standard deviation (ranges)

BMI body mass index, *SST* single stapling technique, *DST* double stapling technique, *LLND* lateral lymph node dissection

Clinical course affected by DS construction

The clinical course affected by DS was also investigated, focusing on the necessity of urgent abdominal reoperation for anastomotic leakage. Nine of 120 (7.5%) patients who underwent LAR with DS experienced leakage. Of these nine, only one patient (11.1%) needed urgent reoperation for peritonitis, and eight patients were treated conservatively. Twenty-four of 209 (11.5%) patients who underwent LAR without DS experienced leakage, and 13 (54.2%) of them needed urgent reoperation, while 11 patients were treated conservatively (Table 6). The need for reoperation was significantly increased in patients without DS compared to those with DS, 54.2% and 11.1%, respectively ($p=0.04$).

Table 5 Multivariate analysis of leakage risk factors

	p-value	Odds ratio (95% CI)
High ligation	0.17	1.9 (0.77–4.54)
Intraoperative bleeding	0.78	1.0 (0.99–1.00)
Simultaneous resection	0.12	2.2 (0.82–6.09)

Discussion

LAR was the safe and preferred option for middle or low rectal cancer patients with very low mortality and an acceptable leakage rate among the institutes participating in this study. DS did not have a statistically significant

Table 6 Clinical course affected by diverting stoma

DS in initial LAR		Leakage		Conservative therapy	Urgent operation	Rate of urgent operation	
			%			%	
DS(+)	120	9	7.5	8	1	11.1	p=0.04
DS(−)	209	24	11.5	11	13	54.2	

relationship with the overall leakage rate. Although we cannot conclude the value of DS in terms of leakage prevention from this retrospective study, DS did seem to mitigate the consequences of leakage and reduce the need for urgent abdominal reoperation for leakage. There have been few reports about this issue in multicenter studies with a large number of patients from Japan.

With the advances in surgical procedures and devices in recent decades, sphincter-preserving surgery has become the treatment of choice for rectal cancer patients. In addition, simple and easy reconstruction has become possible thanks to circular stapling devices, even in low-level anastomosis within a narrow pelvis.

However, anastomotic leakage is still a major problem in rectal cancer surgery, sometimes resulting in severe morbidity or mortality. Since stapled anastomosis developed in the 1970s, the mortality of sphincter-preserving operations has decreased. In 1975, Fain et al. [11] reported their experience of mechanical suturing in 165 rectal cancer patients with a mortality of 2.4%. Now, symptomatic anastomotic leakage has been reported to occur in 5% to 20% of cases [12–20], and when present, the associated risk of postoperative mortality is increased to between 6% and 22% [15]. The present study encountered very low mortality (1/329; 0.3%), which is not inferior to the 0.8% recently described [2]. Our result shows the obviously improved safety of LAR using mechanical anastomosis in the Japanese cancer centers participating in this study.

Several risk factors for anastomotic leakage have been reported [12–20], and the relationship between DS and leakage was discussed in many retrospective or nonrandomized prospective studies. Wong et al. [21] reported no statistical difference between patients who were defunctioned (3.8%; 28/742) and those who were not (4%; 13/324). So, they concluded that DS did not reduce the postoperative leak rate. They also concluded that a stoma carried a certain morbidity and also added to the cost of the entire operation, so it should not be performed routinely. On the other hand, Peeters et al. [18] reported that the absence of DS was significantly associated with a higher leakage rate: 43 (8.2%) of 523 patients with DS had leakage, compared with 64 (16.0%) of 401 patients without DS (p<0.001). In the present study, DS construction had no association with the overall anastomotic leakage rate. This reflects our low leakage rate in cases without DS (11.5%; 24 of 209). This rate is comparable to the leakage rate in cases with DS in a randomized controlled trial by Matthiessen et al. (10.3%; 12 of 116) [1].

Although absence of DS was not a risk factor of leakage in this study, because of a general selection bias of nonrandomized study including ours, we cannot conclude whether or not DS can prevent the leakage. This bias results from the selective creation of DS for the patients anticipated to undergo "risky" anastomosis by each surgeon as shown in this investigation. We can also point out another bias, namely that clinically unapparent leakages might have been missed in either group because no systematic assessment of the anastomosis for clinically stable patients was performed in the present study.

Only four randomized control studies sought to investigate the association between DS and leakage [1, 2, 22, 23]. Matthiessen et al. [1] reported the result of intraoperative randomization of a patient undergoing LAR for rectal cancer within 15 cm from the anal verge, and anastomosed within 7 cm. 10.3% (12 of 116) of patients with defunctioning stoma (n=116) had symptomatic leakage, against 28.8% (33 of 118) of those without stoma (n=118). They concluded that defunctioning stoma significantly decreased the rate of symptomatic leakage and was therefore recommended in LAR for rectal cancer. Pakkastie et al. [22] and Graffner et al. [23], on the other hand, could not find any statistical difference between the two groups in their randomized studies comprising 50 and 38 patients, respectively. But due to the small sample, no firm conclusion could be made. So, it is still controversial whether DS can prevent anastomotic leakage. The problem is the limited evidence about this issue. The value of DS in preventing leakage should be evaluated by more prospective studies in the future. And prospective, randomized studies are also warranted to address this issue.

Other reported risk factors include male gender [13–16], level of anastomosis [12–15], previous radiation therapy [13, 14], absence of pelvic drainage [18], poor bowel preparation [12], blood transfusion [12], immunosuppression, and underlying vascular insufficiency. Among these risk factors, male gender and level of anastomosis were widely accepted as significant for leakage. In the present study, there were increased impacts on leakage in male gender, bowel obstruction, massive intraoperative bleeding, and simultaneous resection of other organs. Although statistical significance was not reached, these factors were

comparable to those in previous reports. In the present investigation, due to the retrospective nature of the study design, the level of anastomosis was calculated from the tumor location and distal resection margin when data were not available. And in some patients, tumor location was measured only by digital examination and not by rectoscopy, these might introduce bias. Although the anastomotic level was not associated with leakage, this data should be evaluated with caution.

High ligation of IMA was the only leakage risk factor on univariate analysis in the present study. Lange et al. [24] systematically reviewed the literature concerning the level of ligation and concluded that preserving IMA and left colic artery was anatomically less invasive with respect to circulation and autonomous innervations of the proximal limb of anastomosis. Seike et al. [25] measured the colonic blood flow at the proximal site of the anastomosis by laser Doppler flowmetry to evaluate the influence of high ligation. They proved a significant reduction of colonic blood flow at the proximal site after clamping IMA. Our result also suggested the possibility that blood flow reduction on anastomotic sites leads to more leakage.

In the present study, we reported our low leakage rate in cases without DS (11.5%; 24 of 209). This rate is comparable to the leakage rate in cases with DS in a randomized controlled trial by Matthiessen et al. (10.3%; 12 of 116) [1]. This may have some association with our patient population that neoadjuvant radiotherapy or chemo-radiotherapy was not performed in this series. Neoadjuvant radiation therapy is considered to be a risk factor by some authors [13, 14]. Although randomized multicenter trials have shown that neoadjuvant radiation does not increase postoperative morbidity [26–28], Peeters et al. [18] retrospectively analyzed risk factors from the database of the Dutch Colorectal Cancer Group, and reported that a defunctioning stoma was constructed more often in patients who had received radiation, and that the absence of a DS was significantly associated with a higher leakage rate.

We also reported our low mortality. This reflects our low leakage rate in cases without DS and our appropriate decision of reoperation for peritonitis in cases without DS. We considered that our appropriate decision lead to low mortality rate and high reoperation rate (54.2%). In the present study, a DS constructed at the time of initial surgery obviously reduced the necessity of an urgent reoperation after overt leakage, proving the clinical benefits of DS in this regard. The important objective of DS was not to eliminate leakage but to decrease the risk of reoperation. However, DS construction did not guarantee the complete safety of LAR. In fact, we experienced one mortality in a patient with DS in this series, so complete elimination of leakage and severe septic complications was not feasible.

In conclusion, we clearly demonstrated the outstanding safety of LAR with very low mortality and acceptable leakage rate in our group. Although this retrospective study could not prove whether DS can prevent leakage itself, we found that it could mitigate the need for urgent abdominal reoperation for leakage. To define clear criteria for DS construction, a well-designed randomized control study is genuinely needed in the future.

Acknowledgments This study was supported by the "Studies on the standardization for diagnosis, treatment, and follow-up of colorectal cancer patients", sponsored by Grant-in-Aid 18-2 for Cancer Research from the Ministry of Health, Welfare and Labor of Japan. The authors thank the following surgeons for generously providing data: S. Yamamoto (National Cancer Center Hospital), S. Noura (Osaka Medical Center for Cancer and Cardiovascular Diseases), Y. Komori (Aichi Cancer Center Hospital), and T. Kobatake (National Hospital Organization Shikoku Cancer Center Hospital).

References

1. Matthiessen P, Hallbook O, Rutegard J, Simert G, Sjodahl R (2007) Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 246:207–214
2. Chude GG, Rayate NV, Patris V, Koshariya M, Jagad R, Kawamoto J et al (2008) Defunctioning loop ileostomy with low anterior resection for distal rectal cancer: should we make an ileostomy as a routine procedure? A prospective randomized study. Hepatogastroenterology 55:1562–1567
3. Huser N, Michalski CW, Erkan M, Schuster T, Rosenberg R, Kleeff J et al (2008) Systematic review and meta-analysis of the role of defunctioning stoma in low rectal cancer surgery. Ann Surg 248:52–60
4. Tan WS, Tang CL, Shi L, Eu KW (2009) Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. Br J Surg 96:462–472
5. Japanese Classification of Colorectal Carcinoma 2nd English edition, Japanese Society for Cancer of the Colon and Rectum. Tokyo: Kanehara; 2009
6. JSCCR Guidelines 2009 for the Treatment of Colorectal Cancer, Japanese Society for Cancer of the Colon and Rectum. Tokyo: Kanehara; 2009
7. Zaheer S, Pemberton JH, Farouk R, Dozois RR, Wolff BG, Ilstrup D (1998) Surgical treatment of adenocarcinoma of the rectum. Ann Surg 227:800–811
8. Sato H, Maeda K, Hanai T, Matsumoto M, Aoyama H, Matsuoka H (2006) Modified double-stapling technique in low anterior resection for lower rectal carcinoma. Surg Today 36:30–36
9. Moriya Y, Hojo K, Sawada T, Koyama Y (1989) Significance of lateral node dissection for advanced rectal carcinoma at or below the peritoneal reflection. Dis Colon Rectum 32:307–315
10. Sobin LH (2002) TNM classification of malignant tumours, 6th edn. Wiley-Liss, New York
11. Fain SN, Patin CS, Morgenstern L (1975) Use of a mechanical suturing apparatus in low colorectal anastomosis. Arch Surg 110:1079–1082
12. Yeh CY, Changchien CR, Wang JY, Chen JS, Chen HH, Chiang JM et al (2005) Pelvic drainage and other risk factors for leakage after elective anterior resection in rectal cancer patients: a prospective study of 978 patients. Ann Surg 241:9–13

13. Eriksen MT, Wibe A, Norstein J, Haffner J, Wiig JN (2005) Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. Colorectal Dis 7:51–57
14. Matthiessen P, Hallbook O, Andersson M, Rutegard J, Sjodahl R (2004) Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis 6:462–469
15. Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M (1998) Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 85:355–358
16. Law WI, Chu KW, Ho JW, Chan CW (2000) Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. Am J Surg 179:92–96
17. Pakkastie TE, Luukkonen PE, Jarvinen HJ (1994) Anastomotic leakage after anterior resection of the rectum. Eur J Surg 160:293–297, discussion 299–300
18. Peeters KC, Tollenaar RA, Marijnen CA, Klein Kranenbarg E, Steup WH, Wiggers T et al (2005) Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 92:211–216
19. Hallbook O, Pahlman L, Krog M, Wexner SD, Sjodahl R (1996) Randomized comparison of straight and colonic J pouch anastomosis after low anterior resection. Ann Surg 224:58–65
20. Marusch F, Koch A, Schmidt U, Geibetaler S, Dralle H, Saeger HD et al (2002) Value of a protective stoma in low anterior resections for rectal cancer. Dis Colon Rectum 45:1164–1171
21. Wong NY, Eu KW (2005) A defunctioning ileostomy does not prevent clinical anastomotic leak after a low anterior resection: a prospective, comparative study. Dis Colon Rectum 48:2076–2079
22. Pakkastie TE, Ovaska JT, Pekkala ES, Luukkonen PE, Jarvinen HJ (1997) A randomised study of colostomies in low colorectal anastomoses. Eur J Surg 163:929–933
23. Graffner H, Fredlund P, Olsson SA, Oscarson J, Petersson BG (1983) Protective colostomy in low anterior resection of the rectum using the EEA stapling instrument. A randomized study. Dis Colon Rectum 26:87–90
24. Lange MM, Buunen M, van de Velde CJ, Lange JF (2008) Level of arterial ligation in rectal cancer surgery: low tie preferred over high tie. A review. Dis Colon Rectum 51:1139–1145
25. Seike K, Koda K, Saito N, Oda K, Kosugi C, Shimizu K et al (2007) Laser Doppler assessment of the influence of division at the root of the inferior mesenteric artery on anastomotic blood flow in rectosigmoid cancer surgery. Int J Colorectal Dis 22:689–697
26. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T et al (2001) Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 345:638–646
27. Swedish Rectal Cancer Trial (1997) Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 336:980–987
28. Bosset JF, Calais G, Daban A, Berger C, Radosevic-Jelic L, Maingon P et al (2004) Preoperative chemoradiotherapy versus preoperative radiotherapy in rectal cancer patients: assessment of acute toxicity and treatment compliance. Report of the 22921 randomised trial conducted by the EORTC Radiotherapy Group. Eur J Cancer 40:219–224

日鏡外会誌 16：181-186, 2011

原著

治癒切除不能 StageⅣ大腸癌に対する腹腔鏡下手術と開腹手術の比較検討

枝園 和彦* 久保 義郎 小畠 誉也 羽藤 慎二
大田 耕司 野崎 功雄 棚田 稔 栗田 啓

Key words ◆ 大腸癌，stageⅣ，腹腔鏡下手術

◆要旨：【目的】治癒切除不能 StageⅣ大腸癌の原発巣切除に対する腹腔鏡下手術の安全性，妥当性を検討した．【対象・方法】StageⅣ大腸癌の原発巣切除のうち，1995年4月～2007年8月の腹腔鏡補助下大腸切除術（以下，LAC）14例と，2006年3月から2007年12月の開腹大腸切除術（以下，OC）21例を retrospective に比較した．【結果】LAC群で有意に年齢が高かったが，性別，BMI，手術時間および術後合併症に差を認めなかった．術中出血量，術後の離床および化学療法開始までの日数はLAC群で有意に良好であった．1・2年生存率は両群間に差を認めなかった（$p=0.26$）．【結論】治癒切除不能 StageⅣ大腸癌の原発巣切除に対する LAC は，OC と比較して術後経過が良好で早期に化学療法を開始できることより，よい適応と考えられた．

はじめに

大腸癌は近年，スクリーニング技術の発達により早期に発見される例が増える一方で，依然として20%の例では診断時に遠隔転移を有した状態で発見されている[1]．遠隔転移を有するStageⅣ大腸癌症例のうち，原発巣とともに肝切除や肺切除などを行って根治を得られる症例も存在するが，多くは切除不能で，その5年生存率は8%程度との報告もある[1]．これまで，転移巣の切除不可能なStageⅣ大腸癌に対する原発巣切除は，腫瘍による腸管閉塞や穿孔，出血のコントロールなどを目的として行われてきたが，化学療法の進歩に伴い原発巣の切除が予後を延長する可能性を示唆する報告もある[2]．今回，筆者らはStageⅣ大腸癌に対し，より低侵襲と考えられる腹腔鏡補助下に原発巣切除を行った症例の安全性，妥当性を検討した．

対象および方法

治癒切除不能なStageⅣ大腸癌に対して当科で行った原発巣切除のうち，1995年4月～2007年8月の腹腔鏡補助下大腸切除術（laparoscopy-assisted colectomy；以下 LAC）14例と，2006年3月～2007年12月の開腹大腸切除術（open colectomy；以下，OC）21例において，患者背景，

*国立病院機構四国がんセンター外科
別刷請求先：枝園和彦　岡山大学大学院医歯薬学総合研究科腫瘍・胸部外科（〒700-8558　岡山市北区鹿田町2-5-1）

表1 患者背景

	LAC (n=14)	OC (n=21)	p 値
性別			0.68
男	7	12	
女	7	9	
年齢(歳)			0.04
中央値(範囲)	66(52～85)	59(32～82)	
BMI(kg/m^2)			0.21
中央値(範囲)	23(16～29)	22(16～32)	
術前内視鏡通過の可否			0.89
通過可能	5	8	
通過せず	9	13	
病変部位			0.73
盲腸	0	1	
上行結腸	2	1	
横行結腸	2	1	
下行結腸	2	3	
S状結腸	5	6	
Rs	2	4	
Ra	1	3	
Rb	0	2	
cT因子			0.73
cT 1	0	0	
cT 2	2	0	
cT 3	12	18	
cT 4	0	3	
原発腫瘍最大径(cm)			0.04
中央値(範囲)	3.5(2.0～5.0)	5.0(3.0～8.0)	
遠隔転移臓器			0.53
肝	10	12	
肺	4	5	
リンパ節	1	4	
腹膜	1	6	
その他	0	2	

術中および術後経過，予後に関して retrospective に比較検討した．腹腔鏡下手術の適応としては，①術前の CT 検査にて腫瘍最大径が 6 cm 以下で，②腫瘍の他臓器への直接浸潤がなく，③術前にイレウス症状を呈していないこと，を条件とした．統計学的解析には χ^2 検定，Mann-Whitney 検定を用いた．また，累積生存率曲線は Kaplan-Meier 法にて算出し，logrank 法にて生存率の差を検討した．いずれの検定においても，$p<0.05$ をもって有意差ありとした．

結 果

患者の背景因子を**表1**に示す．年齢中央値は LAC 群 66 歳，OC 群 59 歳と LAC で高かった ($p=0.04$)．性別，Body Mass Index (BMI)，内視鏡通過の可否および病変部位に関して両群間に有意差を認めなかった．術前 CT における原発腫瘍の臨床病期（cT 因子）は両群間に差を認めなかったが，腫瘍最大径中央値は LAC 群 3.5 cm (範囲 2.0～5.0 cm)，OC 群 5.0 cm（範囲 3.0～8.0 cm）で，OC 群で有意に大きかった ($p=0.04$)．遠隔転移臓器（M 因子）は，両群間に差を認めなかった．OC 群のうち，術前 CT で腫瘍径が 6 cm を超えていたものは 4 例，他臓器浸潤を認めたものは 3 例，イレウス症状を認めたものは 5 例であった．これらのいずれも認めなかったが開腹術を施行した症例は 11 例であった．

手術成績を**表2**に示す．手術時間中央値は LAC 群 135 分（範囲 75～280 分），OC 群 145 分 (102～476 分）で両群間に差を認めなかったが，術中出血量中央値は LAC 群 70 g（範囲 15～500 g)，OC 群 275 g（80～1,145 g）で，LAC 群で有意に少なかった ($p<0.01$)．LAC 群のうち，1 例で術中に腫瘍の膀胱前腹膜への直接浸潤を認めたために開腹術へ移行した．切除標本による原発腫瘍の病理病期（pT 因子）は両群間に有意差を認めなかったが，病理学的検索による腫瘍長軸径は OC 群で有意に大きかった ($p=0.03$)．LAC 群で腫瘍長軸径が 6 cm を超えていたものはなかった．

術後経過を**表3**に示す．術後の食事開始までの日数（中央値：両群とも 3 日）および術後入院日数（中央値：LAC 群 12 日・OC 群 15 日）に差を認めなかったが，術後の離床までの日数（中央値：LAC 群 1 日・OC 群 2 日)，解熱までの日数（中央値：LAC 群 2 日・OC 群 4 日)，腸蠕動回復までの日数（中央値：LAC 群 1 日・OC 群 2 日）は，いずれも LAC で有意に早かった．

LAC 群 9 例(64%)，および OC 群 18 例（86%）で，術後に何らかの化学療法を行った．術後から化学療法開始までの日数中央値は，LAC 群 21 日（範囲 12～66 日)，OC 群 43 日（範囲 24～70 日）